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VIA ELECTRONIC MAIL TO: CAGInquiries@cms.hhs.gov
Centers for Medicare & Medicaid Services (CMS)
Coverage and Analysis Group (CAG)
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Ms. Joanna Baldwin & Ms. Nina Arya,

Edwards Lifesciences commends CMS's prioritization of the reconsideration request for the National Coverage Determination (NCD) for Transcatheter Aortic Valve Replacement (TAVR). We are grateful for your responsiveness to the evolving needs of Medicare beneficiaries with aortic stenosis (AS). The posting of this tracking sheet marks a critical step toward ensuring timely, equitable access to lifesaving AS treatment for Medicare beneficiaries.

Over the past two decades, AS management has undergone a dramatic transformation– from a condition with limited evidence to one of the most rigorously studied areas in cardiovascular medicine. We appreciate the opportunity to comment, and Edwards believes that a future NCD policy should respond to AS patients' needs, anticipate the future needs of AS patients, and support evolving care delivery systems.

The recommendations in our full comment are focused on these key priorities:

- Aligning TAVR coverage with approved FDA indications, including asymptomatic AS.
- Recognizing that TAVR is a reasonable and necessary procedure for AS that has satisfied its Coverage with Evidence Development (CED) requirements, while continuing to support contemporary engagement with national registries as an ongoing cornerstone of quality and transparency.
- Preserving and supporting the critical importance of the multidisciplinary Heart Team (including an interventional cardiologist and cardiac surgeon), while permitting flexibility to address evolving models of treatment for AS patients.

Edwards believes updating this NCD will not only advance care, but will also improve patient outcomes, provide equitable access for all patients with AS, and reduce long-term Medicare costs.

Thank you for consideration of our comments.

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Introduction

For more than 60 years, Edwards Lifesciences ("Edwards") has been driven by a passion to improve patient lives, becoming 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 in the United States, implanted in more than 500,000 patients nationally.

We value CMS's recognition of the opportunity to improve health outcomes for Medicare beneficiaries by updating the Medicare coverage policy to meet the evolving needs of patients with aortic stenosis (AS). Edwards believes updating this NCD will not only advance care, but will also improve patient outcomes, provide timely and equitable access for all patients with AS, and reduce long-term Medicare costs.

1.0 The clinical and population value of AVR

The clinical evidence remains clear; aortic valve replacement (AVR), whether performed surgically or via transcatheter intervention, represents one of the most efficient and effective lifesaving interventions in modern medicine. A recent meta-analysis demonstrates that AVR confers a substantial survival benefit compared to conservative management for severe AS:

- *Five-year mortality:* AVR is associated with a 17.7% absolute survival benefit compared to medical therapy alone [1].
- *Number Needed to Treat (NNT):* Only 5.7 patients must be treated with AVR to save one life at five years [1].

2.0 TAVR has transformed AS care

AS is a deadly, growing disease burden in the United States. The prevalence of AS increases consistently with age, with a prevalence of almost 3% among adults aged 60-74 years and increasing to over 13% among those aged over 75 years [2]. Without treatment, Medicare patients with AS face up to a 50 percent mortality rate within one year of diagnosis, yet less than half of indicated patients receive valve replacement, highlighting the substantial undertreatment of this condition [3, 4]. Moreover, patients awaiting treatment encounter numerous challenges, including provider shortages and hospital capacity constraints, contributing to disparities in access and delays in treatment that lead to increased morbidity and unnecessary mortality [4-9].

The introduction and expansion of TAVR have fundamentally transformed the landscape of AS care in the United States. With U.S. Food and Drug Administration (FDA) approval in 2011, TAVR provided a vital option for high-risk and inoperable patients who were not candidates for surgical aortic valve

replacement (SAVR), demonstrating excellent outcomes and safety in populations where surgery was previously the only alternative [10, 11]. TAVR has evolved to become the AVR treatment for most Medicare beneficiaries and is now routinely offered to patients across all surgical risk profiles [12]. Population-level data reveal a decline in age-adjusted AS mortality rates among older adults, correlating with broader adoption of TAVR [13]. This reduction in AS mortality is especially remarkable given that, over a similar period, age-adjusted cardiovascular disease (CVD) mortality overall has remained essentially flat, with only minimal annual declines [14].

Updating the TAVR coverage policy presents a unique opportunity for CMS to promote its transformation agenda, which will directly enable CMS to deliver on its promise of better health, better care, and smarter spending for the populations it serves.

3.0 Access challenges: The need for policy change

Despite clinical advances, significant geographic and sociodemographic disparities in access to TAVR persist [9, 15-20]. Recent national analyses show that access to TAVR centers is consistently lower than to SAVR centers, particularly in the Western and Southern United States. Nearly one in four Medicare beneficiaries over age 65 years live more than an hour away from a TAVR center, with rural and minority communities disproportionately affected [19]. Addressing these persistent access challenges through thoughtful policy change will ensure that the lifesaving benefits of AVR, especially TAVR, are equitably available to all eligible patients.

4.0 Recommendations, rationale, and evidence for changes to the TAVR NCD

Edwards appreciates CMS's commitment to prioritizing this reconsideration, recognizing the critical importance of timely, equitable access for patients with AS. Edwards believes the future state of the TAVR NCD must ensure high-quality outcomes and improved access for all patients by aligning coverage with approved FDA indications, enabling timely treatment, and maintaining standards that preserve procedural quality. As TAVR has matured into a well-established, lifesaving therapy, Edwards believes CMS's coverage policy should be forward-looking, enduring, and designed to meet the evolving needs of patients and the healthcare system.

The following sections provide specific recommendations and rationale for updating the NCD policy to achieve these goals.

4.1 Patient criteria

To ensure timely access for Medicare beneficiaries to lifesaving therapies such as TAVR, the coverage policy must reflect the current FDA-approved indication for patients with asymptomatic AS. Outdated

coverage criteria risks delaying treatment for patients who meet evidence-based indications – an omission that carries significant consequences for patient survival and quality of life [21-24].

An expanding body of evidence highlights the adverse consequences of delayed treatment of AS. Chronic pressure overload from AS often leads to maladaptive cardiac remodeling and myocardial fibrosis, changes that often remain irreversible even after intervention [25-28]. The long-term clinical consequences of delayed intervention are further highlighted by a recently proposed classification system which stratifies pre-AVR clinical presentation into three categories: asymptomatic or stable valve syndrome (SVS), mildly symptomatic progressive valve syndrome (PVS), and acute valve syndrome (AVS), the latter characterized by abrupt onset of severe symptoms [29, 30]. In a real-world cohort of 24,075 patients, those presenting with AVS faced a 3-fold higher risk of 1-year death and a 4-fold higher risk of heart failure hospitalization after AVR compared to those treated while still in a stable, asymptomatic stage (AVS mortality adjusted hazard ratio (aHR): 2.9; 95% CI: 1.1–7.8; p-value [*p*]=0.03; AVS heart failure hospitalization aHR: 4.1; 95% CI: 1.6–11.1; p=0.005) [31]. In another real-world analysis of 4,069 patients undergoing AVR (TAVR), 50% underwent delayed intervention (i.e., >90 days post-diagnosis or urgent/emergent), which increased the 3-year mortality risk by 50% and heart failure hospitalization risk by 59% compared to timely intervention [32]. Furthermore, delayed care may also contribute to increased urgent/emergent admissions, which are associated with a 2.8 times higher risk of post-AVR mortality and a 2.4 times higher risk of ICU admission compared to elective, planned admissions [33].

Over the past two decades, AS management has undergone a dramatic transformation – from a condition with limited evidence to one of the most rigorously studied areas in cardiovascular medicine. Today, robust randomized trial data and high-quality registries underpin clinical guideline updates and reinforce the clinical imperative for coverage alignment for these patients (*Appendix*).

Recently published European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS) 2025 Guidelines represent a pivotal step forward in the management of patients with significant AS [34]. The new guidelines endorse a more proactive approach, recommending prompt intervention with AVR (TAVR/SAVR) earlier in the treatment pathway. Notably, asymptomatic patients with severe high-gradient AS and preserved heart function (LVEF≥50%) may undergo AVR if procedural risk is low, a departure away from the traditional strategy of 'watchful waiting' (clinical surveillance). This update was supported by recent data from 4 randomized clinical trials (RCTs): EARLY TAVR (NCT03042104), AVATAR (NCT02436655), EVOLVED (NCT03094143), and RECOVERY (NCT01161732) [35-38]. Collectively, these data further strengthen the evidence base that has expanded our understanding of the optimal timing for AVR, particularly in asymptomatic patients with AS who are not addressed under the current coverage policy for TAVR.

EARLY TAVR was the largest RCT to test a strategy of prompt AVR with TAVR in this patient population. The trial showed that prompt intervention with TAVR significantly reduced the composite risk of death, stroke, or heart failure hospitalizations compared to clinical surveillance (26.8% vs. 45.3%; HR: 0.50; 95% CI: 0.40-0.63; p<0.001). Importantly, 87% of patients in the clinical surveillance arm ultimately underwent

AVR during a median follow-up of 3.8 years, often presenting with advanced symptoms (40% at 5 years) [35].

Recent meta-analyses pooling data from the 4 RCTs (1,427 patients) further underscore the benefits of prompt AVR in asymptomatic patients, consistently demonstrating reductions in unplanned cardiovascular or heart failure hospitalizations and stroke, and several reporting reductions in all-cause mortality and cardiovascular mortality [39-45]. Among these, a meta-analysis of reconstructed time-to-event data showed that timely AVR significantly lowered the risk of 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 clinical surveillance [40]. Several studies combining randomized and non-randomized evidence yielded directionally consistent results [41, 46-57]. In a recent meta-analysis by Généreux et al. evaluating 16 studies (5,346 patients), AVR was associated with significantly reduced all-cause mortality (incidence rate ratio [IRR]: 0.42; 95% CI: 0.31-0.58; p<0.01; I^2=72%), cardiovascular mortality (IRR: 0.46; 95% CI: 0.28-0.78; p<0.01; I^2=68%), and unplanned cardiovascular or heart failure hospitalizations (IRR: 0.34; 95% CI: 0.21-0.55; p<0.01; I^2=50%). Sub-analyses of RCT data also showed significant reductions in unplanned cardiovascular or heart failure hospitalizations (IRR: 0.42; 95% CI: 0.26-0.65; p<0.01; I^2=27%) and stroke (IRR: 0.63; 95% CI: 0.40-0.98; p=0.04; I^2=0%) [50].

Evolving insights into the progressive nature of AS and the risks associated with delayed treatment, coupled with improvements in patient selection, the well-established role of TAVR in managing AS, and the robust body of evidence supporting timely intervention in asymptomatic AS, all collectively underscore the urgent need to modernize the TAVR coverage policy. The current coverage language which covers ‘symptomatic’ aortic valve stenosis no longer reflects best clinical practice and further exacerbates delays in care. To ensure appropriate access to a therapy and indication that is now proven and supported by high-quality data, Edwards urges CMS to amend its coverage language to apply to ‘aortic valve stenosis.' The change is essential to streamline care pathways, align policy with evidence-based recommendations, and optimize patient outcomes.

4.2 Coverage with Evidence Development

Coverage with Evidence Development (CED) lets CMS condition coverage on participation in an approved study or registry when evidence is promising but incomplete; CMS explicitly states CED should not last indefinitely and has published updated guidance (August 7, 2024) reinforcing time-limited, fit-for-purpose approaches.

In the early stage of TAVR adoption more than 14 years ago, CMS applied CED in service of developing the evidence necessary to support a future and permanent coverage decision. Through its CED decision, CMS imposed conditions of Medicare coverage, including on eligible patient populations, provider and facility requirements, mandatory registry participation, and additional procedural and reporting obligations.

Appropriately applied CED policy accelerates access to innovative therapies while ensuring quality outcomes by exploring clinically relevant, unresolved questions, and assessing therapy performance in a real-world setting. It is also critical that innovators have a clear end goal and clear timeline to ensure that evidence generation leads to meaningful coverage decisions. In the case of TAVR, coverage under CED successfully expedited Medicare beneficiary access to innovative AS treatment while ensuring safeguards were in place to protect patient safety and quality outcomes as the therapy matured. TAVR is among the most rigorously studied medical device technologies subject to CED [58]. Through this NCD reconsideration, CMS has an opportunity to demonstrate responsiveness to the extensive evidence collected to date by establishing a successful end to CED for TAVR.

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 that CED should no longer be required as a condition of coverage and TAVR is reasonable and necessary for AS. All CED questions posed by CMS have been thoroughly addressed by a robust body of clinical trials and registry studies published over the past decade (*Appendix*). Published registry outcomes across all surgical risk levels demonstrate outstanding TAVR performance in real-world practice, mirroring results from pivotal clinical trials [10-12, 35, 59, 60]. TAVR has demonstrated excellent durability through 5 years for high-risk patients, 10 years for intermediate-risk patients, and 7 years for low-risk patients in the PARTNER trials, with additional real-world data confirming valve durability through 10 years among Medicare beneficiaries [61-64]. Furthermore, there is a comprehensive understanding of the morbidity and procedural factors influencing TAVR outcomes, which has been incorporated into a 30-day composite performance measure, eliminating the need for proxy measures for quality [65].

The evolution of the TAVR evidence base now clearly satisfies both standards that govern CMS's coverage approaches: first, that TAVR is "reasonable and necessary" under section 1862(a)(1)(A) of the Social Security Act; and second, that the remaining conditions for CED have been fully met and therefore should be sunset. Accordingly, Edwards believes CMS should now transition TAVR coverage to a durable "reasonable and necessary" framework without CED and structurally align the TAVR NCD with coverage policies for comparable cardiovascular interventions.

Registry reporting for TAVR has been instrumental in enabling the expansion of treatment to new patient populations and providing insights that have guided clinical practice and ensured quality outcomes through the evolution of TAVR. We support continuing the national registry reporting as a cornerstone of quality and transparency, while aligning with CMS's 2024 guidance to retire mandatory CED when appropriate. The evidence base is mature, national registry quality functions remain valuable, and voluntary participation – with incentives via public reporting and dashboards – can sustain quality without tying coverage to mandatory participation. Edwards anticipates that voluntary registry reporting will continue for TAVR, as today providers submit non-mandatory reporting for over 95% of SAVR cases reported to the STS registry [66].

4.3 Procedure operator requirements

Edwards strongly believes CMS should give Heart Teams the flexibility to determine which combination of qualified member(s) perform TAVR procedures, tailoring participation to procedural complexity and patient clinical needs. Permitting this flexibility would reduce provider burden and capacity constraints, support continued excellent TAVR outcomes, enable more timely treatment, and help address undertreatment of AS.

The CMS policy requirement for both an interventional cardiologist and a cardiac surgeon to jointly participate in all TAVR procedures has become outdated due to the significant evolution of practice patterns, patient selection criteria, expanded indications across all surgical risk categories, and technological innovations that have consistently produced excellent outcomes and patient safety.

TAVR is now a routine AVR treatment option with consistent excellent outcomes [12]. Further, the rate of conversion to surgery is comparable to percutaneous coronary intervention (PCI) in contemporary practice (0.4%) with a notable decrease (-40%) in post-conversion mortality from 2017 to 2021 [67-69].

Multiple studies have found that allowing qualified Heart Team members flexibility in performing TAVR does not compromise patient outcomes. For example, a review of five seminal European studies found that centers without on-site cardiac surgery achieved similar in-hospital, 30-day, 1-year, or 3-year mortality outcomes for TAVR procedures as those with on-site cardiac surgery [70]. Importantly, global patient population characteristics are similar to Medicare patients, as AS patients are typically elderly with high comorbidity [2]. In the United States, experience during the COVID-19 Public Health Emergency (PHE) demonstrated that allowing operator flexibility enabled local heart valve teams to make appropriate decisions for patient care with no decrement to TAVR outcomes [71].

Widespread undertreatment of AS, increased patient demand for TAVR and structural heart procedures overall, as well as increasing provider shortages, especially for cardiac surgeons, are creating significant constraints on patient access to timely TAVR under existing requirements [7]. Procedural operator requirements have been identified by TAVR programs as a leading source of burden, resulting in unnecessary program shutdowns, cancellations, and delays in patient care across multiple regions [5]. Coordinating the availability of both interventional cardiologists and surgeons often delays urgent TAVR cases and complicates care delivery, while staffing shortages and scheduling difficulties force patients onto long waiting lists or require travel to more distant centers, which can lead to emergency admissions and longer hospital stays [6, 9, 19, 72].

4.4 Patient evaluation

When TAVR was first introduced, high-risk-only indications necessitated patient evaluation centered on surgical risk and conducted by a surgeon. Since 2012, TAVR indications and patient profiles have expanded with excellent outcomes consistently documented across surgical risk profiles [12]. Guidelines recognize TAVR as a routine procedure which has become less complex over time [73]. Over 95% of TAVR procedures are now performed via transfemoral access [12]. Now that TAVR is approved for all surgical risk, TAVR assessment is centered on anatomical suitability, not surgical risk, which evolves

provider qualifications to evaluate suitability. Based on their training and experience, either an interventional cardiologist or a cardiac surgeon is qualified to assess if a patient is a candidate for TAVR. Training and experience, rather than provider specialty, enable a provider's capability to evaluate suitability for TAVR [74]. Two evaluations are not always necessary.

Clinical consensus recommendations now support updating evaluation requirements to streamline the process for patients who are clear TAVR candidates, allowing heart valve teams to focus their review and discussion on more complex cases [75]. NCD flexibilities provided during the COVID-19 PHE to remove face-to-face evaluation requirements did not impact TAVR outcomes, providing further evidence for a simplified evaluation process [71].

Unnecessary evaluation requirements can delay patient care and contribute to increased mortality among those waiting for TAVR. Scheduling multiple evaluations can be challenging in some regions, especially with provider shortages [7]. Many centers report delays for evaluations extending from weeks to months. The observed mortality rate on waiting lists is about 5%, with two-thirds of deaths occurring during the first 60 days [76]. Additionally, TAVR patients experience a median delay of 59 days longer from AS diagnosis to treatment compared to SAVR patients (157 days and 98 days, respectively) [6]. Patients who experience delays of greater than 90 days between AS diagnosis and receiving TAVR have a 50% higher three-year mortality risk and a 59% higher risk of heart failure hospitalization compared to those who receive timely intervention [32]. Delays also contribute to increased rates of urgent or emergent admissions, which are associated with a 2.8-fold higher risk of post-AVR mortality and a 2.4-fold higher risk of ICU admission compared to elective procedures [72].

4.5 Site requirements

Hospitals have consistently demonstrated excellent TAVR outcomes over time. New centers opened after CMS relaxed the volume criteria in the 2019 NCD achieved comparable TAVR outcomes to those at established, higher-volume programs, with no significant difference in mortality, stroke or vascular complications [77]. Similarly, outcomes data from the COVID-19 PHE demonstrate that there was no significant difference in TAVR outcomes following implementation of flexibilities to volume criteria within the TAVR NCD [71].

In contemporary practice, composite outcomes, such as direct measures of quality, more accurately identify high-performing centers than volume-based criteria. Many low-volume centers achieve excellent outcomes and strict volume requirements unnecessarily limit centers offering TAVR, reducing access without improvement in outcomes [78].

Site volume requirements contribute to access disparities. Substantial evidence documents geographic inequities and barriers to accessing TAVR [9, 15-19, 78, 79]. These disparities in access are higher for TAVR versus other procedures, such as SAVR and CABG, and are influenced by NCD site requirements [15]. Volume criteria limiting hospital eligibility to perform TAVR contributes to the creation of geographic regions with limited access to TAVR centers, forcing some patients to travel long distances for care and worsening healthcare disparities among low-income and rural Medicare beneficiaries [9]. Many patients

are unwilling to travel outside of their trusted communities for care, regardless of local referral to larger volume programs [80].

A number of established cardiovascular coverage policies, such as percutaneous transluminal angioplasty (PTA), demonstrate clear precedent for NCDs without procedural volume restrictions. Additionally, SAVR, and balloon aortic valvuloplasty (BAV), the alternative AS treatment options, are broadly covered and widely accessible, with no historical requirement for minimum procedural volumes for patient access.

TAVR quality can be measured directly to enable timely patient access. With the availability of a validated quality measure for TAVR, outcomes at the site level can now be assessed directly, eliminating the need to use procedural volume as a proxy [65]. Reporting on this measure demonstrates that local hospital outcomes data in the STS/TVT Registry can be 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. Other quality reporting metrics include the AHA Target AS Registry disease quality metric, as well as ACC/AHA Clinical Performance and Quality Metrics [81, 82].

TAVR program quality is now reported to enable patient choice and mirrors the existing quality indicators in place for SAVR procedures. The STS/ACC TVT Registry enables participants to voluntarily report and inform the public of their hospital or program procedure scores and star ratings. In addition, U.S. News & World Report evaluates and publicly reports on high-performing TAVR hospitals that have better patient outcomes compared to other hospitals.

Rather than relying on procedural volume thresholds, CMS can modernize NCD site requirements to empower programs to maintain institutional and physician standards for TAVR centers, such as credentialing processes, monitoring of physician and program outcomes, and ensuring appropriate staff training, facility infrastructure, and quality improvement processes. The PTA NCD provides an example of criteria that both empowers programs and defines expectations for facilities to establish and maintain institutional and physician standards that could be adapted by CMS to describe program requirements in an updated TAVR NCD.

4.6 Heart Team

The multidisciplinary Heart Team has been central to the success of TAVR, ensuring that patients benefit from collaborative expertise and coordinated care throughout the evolution of this therapy. This collaborative approach has contributed to excellent patient outcomes and the safe adoption of TAVR as a standard of care in valve disease treatment. After many years of Heart Team collaboration, Edwards believes the concept is firmly embedded in practice and remains an important component of patient-centered care.

Edwards believes that the current NCD Heart Team language may be burdensome, inefficient, and limits the flexibility for Heart Teams to determine provider participation based on patient needs. Experience during the three-year period of COVID-19 PHE demonstrated that increased flexibility in Heart Team

requirements did not compromise patient care. This period highlighted that the technologies, procedural practices, and role of the Heart Team, had matured beyond existing NCD requirements [71]. By simplifying the Heart Team language in the NCD, CMS can empower local teams to adapt provider participation and collaboration to reflect local patient characteristics, facility capabilities, provider expertise, and preferred methods of communication between members. This flexibility would support more responsive and efficient care delivery, ensuring that services remain aligned with the needs of Medicare beneficiaries.

5.0 Conclusion

Edwards is deeply committed to advancing patient care in structural heart disease and to being a collaborative partner with CMS. We appreciate CMS's prioritization of this NCD reconsideration, recognizing the critical importance of timely, equitable access for patients with AS. Edwards will continue to support evidence-based policy updates and work alongside CMS to achieve high-quality outcomes and improved access for all AS patients.

Key Takeaways and Recommendations for Updated NCD Policy

- **New Indications:** A robust evidence base strongly supports expanding TAVR coverage to include asymptomatic patients with AS, with data from randomized trials and registries demonstrating that timely AVR improves outcomes, reduces hospitalizations, and enhances quality of life in this patient population.
- **CED:** All CED questions posed by CMS have been thoroughly addressed by more than a decade of clinical trials and registry studies. TAVR demonstrates excellent long-term outcomes and durability, supporting a successful end to CED requirements.
- **Flexibility for Qualified Heart Team Members:** Policy updates should allow Heart Teams to determine which combination of qualified members perform TAVR procedures, reflecting evolving practice patterns, expanded indications, increasing provider shortages, and evidence of continued excellent outcomes with operator flexibilities. This approach will help address undertreatment and improve timely access for patients.
- **Heart Team Evaluations:** The requirement for independent evaluations by *both* an interventional cardiologist and a cardiac surgeon is no longer consistent with the clinical needs of many AS patients and may contribute to delays in care. Streamlining these evaluations will reduce delays and improve patient outcomes.
- **Quality Measures:** Site volume is no longer an appropriate proxy for program quality. Hospitals can achieve excellent outcomes without strict procedural volume requirements. Empowering programs to adopt validated quality measures will reduce access disparities and support continuous improvement.

- **Heart Team Collaboration:** The multidisciplinary Heart Team remains central to TAVR's success, and maintaining high quality AS care and excellent patient outcomes. Simplifying NCD language will allow local teams to adapt provider participation to best meet patient needs, facility capabilities, and evolving trends.

6.0 Appendices

6.1 TAVR NCD Policy Recommendations

NCD Topic	Language
Patient Population	TAVR is covered for the treatment of aortic valve stenosis when furnished according to a Food and Drug Administration (FDA)-approved indication. The procedure is furnished with a complete aortic valve and implantation system that has received FDA premarket approval (PMA) for that system's FDA approved indication.
Heart Team	The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care. The heart team includes the following: a. Interventional cardiologist(s) and cardiac surgeon(s) experienced in the care and treatment of aortic stenosis. b. Providers from other physician groups as well as advanced patient practitioners, nurses, research personnel and administrators.
Patient Evaluation	The heart team's interventional cardiologist or cardiac surgeon must evaluate the patient to determine if the patient is a suitable candidate for TAVR.
Procedure Operator Requirements	The procedure must be performed by an interventional cardiologist(s), or cardiac surgeon(s) from the heart team with appropriate qualified procedural assistance. The heart team's interventional cardiologist(s) and cardiac surgeon(s) may jointly participate in the intra-operative technical aspects of TAVR as appropriate.
Site Requirements	Qualifications for all TAVR hospital programs: facilities must establish and maintain institutional and physician standards, including a heart team, to support a TAVR program. These standards must at least include and ensure the following: a. Facilities have a clearly delineated program for granting TAVR privileges and for monitoring patient outcomes for individual physicians and the program. b. Facilities have appropriately trained staff capable of fulfilling roles and responsibilities as delineated under the dedicated TAVR program. c. Facilities have appropriate supporting personnel and equipment for imaging, emergency management, advanced physiologic monitoring, and other ancillary care. d. Facilities must ensure continuous quality improvement by assessing procedural outcomes and making necessary programmatic adjustments to assure patient safety. Facilities are encouraged to participate in a prospective, audited, national registry.

6.2 Key Coverage Parameters

Proposed NCD	Rationale	Evidence to Support
Patient Criteria TAVR is covered for the treatment of aortic valve stenosis when furnished according to a FDA-approved indication. The procedure is furnished with a complete aortic valve and implantation system that has received FDA premarket approval (PMA) for that system's FDA approved indication.	20+ years of high-quality registry data and an expanding RCT evidence base underpin recent clinical guideline updates that endorse prompt intervention with AVR over 'watchful waiting' (clinical surveillance) and reinforce the clinical imperative for coverage alignment for asymptomatic patients not addressed under the current coverage policy. Despite FDA approval of this indication and new evidence demonstrating that timely treatment of AS prevents heart disease progression, improves patient outcomes, and reduces avoidable Medicare spending, asymptomatic AS patients are being denied access to care. Maintaining outdated coverage criteria risks delaying treatment for patients who meet evidence-based indications- an omission that carries significant consequences for patient survival and quality of life [21-24].	1) Asymptomatic AS carries a risk of sudden cardiac death and irreversible cardiac damage that develops during the asymptomatic phase and may not be corrected or reduced with later AVR [25-28, 83-85]. 2) Several studies exploring the various stages of cardiac damage found that prompt intervention for severe AS patients before symptoms develop improves survival and reduces healthcare resource utilization [25-28]. 3) TAVR performed after the progression of AS symptoms is significantly more expensive and requires more healthcare utilization compared to TAVR in asymptomatic patients. Additionally, patients presenting with acute or advanced symptoms at the time of AVR had nearly a 3x higher risk of death after 1 year and over 4x higher risk in the risk of heart failure hospitalization compared to asymptomatic patients [29]. 4) Recent ESC/EACTS 2025 Guideline updates endorse a more proactive approach in aortic valve disease management and recommend that AVR should be considered for asymptomatic patients, regardless of heart function, in contrast to the prior practice of 'watchful waiting' [34]. This update was supported by data from 4 RCTs demonstrating the benefits of AVR in asymptomatic AS patients (EARLY TAVR, AVATAR, EVOLVED, and RECOVERY) [35-38]. Notably, EARLY TAVR showed that timely TAVR resulted in: • a 50% reduction in the composite risk of death, stroke, or unplanned cardiovascular hospitalizations (at 2 years and a median follow-up of 3.8 years) • a 68% lower risk of hospitalization for heart failure through 5 years • prevented a decline in quality of life and improved measures of left ventricular and left atrial health at 2-years • numerically lower rates of stroke through 5 years [35]

Proposed NCD	Rationale	Evidence to Support
Patient Criteria (cont.)		5) Observational studies find timely intervention with AVR is associated with improved survival and lower rates of heart failure related hospitalizations [27, 29, 83, 84, 86-93]. 6) Recent meta-analyses pooling data from 4 RCTs further underscore the benefits of prompt AVR in asymptomatic patients, consistently demonstrating reductions in unplanned cardiovascular or heart failure hospitalizations and stroke, with several also reporting reductions in all-cause mortality and cardiovascular mortality [39-45]. Several meta-analyses combining randomized and non-randomized evidence yielded directionally similar results [41, 46-57].
Coverage with Evidence Development (CED)	All CED questions posed by CMS under CED have been satisfactorily answered by an abundance of clinical trials and registry studies.	1) Published registry outcomes across all surgical risk levels demonstrate excellent TAVR performance in real-world practice similar to pivotal clinical trials [10-12, 59, 60]. 2) TAVR has excellent, well-evidenced, long-term outcomes in pivotal clinical studies [35, 64, 94, 95]. 3) TAVR has demonstrated excellent durability through 5 years for high-risk patients, 10 years for intermediate-risk patients, and 7 years for low-risk patients in the PARTNER trials [62, 64, 95]. Additionally, the excellent durability of TAVR valves in a real-world population of Medicare beneficiaries has been demonstrated through 10 years [63]. 4) 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 [65].

Proposed NCD	Rationale	Evidence to Support
Procedure Operator Requirements The procedure must be performed by an interventional cardiologist(s) or cardiac surgeon(s) from the heart team with appropriate qualified procedural assistance. The heart team's interventional cardiologist(s) and cardiac surgeon(s) may jointly participate in the intra-operative technical aspects of TAVR as appropriate.	Policy mandating interventional cardiologist(s) and cardiac surgeon(s) jointly participate in all TAVR cases has become outdated due to the significant evolution of practice patterns, patient selection criteria, indication expansion across all surgical risk categories, and technological innovation for TAVR that have contributed to excellent outcomes and patient safety. Policy updates are now warranted to permit heart teams the flexibility to determine which combination of qualified member(s) perform TAVR procedures based on procedural complexity and patient clinical need. Flexibility to the operator criteria would relieve provider burden and capacity constraints, while ensuring excellent TAVR outcomes in the future by facilitating more timely treatment for referred patients and improving undertreatment for AS.	1) TAVR procedure outcomes are excellent overall, and the rate of conversion to surgery is comparable to percutaneous coronary intervention (PCI) in contemporary practice (0.4%) [67, 68, 96]. 2) A review of five seminal European studies found that centers without on-site cardiac surgery achieved similar in-hospital, 30-day, 1-year, or 3-year mortality outcomes for TAVR procedures as those with on-site cardiac surgery [70]. 3) Continued excellent outcomes during the public health emergency (PHE) with operator flexibilities demonstrated that local Heart Valve teams can make appropriate decisions for best patient care, specifically for operator requirements [71]. 4) Future TAVR procedure growth due to increased patient demand and widespread AS undertreatment, as well as a growing demand for structural heart procedures overall, and increasing provider shortages, contribute to program and provider constraints to provide timely treatment under this requirement [6, 7, 9, 19].

Proposed NCD	Rationale	Evidence to Support
Site Requirements Qualifications for all TAVR hospital programs: facilities must establish and maintain institutional and physician standards, including a heart team, to support a TAVR program. These standards must at least include and ensure the following: ▪ Facilities have a clearly delineated program for granting TAVR privileges and for monitoring patient outcomes for individual physicians and the program. ▪ Facilities have appropriately trained staff capable of fulfilling roles and responsibilities as delineated under the dedicated TAVR program. ▪ Facilities have appropriate supporting personnel and equipment for imaging, emergency management, advanced physiologic monitoring, and other ancillary care. ▪ Facilities must ensure continuous quality improvement by assessing procedural outcomes and making necessary programmatic adjustments to assure patient safety. Facilities are encouraged to participate in a prospective, audited, national registry.	Site volume is not an appropriate or necessary proxy for TAVR program quality and contributes to access disparities. Hospitals have proven their ability to maintain excellent TAVR outcomes without strict volume criteria. Programs should be empowered to ensure best practices. The percutaneous transluminal angioplasty (PTA) NCD provides an example of criteria that both empowers programs and defines expectations for facilities to establish and maintain institutional and physician standards that could be adapted by CMS to describe infrastructure program requirements in an updated TAVR NCD.	1) A validated quality measure is now available for TAVR, negating the need to use volume as a proxy for quality to assess TAVR outcomes [65]. 2) There was no significant difference in TAVR complication rates at new centers following relaxed 2019 NCD criteria [77]. 3) There was no significant difference in TAVR outcomes following flexibilities to volume criteria during the PHE [71]. 4) Geographic inequity and access barriers to TAVR are well-documented [9, 15, 17-19, 97, 98]. Disparities in access are higher for TAVR versus other procedures (SAVR and CABG) and may be driven by NCD site requirements [16].

Proposed NCD	Rationale	Evidence to Support
Patient Evaluation The heart team's interventional cardiologist or cardiac surgeon must evaluate the patient to determine if the patient is a suitable candidate for TAVR.	When TAVR first launched, high-risk-only indications necessitated patient evaluation centered on surgical risk and conducted by a surgeon. Now that TAVR is approved for all surgical risk levels, TAVR assessment is centered on anatomical suitability, not surgical risk, which evolves provider qualifications to evaluate suitability. Two evaluations are not always necessary. Unnecessary evaluation requirements contribute to a growing challenge of delayed treatment for patients that can lead to excess mortality.	1) TAVR indications and patient profiles have expanded with well-documented excellent outcomes since 2012 [12]. Guidelines recognize TAVR as a routine procedure, becoming less complex over time [73, 99]. Over 95% of TAVR procedures are performed via transfemoral access [12]. 2) Based on their training and experience, either an IC or a CTS is qualified to assess if a patient is a candidate for TAVR. Training and experience, rather than provider specialty, enable a provider's capability to evaluate suitability for TAVR [74]. 3) Burdensome requirements delay patient care, with a high mortality on the TAVR waiting list (5%, with two thirds of deaths within first 60 days) [76]. TAVR patients have a 59 day longer median time from AS diagnosis to treatment than SAVR patients (157 days and 98 days, respectively) [6]. Delays over 90 days also result in 50% higher 3-year mortality risk and 59% higher heart failure rehospitalization risk, and contribute to increased urgent/emergent admissions with higher mortality and ICU admissions [32, 72]. 4) Scheduling multiple evaluations can be challenging in some regions, especially with provider shortages [7]

Proposed NCD	Rationale	Evidence to Support
Heart Team The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care. The heart team includes the following: a. Interventional cardiologist(s) and cardiac surgeon(s) experienced in the care and treatment of aortic stenosis. b. Providers from other physician groups as well as advanced patient practitioners, nurses, research personnel and administrators.	Heart Team collaboration remains an important component of patient-centered care. Specifications in the current TAVR NCD Heart Team language may be burdensome, inefficient, and limit the flexibility for heart teams to determine provider participation based on patient needs. Simplifying the Heart Team language in the NCD would create efficiencies in resource utilization and capacity for local heart teams to address local trends in patient profiles, facility capabilities, provider expertise, and preferred methods of communication between members to ensure timely access to care for patients with AS.	PHE waivers in place for 3 years demonstrated that flexibilities to NCD heart team requirements did not compromise patient care, as the technologies, procedural aspects, and role of the Heart Team, had matured beyond existing NCD requirements [71].

6.3 Evidence-Based Responses to TAVR CED Questions

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.
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.

"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 [12]. 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 [60, 100, 101]. Among asymptomatic patients undergoing TAVR in the EARLY TAVR trial, the 30-day all-cause mortality rate was 0.2%, which was lower than rates reported for low-risk patients in recent TVT registry data [12, 102]. Similarly, rates of stroke (0.9%), new permanent pacemaker implantation (PPMI) (5.7%), and vascular complications (1.4%) were also comparatively low in patients who underwent prompt TAVR in the EARLY TAVR trial [35].

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 **[12]**	**6.06**	**2**	**3.8%**	**2.7%**	**11.8%**	**1.8%**
	PARTNER 1 **[10]**	**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 **[101]**	**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 **[60]**	**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

"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 [62]. Since then, durability data for all risk levels has been published from 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** [63].

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) [103]. Among 783 propensity matched pairs of TAVR patients from the PARTNER 2 S3i Registry and SAVR patients from the PARTNER 2A trial (hereinafter "the PARTNER 2 S3i study"), 5-year rates of VARC 3-defined structural valve deterioration (SVD) were similarly low for TAVR with SAPIEN 3 (stage 2 & 3 hemodynamic valve deterioration: 0.6 per 100 exposure years; bioprosthetic valve failure (BVF): 0.6 per 100 exposure years) and SAVR. In 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) [104].

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 TAVR and SAVR 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 [105]. Low rates of aortic valve reintervention with TAVR and SAVR were also demonstrated in the 5-year follow-up of the Evolut Low Risk Trial of 730 TAVR patients (3.3% vs. 2.5%, p=0.44) [106]. 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) [107]. Among asymptomatic patients in the EARLY TAVR trial, more than 70% of patients randomized to clinical surveillance ultimately underwent TAVR within 2 years. Although the study did not capture rates of BVF or subsequent aortic valve reintervention, the high crossover rate limits the relevance of any potential differences in valve durability between treatment groups in the trial [35].

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) [63]. 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%)), with 93.5% of patients free from SVD and BVF at 10-year follow-up and aortic valve reintervention was rare (n=2) [108]. 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 [109].

> ***Recently released evidence:*** *The excellent transcatheter valve durability findings in intermediate- and low-risk patients at 5 years in the PARTNER 2 S3i study and PARTNER 3 Trial persisted at 10 and 7 years, respectively. At 10-year follow-up in the PARTNER 2 S3i study, TAVR and SAVR patients had similarly low rates of aortic valve reintervention (3.0% vs.3.2%; HR: 1.39; 95% CI: 0.57-3.41; p=0.47) and mean gradients were stable from 1-10 years in both groups [64]. At 7-year follow-up in the PARTNER 3 Trial, TAVR and SAVR patients experienced similar rates of VARC-3 defined BVF (*6.9% vs. 7.3%; HR: 0.93; 95% CI: 0.56-1.54*), aortic valve reintervention (*4.7% vs. 4.0%*), and SVD (*1.7% vs. 2.8%*) [61]. An observational study of 410,720 Medicare beneficiaries who underwent TAVR between 2012 to 2024 demonstrated low reintervention rates after TAVR through 12 years (crude 12-year reintervention rate: 0.91%) [110].*

"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 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) [94, 111]. 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) [104, 112]. 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) [106, 107, 113]. Among asymptomatic patients in EARLY TAVR, 5-year all-cause mortality was comparable between TAVR and clinical surveillance (8.4% vs. 9.2%; HR: 0.93; 95% CI: 0.60-1.44). Notably, the attenuated mortality difference likely reflects the high quality of clinical surveillance in EARLY TAVR, including the rapid crossover to AVR and the very short interval between symptom onset and TAVR in the clinical surveillance group (median 32 days) [35].

> ***Recently released evidence:*** *Similar mortality rates were observed for TAVR and SAVR patients through 10 years among propensity-matched intermediate-risk patients in the PARTNER 2 S3i study (83.4% vs. 82.3%; HR: 1.01; 95% CI: 0.91-1.13, p=0.82) and through 7 years among low-risk patients in the PARTNER 3 trial (with vital-status sweep: 19.5% vs. 16.8%; HR: 1.17; 95% CI: 0.86-1.59) [61, 64].*

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) [94, 111]. 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) [112, 114]. 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) [106, 107, 113]. In the EARLY TAVR trial, asymptomatic patients who underwent TAVR had lower rates of stroke at 5 years compared to patients in the clinical surveillance arm (4.2% vs. 6.7%; HR: 0.62; 95% CI: 0.35-1.10), including lower rates of disabling stroke (1.8% vs. 2.9%) [35].

> ***Recently released evidence:*** *Similar rates of disabling stroke were observed for TAVR and SAVR patients through 7 years among low-risk patients in the PARTNER 3 trial (5.1% vs. 3.6%; HR: 1.37; 95% CI: 0.70-2.68) [61].*

New permanent pacemaker implantation

Across 7 RCTs and all risk levels, TAVR has demonstrated similar or higher rates of new PPMI than SAVR. For high-risk patients, the need for new PPMI 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) [94, 111] The 5-year incidence rate of new PPMI 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) [112, 114]. 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 5 years in the Evolut Low-risk RCT and 10 years in the NOTION trial (Evolut: 27% vs 11.3%; P < 0.001; NOTION: 44.7% vs. 14.0%, p<0.0001) [106, 107, 113].

> ***Recently released evidence:*** *Rates of new PPMI were comparable for TAVR and SAVR patients through 7 years among low-risk patients in the PARTNER 3 trial (17.3% vs. 12.8%; HR: 1.38; 95% CI: 0.97-1.97) [61].*

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) [94, 111]. 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) [59]. 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) [115]. Long-term rates of major bleeding have not been reported from the PARTNER 2 S3i, SURTAVI, or NOTION studies.

> ***Recently released evidence:*** *Rates of serious bleeding events were comparable for TAVR and SAVR patients through 7 years among low-risk patients in the PARTNER 3 trial (15.6% vs. 18.5%; HR: 0.79; 95% CI: 0.57–1.09) [61].*

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) [94, 111]. 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) [59]. 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) [106].

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

HIGH-RISK						
	PARTNER 1			**CoreValve High-risk**		
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 PPMI	**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**		
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 PPMI	**16.2%**	**11.7%**	**TAVR higher**	**39.1%**	**15.1%**	**TAVR higher**
Bleeding	**13.6%**	**44.7%**	**TAVR lower[1]**	**-**	**-**	**-**
Vascular complications	**9.0%**	**4.5%**	**TAVR higher[1]**	**-**	**-**	**-**

LOW-RISK									
	PARTNER 3 (7-yr Outcomes)			**Evolut Low-risk** (5-yr Outcomes)			**NOTION** (10-yr Outcomes)		
Outcomes	TAVR	SAVR	Relationship	TAVR	SAVR	Relationship	TAVR	SAVR	Relationship
All-cause mortality	**19.5%**	**16.8%**	**NS**	**13.5%**	**14.9%**	**NS**	**62.7%**	**64.0%**	**NS**
Stroke*	**5.1%**	**3.6%**	**NS**	**3.6%**	**4.0%**	**NS**	**9.7%**	**16.4%**	**NS**
New PPMI	**17.3%**	**12.8%**	**NS**	**27.0%**	**11.3%**	**TAVR higher**	**44.7%**	**14.0%**	**TAVR higher**
Bleeding	**15.6%**	**18.5%**	**NS**	**4.5%**	**9.8%**	**TAVR lower†**	**-**	**-**	**-**
Vascular complications	**-**	**-**	**-**	**4.1%**	**3.9%**	**NS**	**-**	**-**	**-**

ASYMPTOMATIC			
	EARLY TAVR		
5-yr Outcomes‡	TAVR	Clinical Surveillance	Relationship
All-cause mortality	**8.4%**	**9.2%**	**NS**
Stroke	**4.2%**	**6.7%**	**NS**
Disabling Stroke	**1.8%**	**2.9%**	**NS**
Unplanned hospitalization for cardiovascular causes	**20.9%**	**41.7%**	**TAVR lower**

*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 ‡Median follow-up of 3.8 years

[1]PARTNER 2A

PPMI: permanent pacemaker implantation; TAVR: transcatheter aortic valve replacement; RCT: randomized clinical trial; yr: year; Sig: significant; NS: no significant difference (p>0.05 or 95% confidence intervals overlapping 1.0)

"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 [65]. 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.

Morbidity and 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 that cause substantial morbidity and mortality and health status [65]. 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 PPMI.

The composite measure developed using TVT Registry data has been used in research investigating changes in TAVR outcomes over time. For example, from 2012 to 2018 in the TVT Registry, significant improvements in the 30-day rate of the composite outcome (death, stroke, stage 3 acute kidney injury, major/life-threatening/ disabling bleeding, and moderate or severe paravalvular regurgitation) have been observed. Much of the decrease in 30-day adverse event rates are explained by advances in device technology and procedural factors, which explain 35% and 33% of the improved outcomes, respectively [116].

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 [81]. In addition, performance measures such as time to intervention within 90 days following diagnosis have been published and can be tracked by institutions [82].

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. The outcomes of TVT Registry patients are similar to those observed in the PARTNER trials and are detailed above as well. 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) [94, 100, 117]. 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) [100]. 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) [118]. 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) [101]. 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) [119]. 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) [120]. 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) [121]. In the EARLY TAVR trial, only one death occurred within 30 days among asymptomatic patients who underwent AVR, with no deaths attributed to cardiovascular causes [35].

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) [100]. 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) [118]. 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 [101]. 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) [119]. 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) [60]. 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) [121]. In the EARLY TAVR RCT, 0.9% of patients in the TAVR group and 1.8% of patients in the clinical surveillance group who had converted to AVR had a stroke within 30 days [35].

New permanent pacemaker implantation

In 6 pivotal clinical studies, TAVR resulted in similar or higher short-term rates of new 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 [94, 100, 117]. 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) [100]. 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) [118]. 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) [101]. 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) [119]. In the PARTNER 3 trial, rates of new PPI were comparable between TAVR and SAVR across all follow-up periods in low-risk patients [60, 122]. 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) [60]. 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) [121]. Among asymptomatic patients in the EARLY TAVR trial, 30-day rates of new PPI were lower in patients undergoing TAVR compared with patients in the clinical surveillance group who later converted to AVR (5.7% vs. 8.4%) [35].

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 [94, 100, 117]. 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) [100]. 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) [118].

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) [101]. 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) [119]. 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) [120]. 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) [121]. In the EARLY TAVR trial, rates of life-threatening/disabling or major bleeding was lower among asymptomatic TAVR patients than clinical surveillance patients who eventually underwent AVR at 30 days (2.5% vs. 3.6%) [35].

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) [100]. 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) [118]. 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) [101]. 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) [119]. 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) [120]. 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) [121]. In the EARLY TAVR trial, the 30-day rates of major vascular complications were low and similar among asymptomatic patients undergoing TAVR and those managed with clinical surveillance who later underwent AVR (1.4% vs. 1.0%) [35].

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) [10]. 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%) [101]. 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%) [60]. 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%) [119, 121]. In the EARLY TAVR trial, the 30-day incidence of AKI were low and comparable for asymptomatic patients undergoing TAVR as well as those in the clinical surveillance group who later underwent AVR (2.5% vs 3.6%) [35].

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 PPMI	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 PPMI	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 PPMI	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
ASYMPTOMATIC										
EARLY TAVR RCT										
	30-Day†									
	TAVR					**CS with AVR**				
All-cause mortality	0.2%					0%				
Major Stroke	0.9%					1.8%				
New PPMI	5.7%					8.4%				
Bleeding	2.5%					3.6%				
Vascular complications	1.4%					1.0%				
Acute Kidney Injury	2.5%					3.4%				

*Significant difference at 1-year

†Outcomes reported for CS group who underwent AVR; relationship between treatment groups not reported

AVR: aortic valve replacement; CS: clinical surveillance; PPMI: permanent pacemaker implantation; RCT: randomized clinical 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 (4.7% vs. 4.0%])[95]. In the 10-year follow up of the PARTNER 2 S3i study, rates of reintervention were not different between TAVR and SAVR (3.0% vs 3.2%; p=0.47) [64]. 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 [62]. 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 [123].

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 [124]. 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 [125]. 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) [126]. 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 [111].

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) [127]. At 12 months, this difference corresponded to a large, clinically important improvement (i.e., ≥20-point change) [124]. 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) [127]. 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 [128, 129]. 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) [129].

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 [130]. 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) [130]. 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) [113]. 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 [121]. In the EARLY TAVR trial, favorable QoL (alive with a KCCQ score ≥75 and a ≤10-point decline from baseline) was achieved by 86.6% of patients in the early TAVR arm compared with 68.0% of patients in the clinical surveillance arm at 2 years (p<0.001). Prompt TAVR was also associated with greater improvement in left-ventricular and left-atrial health (48.1% vs. 35.9%; p=0.001) [35].

"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 [62]. 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 [111].

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 [101, 104]. 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 [114]. 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 [131]. 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 [112].

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 [132]. 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) [105]. 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 [133]. In the 5-year follow-up of the Evolut Low-risk RCT of self-expanding valve recipients, TAVR had significantly lower aortic valve mean gradients (10.7 mm Hg vs 12.8 mm Hg P < 0.001) and greater effective orifice areas (2.1 cm^2 vs 1.9 cm^2 ; P < 0.001) compared to SAVR [106]. 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.

Recently released evidence: The improvements in mean gradients observed after TAVR and SAVR in intermediate risk patients in the PARTNER 2 S3i study were maintained through 10 years according to echocardiographic assessments [64]. Among low-risk patients in the PARTNER 3 trial, TAVR and SAVR resulted in similar and stable mean aortic valve gradients (13.1±8.5 mm Hg vs. 12.1±6.3 mm Hg) and mean aortic valve areas (1.9±0.6 cm^2 and 1.8±0.5 cm^2) through 7 years [61].

"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)

In much of cardiovascular medicine, underuse of guideline-recommended therapies is the biggest challenge impacting patients [134]. An emerging body of evidence highlights the lack of timely treatment as a large contributor to poor prognosis with AS. The diagnosis of significant AS remains low, with 48% of patients with echo-confirmed moderate or severe AS lacking a diagnosis within a year [135]. Among symptomatic severe AS patients with a diagnosis and indication for treatment, significant undertreatment persists with fewer than 50% of patients undergoing AVR and as few as 19% of ssAS patients undergoing timely AVR (i.e., within 90 days of diagnosis) [24, 136]. There are **substantial clinical consequences to delayed intervention compared to timely intervention for severe AS patients**. In a real-world sample of 4,069 clinically significant AS patients that underwent TAVR, 50% underwent delayed intervention (i.e., > 90 days following diagnosis or urgent/emergent), which increased the 3-year mortality risk by 50% and heart failure hospitalization risk by 59% compared to timely intervention [32]. Delays in diagnosis or referral may contribute to disease progression prior to intervention. A recently proposed classification system categorizes clinical presentation before aortic valve replacement into three groups: stable valve syndrome (SVS), mildly symptomatic progressive valve syndrome, and acute valve syndrome (AVS) characterized by severe, sudden symptoms. Among 24,075 real-world AVR patients, the 1-year risks of death and heart failure hospitalization were significantly higher for patients with acute valve syndrome compared to stable valve syndrome (AVS mortality HR: 2.9 [95% CI, 1.1–7.8]; *P*=0.03; AVS HF hospitalization HR: 4.1 [95% CI, 1.6–11.1]; *P*=0.005) [31]. Delayed care may also contribute to increased urgent/emergent admissions, which have 2.8 times higher risk of post-AVR mortality as well as 2.4 times higher risk of ICU admissions compared to elective

admissions [33]. The recent findings of the EARLY TAVR Trial indicate that **the benefits of timely intervention extend beyond symptomatic patients to asymptomatic severe AS patients** as well [35].

Patient subgroups

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. 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" [73]. 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 diminished post-TAVR benefits. However, the guidelines recommend the use of the STS estimated surgical risk score as an indicator of patient comorbidities that can assist in decision-making [73]. **In patients of all STS surgical risk scores, TAVR with a balloon-expandable valve has proven to be safe and effective in the PARTNER Trial series.**

The PARTNER trials of high, intermediate, and low-risk patients that underwent TAVR or SAVR included subgroup analyses of the respective trial's primary endpoint and found limited to no heterogeneity in treatment effects by subgroups based on patient characteristics or comorbidities. In the PARTNER A trial of high-risk patients, the treatment effect of TAVR on 1-year mortality differed by sex and CABG status, favoring transcatheter replacement in women and in patients without a history of CABG; the effect did not differ by other subgroups explored [100]. Among intermediate risk patients in the PARTNER 2A trial, there was no significant difference in the treatment effect of TAVR on 2-year death or disabling stroke in the patient subgroups explored [59]. Among low risk patients in the PARTNER 3 trial, subgroup analyses of the 1-year rate of death, stroke, or rehospitalization demonstrated no heterogeneity of treatment effects in the subgroups explored [120].

When considering patient characteristics and procedural factors impacting outcomes, 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). While improvements in 30-day mortality and adverse events were explained most by device factors, the improvement in 1-year mortality following TAVR 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) [116]

Shared decision making

Shared decision making and patient-centered outcomes were improved when decision aids for were used by Heart Team clinicians [137]. 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 [138]. 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; $p<0.001$) [139]. 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 [140].

"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 [141]. 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 ($p<0.001$) [116]. 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 [142]. 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) [114]. 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) [132]. 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) [113].

Permanent pacemaker implantation

Rates of new pacemaker in contemporary practice with SAPIEN 3 are low and comparable with surgery [120, 132]. 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 [143].

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) [60]. 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 [144].

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" [145].

6.4 Timely AVR in Asymptomatic AS

AS is one of the most common valvular heart conditions in Western countries, and its prevalence has increased dramatically over the past two decades due to population aging [146, 147]. Untreated severe AS is associated with increased mortality and lower quality of life. For more than 50 years, clinical practice has been shaped by the seminal work of Ross and Braunwald, which first described the natural history of the disease and linked symptoms such as chest pain, shortness of breath, and exertional syncope to poor outcomes [148]. The perspective introduced the concept of a prolonged asymptomatic phase prior to symptom onset, initially considered benign.

Current ACC/AHA guidelines recommend AVR when symptoms appear or left ventricular dysfunction occurs [73]. The current approach for the majority of asymptomatic patients with severe AS is a strategy of 'watchful waiting' (also known as clinical surveillance). However, studies have shown that maladaptive left ventricular remodeling, fibrosis, and diastolic dysfunction develop well before patients present symptoms and may be irreversible even after undergoing AVR [149-153]. Assessing symptoms is often challenging, particularly in older adults with frailty, limited mobility, or multiple comorbidities, and symptoms are frequently underreported by patients. Furthermore, although it is often assumed that symptoms in AS develop gradually, recent evidence demonstrates that up to 30–40% of patients with initially asymptomatic severe AS experience a sudden onset of severe symptoms, newly referred to as 'acute valve syndrome' [29, 30].

The 2025 ESC/EACTS Guidelines on Valvular Heart Disease (VHD) mark a significant shift towards a more proactive approach to the management of severe AS, recommending timely intervention with either TAVR or SAVR for a broader population of asymptomatic patients [34]. This paradigm shift towards timely AVR in asymptomatic severe AS is further supported by the evidence base comparing prompt AVR with clinical surveillance, as well as the recent data highlighting both the clinical and economic value of timely treatment, summarized below.

Synthesis of Evidence: Timely AVR versus Clinical Surveillance

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 clinical surveillance in asymptomatic patients with 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 [154, 155]. 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 1**).

Appendix Table 1. PICOS framework (Updated)

	Inclusion Criteria
Population	Patients with asymptomatic severe or very severe AS
Intervention	AVR: either surgical AVR (SAVR) or transcatheter AVR (TAVR)
Comparator	Clinical surveillance
Outcomes	• **Clinical outcomes:** all-cause mortality, cardiovascular mortality, heart failure hospitalization, unplanned cardiovascular or heart failure hospitalizations, stroke, sudden cardiac death (SCD), and myocardial infarction (MI) • **QoL outcomes:** Kansas City Cardiomyopathy questionnaire (KCCQ)
Study Design	• RCTs • Observational studies (prospective and retrospective)

	Inclusion Criteria
	• Post-hoc analyses

AS: aortic stenosis; AVR: aortic valve replacement; QoL: quality of life; RCTs: randomized clinical trials

PubMed, EMBASE, and clinicialtrials.gov were systematically searched using pre-specified criteria from their inception to November 11, 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 2** below.

Appendix Table 2. Search Strategy (Updated)

Database	Time Period	Raw text string	MeSH terms
PubMed	Inception to November 11, 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

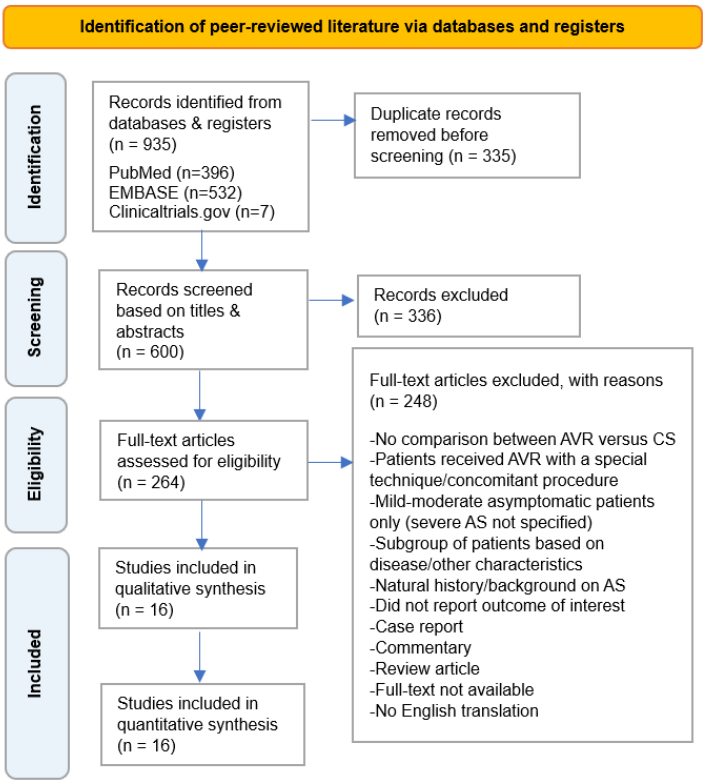
demographics, interventions, and outcomes of interest. Study quality was assessed using the Cochrane Risk of Bias 2 (RoB2) tool and the Newcastle-Ottawa Scale (NOS) for randomized and non-randomized studies, respectively [156, 157].

The search identified a total of 928 records from PubMed and Embase and seven additional records from Clinicaltrials.gov. Thereafter, 336 duplicates and 248 additional irrelevant titles and abstracts were excluded. The remaining 264 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 1**) [35-38, 83, 84, 86-93, 158, 159].

In addition to the 16 studies comparing AVR to clinical surveillance noted above, two studies that did not meet full criteria for inclusion in the review were evaluated separately for the purpose of summarizing quality of life (QoL) data (in addition to EARLY TAVR): 1) one study comparing TAVR in minimally symptomatic versus moderate/severe symptomatic patients with severe AS; 2) another study comparing timely SAVR versus TAVR in low-risk asymptomatic patients with severe AS [35, 160, 161]. 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 ($\geq$ 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 clinical surveillance. 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 weighted age of patients 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) [35-38, 83, 84, 86-93, 158, 159].

Appendix Figure 1. PRISMA Flow Diagram



Assessment of Study Quality/Risk of Bias

The quality assessment for the 4 RCTs and post-hoc analysis utilized the RoB 2 Tool from the Cochrane Handbook for RCTs [154, 156]. The overall RoB was assessed as 'low' for the majority of studies. Risk of bias was rated as 'unclear/some concerns' for 2 studies (**Appendix Table 3**). The observed factors which had the greatest impact on these assessments included:

- Post-randomization cross-over (addressed by intention-to-treat)
- Post-hoc analysis of asymptomatic subgroup not pre-specified [161]
- Protocol amendment modifying inclusion criteria [161]
- Imbalanced enrollment by sites, with 75% of patients enrolled at one site [37]

Appendix Table 3. Risk of Bias Assessment, Cochrane Risk-of-Bias Tool for RCTs V2*

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†	+	+	+	+	!	!

*Judgements of risk for each domain include low risk of bias (+), some concerns (!), or high risk of bias (-); †Study included only in QoL evaluation

Similarly, RoB was assessed for the 12 observational studies (as well as Huded et al.) using the NOS for observational studies [157]. 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 et al.). This study had a low rating for comparability because very little detail was provided for the baseline characteristics of the AVR and clinical surveillance groups (**Appendix Table 4**).

Appendix Table 4: 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**
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 RCTs

Four published RCTs provide the strongest evidence to date supporting timely AVR in the management of asymptomatic patients with severe AS **(Appendix Table 5**) [35-38]. The trials slightly differ in the enrolled populations, conversion rates, timing of AVR in the clinical surveillance arms, and timeliness of AVR within each treatment group. RECOVERY enrolled younger patients with very severe AS. AVATAR also enrolled younger patients with very severe AS, and a negative exercise test was mandatory for inclusion in the trial. Although the number of patients and clinical events was relatively small, both RECOVERY and AVATAR demonstrated a survival benefit with timely intervention (SAVR).

EARLY TAVR was the largest randomized trial (901 patients) to test a strategy of timely AVR with TAVR in asymptomatic patients with severe AS. The trial demonstrated a 50% reduction (45.3% vs. 26.8%, HR: 0.50; 95% CI: 0.40-0.63; $p<0.001$) of the primary composite of death, stroke, or heart failure hospitalization with timely TAVR compared to clinical surveillance. EVOLVED evaluated AVR (either TAVR or SAVR) against clinical surveillance in asymptomatic patients with severe AS and myocardial fibrosis. Although EVOLVED did not demonstrate a reduction in its primary endpoint, the trial was underpowered and had a median 5-month delay between randomization and AVR in the timely AVR group. Notably, 9 of 20 (45%) primary endpoint events in this group occurred before AVR was performed. The trial did however show a significant reduction in unplanned AS-related hospitalizations, as well as improvements in symptom status at one year. Both EARLY TAVR and EVOLVED enrolled older patients with multiple comorbid conditions.

From these trials, the most evident benefit of timely intervention in asymptomatic patients with severe AS is an approximately 70% reduction in the risk of heart failure hospitalizations, along with a decreased risk of stroke based on pooled analyses [39].

Appendix Table 5: Summary of RCTs [35-38]

First Author (Year), Trial, 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 & CANADA (MC); 2017-2021	901	TAVR: 455	446	75.8	3.7 (3.0,5.1) years	3.8 (2.8, 4.8) years	14 (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
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	KOREA (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; CMR: cardiac magnetic resonance; CS: clinical surveillance; IQR: interquartile range; LGE: late gadolinium enhancement; LVEF: left ventricular ejection fraction; MAG: mean aortic valve gradient; MC: multicenter; NCT: national clinical trial; Pmean: mean transaortic valvular gradient; RCT(s): randomized clinical trial(s); SAVR: surgical aortic valve replacement; STS: Society of Thoracic Surgeons; TAVR: transcatheter aortic valve replacement; US: United States; Vmax: maximal systolic aortic flow velocity

Overview of Observational Studies

Key study characteristics of the 12 observational studies included in the review are summarized in **Appendix Table 6** below.

Appendix Table 6: Summary of Observational Studies [83, 84, 86-93, 158, 159]

First Author; (Year); Country		Study Period	Number of Patients			Mean Age	Follow up (months)	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

First Author; (Year); Country		Study Period	Number of Patients			Mean Age	Follow up (months)	Time to AVR	LVEF Criteria	ST (% pts)	AS Severity
			Total	AVR	CS						
											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
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; 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

Outcomes

All 16 studies assessed all-cause mortality, 7 studies assessed cardiovascular mortality, 5 studies assessed heart failure hospitalizations, 6 studies assessed unplanned cardiovascular or heart failure hospitalizations, 6 studies assessed stroke, 5 studies assessed SCD, 6 studies assessed MI, 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 clinical surveillance across the majority of studies (14 of 16) (**Appendix Table 7**). Two RCTs demonstrated lower rates of all-cause mortality with SAVR, whereas the other two RCTs found no mortality differences. Généreux et al. suggest that these discrepancies are most likely explained by differences in outcomes among the clinical surveillance groups and by

the short 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. Notably, the time from AS symptom onset to AVR varied substantially across trials, particularly between those using SAVR versus TAVR as the mode of intervention [39]. Across eleven observational studies comparing AVR with clinical surveillance, most reported reductions in all-cause mortality associated with AVR: 6 demonstrated a statistically significant reduction, 1 showed a nonsignificant reduction, and 3 reported mortality reductions without statistical comparisons. One additional study observed a numerical increase in all-cause mortality with AVR compared with surveillance, though no statistical comparison was provided.

Appendix Table 7: All-Cause Mortality

	First Author (Year)	Event Counts, AVR vs CS
RCTs	Genereux (2024) – EARLY TAVR	38/455 vs 41/446
	Loganath (2024) – EVOLVED	16/113 vs 14/111
	Banovic (2024) – AVATAR	11/78 vs 27/79*
	Kang (2020) – RECOVERY	5/73 vs 15/72*
Observational Studies	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*
	Heuvelman (2012)	3/22 vs 2/37
	Le Tourneau (2010)	31/160 vs 181/514
	Pai (2006)	9/99 vs 129/239*

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

Primary Endpoints

Three of out 4 RCTs achieved their primary endpoints (**Appendix Table 8**).

Appendix Table 8: Primary Endpoints

First Author (Year) Trial	Primary Endpoint	Events (AVR vs CS)	Key Findings
Genereux (2024) **EARLY TAVR**	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) **EVOLVED**	Composite of all-cause mortality or unplanned AS-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) **AVATAR**	All-cause mortality or major adverse cardiovascular events	18/78 vs 37/79	**· Met primary endpoint (superiority)**

First Author (Year) Trial	Primary Endpoint	Events (AVR vs CS)	Key Findings
	(MACEs) composed of acute myocardial infarction, stroke, and unplanned heart failure hospitalization needing intravenous treatment within 5-year follow-up		· 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) **RECOVERY**	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; CI: confidence interval; CS: clinical surveillance; HR: hazard ratio; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement

Cardiovascular Mortality

AVR was associated with a lower rate of cardiovascular mortality when compared to clinical surveillance across the majority of studies (6 of 7) (**Appendix Table 9**).

Appendix Table 9: Cardiovascular Mortality

	First Author (Year)	Event Counts, AVR vs CS
RCTs	Genereux (2024) – EARLY TAVR	18/455 vs 23/446
	Loganath (2024) – EVOLVED	10/113 vs 8/111
	Banovic (2024) – AVATAR	8/78 vs 17/79
	Kang (2020) – RECOVERY	1/73 vs 11/72
Observational Studies	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

Heart Failure Hospitalizations

AVR was associated with a significantly lower rate of heart failure hospitalization events when compared to clinical surveillance across the majority of studies (3 of 5) (**Appendix Table 10**).

Appendix Table 10: Heart Failure Hospitalizations

	First Author (Year)	Event Counts, AVR vs CS
RCTs	Genereux (2024) – EARLY TAVR	15/455 vs 44/446*
	Banovic (2024) – AVATAR	3/78 vs 13/79*
	Kang (2020) – RECOVERY	0/73 vs 8/72
Observational Studies	Kim (2019)	2/221 vs 3/247
	Taniguchi (2015)	10/291 vs 50/291*

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

Unplanned Cardiovascular or Heart Failure Hospitalizations

AVR was associated with a significantly lower rate of unplanned cardiovascular or heart failure hospitalization events when compared to clinical surveillance across the majority of studies (4 of 6) (**Appendix Table 11**).

- Unplanned cardiovascular hospitalizations 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 clinical surveillance arm, including conversion to AVR, and any aortic valve reintervention within 6 months of the procedure in the TAVR arm.
- Unplanned AS hospitalizations 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 11: Unplanned Cardiovascular or Heart Failure Hospitalizations

	First Author (Year)	Event Counts, AVR vs CS
RCTs	Genereux (2024) – EARLY TAVR	95/455 vs 186/446*
	Loganath (2024) – EVOLVED	7/113 vs 19/111*
	Banovic (2024) – AVATAR	3/78 vs 13/79*
	Kang (2020) – RECOVERY	0/73 vs 8/72
Observational Studies	Kim (2019)	2/221 vs 3/247
	Taniguchi (2015)	10/291 vs 50/291*

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

Stroke

AVR was associated with a lower rate of stroke events when compared to clinical surveillance across 3 of 6 studies, with 2 studies showing no differences (**Appendix Table 12**).

Appendix Table 12: Stroke

	First Author (Year)	Event Counts, AVR vs CS
RCTs	Genereux (2024) – EARLY TAVR	19/455 vs 30/446
	Loganath (2024) – EVOLVED	8/113 vs 14/111
	Banovic (2024) – AVATAR	4/78 vs 4/79
	Kang (2020) – RECOVERY	1/73 vs 3/72
Observational Studies	Kim (2019)	4/221 vs 2/247
	Taniguchi (2015)	23/291 vs 18/291

AVR: aortic valve replacement; CS: clinical surveillance; RCTs: randomized clinical trials

Sudden Cardiac Death

Across most studies (4 of 5), AVR was associated with lower rates of SCD compared with clinical surveillance. (**Appendix Table 13**).

Appendix Table 13: Sudden Cardiac Death

	First Author (Year)	Event Counts, AVR vs CS
RCTs	Genereux (2024) – EARLY TAVR	5/455 vs 4/446
	Banovic (2024) – AVATAR	2/78 vs 9/79
	Kang (2020) – RECOVERY	0/73 vs 3/72
Observational Studies	Kang (2010)	0/102 vs 9/95
	Taniguchi (2015)	8/291 vs 18/291

AVR: aortic valve replacement; CS: clinical surveillance; RCTs: randomized clinical trials

Myocardial Infarction

Across most studies (4 of 6), AVR was associated with lower rates of MI compared with clinical surveillance. (**Appendix Table 14**).

Appendix Table 14: Myocardial Infarction

	First Author (Year)	Event Counts, AVR vs CS
RCTs	Genereux (2024) – EARLY TAVR	2/455 vs 1/446
	Loganath (2024) – EVOLVED	0/113 vs 0/111
	Banovic (2024) – AVATAR	1/78 vs 6/79
	Kang (2020) – RECOVERY	0/73 vs 1/72
Observational Studies	Kim (2019)	2/221 vs 4/247
	Taniguchi (2015)	3/291 vs 6/291

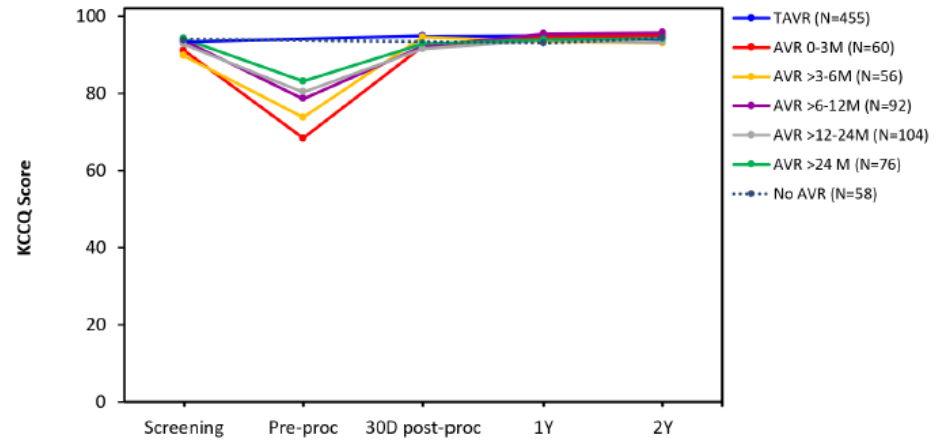
AVR: aortic valve replacement; CS: clinical surveillance; RCTs: randomized clinical trials

Quality of Life

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 clinical surveillance received AVR, with more than one third of these patients assigned to clinical surveillance presenting with advanced signs and symptoms of aortic-valve disease. Patients receiving clinical surveillance 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 clinical surveillance received AVR. Clinical surveillance 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 2**) [35].

Appendix Figure 2: KCCQ Scores by Treatment and Timing of Intervention

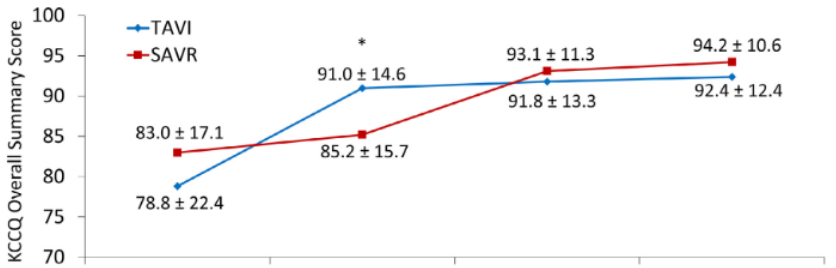


No. of Pts:					
TAVR	441	-	437	422	395
AVR 0-3M	60	56	58	54	50
AVR >3-6M	56	54	55	52	46
AVR >6-12M	91	89	90	85	79
AVR >12-24M	102	94	95	88	71
AVR >24M	76	74	73	55	29
No AVR	55	-	-	46	36

Note: 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 clinical surveillance 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 clinical surveillance patients who did not convert to AVR. The 'no AVR' group did not have a pre-procedure or 30-day post-procedure visit.

In addition to the EARLY TAVR trial, two studies examined patient-reported QoL outcomes following AVR via KCCQ-OS. Merhi et al. reported that at 30 days, patients treated with TAVR demonstrated significantly greater improvement from baseline compared with those treated with SAVR (**Appendix Figure 3**). These differences converged at 6- and 12-month follow-up, suggesting that intervention with both TAVR and SAVR improves patients' long-term QoL, with TAVR offering a more rapid recovery, likely attributable to the less invasive nature of the procedure compared to SAVR [161].

Appendix Figure 3: Summary of QoL Change from Baseline to 12 months



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 TAVR and SAVR asymptomatic patients; KCCQ overall summary (OS) score for asymptomatic patients. Mean KCCQ-OS score for TAVR (blue lines) asymptomatic patients and SAVR (red lines) asymptomatic patients.

Huded et al. 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-OS score ≥75. Clinical and health status outcomes of TAVR in patients with severe AS 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]) [160].

Mortality While Waiting for AVR

Across 13 studies that specifically report 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%) [83-85, 92, 158, 161-168].

The evidence summarized above is based on clinical and QoL data from 4 RCTs and 12 observational studies, including 5,346 asymptomatic patients with severe AS (LVEF ≥50%), 2,406 patients who underwent AVR and 2,940 patients who were managed with a strategy of clinical surveillance, from a diverse geographic and representative age population of asymptomatic patients with severe AS. 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 patients with severe AS, including:

- Reductions in rates of **all-cause mortality** (14 of 16 studies)
- Significant reductions of the **primary composite endpoint** (3 of 4 studies)
- Reductions in rates of **cardiovascular mortality** (6 of 7 studies)

- Significant reductions in rates of **heart failure hospitalizations** (3 of 5 studies)
- Significant reductions in rates of **unplanned cardiovascular or heart failure hospitalizations** (4 of 6 studies)
- Reductions in rates of **stroke** (3 of 6 studies)
- Reductions in rates of **SCD** (4 of 5 studies)
- Reductions in rates of **MI** (4 of 6 studies)
- Significant improvements in patient-reported **QoL** (3 of 3 studies) and a **more rapid improvement** observed with patients who underwent AVR with TAVR (2 of 3 studies).

Taken together, the observational studies of AVR summarized above reinforce the favorable outcomes demonstrated in RCTs such as EARLY TAVR. These findings reflect the ongoing evolution of clinical practice and improvements in patient outcomes since the introduction of TAVR. Recent trial data further support the clinical and QoL benefits of TAVR in asymptomatic patients with severe AS, while also reducing the surgical morbidity associated with SAVR.

Recently Released Evidence: The Value of Timely AVR

A growing body of evidence suggests that delaying AVR until symptom onset carries significant, often underestimated risks, especially for patients lacking routine follow-up. Studies show that waiting until advanced symptoms develop can lead to irreversible cardiac decompensation, even after successful valve replacement [149-153].

Treating AS only after it has progressed to an advanced stage places a substantial economic burden on the health care system, driven by greater procedural complexity, longer hospitalizations, and increased post-operative resource needs. The evidence summarized below illustrates the negative clinical and economic consequences of delayed AVR, assessing patients by both clinical presentation and the degree of structural cardiac damage. Taken together, these data strongly support a shift toward earlier intervention, which is consistently associated with improved patient outcomes and more efficient health care resource utilization.

First Author (Year); Patient Population	**Study Period; Interventions**	**Key Findings**
Généreux (2025) [29] egnite Database (29 hospitals) N = 17,838 patients: 2,504 (14.0%) were asymptomatic (had stable valve syndrome (SVS)), 6,116 (34.3%) had progressive valve syndrome (PVS), and 9,218 (51.7%) presented with acute valve syndrome (AVS) prior to undergoing AVR	2018-2020 Patients who underwent AVR (TAVR/SAVR) for AS who were asymptomatic, had PVS, or presented with AVS	Patients presenting with acute and advanced symptoms (AVS) had a 3-fold increase in the estimated rate of mortality and a 4-fold increase in the estimated rate of heart failure hospitalizations at 2 years after AVR compared with asymptomatic/SVS patients. • 2-year mortality rates post AVR: asymptomatic/SVS= 5.8% (4.6%-7.0%), PVS=7.6% (6.7%-8.4%), and AVS=17.5% (16.5%-18.5%) • 2-year heart failure hospitalization rates post AVR: asymptomatic/SVS=11.1% (9.5%-12.6%), PVS=19.0% (17.8%-20.2%), and AVS=41.5% (40.2%-42.8%)

First Author (Year); Patient Population	**Study Period; Interventions**	**Key Findings**
Généreux (2025) [31] Optum Database N = 24,075 patients: 270 (1.1%) were asymptomatic/had SVS, 10,195 (42.3%) had PVS, and 13,610 (56.5%) presented with AVS during the 1 year before AVR	2017-2023 Patients who underwent AVR (TAVR/SAVR) for AS who were asymptomatic, had PVS, or presented with AVS	• Patients presenting with AVS had a 3-fold increase in 1-year mortality (aHR, 2.93 [95% CI, 1.1–7.8]; p=0.03) and 4-fold increase in heart failure hospitalizations (aHR, 4.15 [95% CI, 1.6–11.1]; p<0.01) compared to those treated while asymptomatic. • Total healthcare costs in the year following AVR were significantly higher in both the PVS (difference $27,410 [$13,507–$41,314]) and AVS groups (difference $36,267 [$22,302–$50,232]) compared with asymptomatic/SVS groups.
Généreux (2025)[169] Delayed TAVR n = 388: 227 (58.5%) presented with PVS,152 (39.2%) with AVS, 9 (2.3%) were asymptomatic Early TAVR n = 444	2017-2021 Sub-analysis of patients who underwent AVR in EARLY TAVR RCT	• Patients undergoing AVR with AVS had the highest rate of the composite outcome of death, stroke, or heart failure hospitalization at 2 years, followed by those undergoing AVR with PVS and those undergoing AVR while asymptomatic (14.9% vs. 8.2% vs. 6.8%, p=0.008). • Patients who presented with AVS at the time of delayed AVR experienced a 2-fold higher risk of adverse outcomes, mainly driven by stroke (HR: 2.92, 95% CI 1.26–6.76, p=0.01).
Généreux (2025) [[27, 29, 83, 84, 86-93] Optum Database N = 24,644 patients across 5 stages of cardiac damage: 8.1% in stage 0, 17.1% in stage 1, 37.3% in stage 2, 36.2% in stage 3, and 1.4% in stage 4 in the year prior to undergoing AVR	2016-2022 Patients who underwent AVR (TAVR/SAVR) for AS, by 5 stages of cardiac damage	The extent of cardiac damage was associated with increased mortality, healthcare resource utilization, and healthcare costs in the year following AVR. • Average LOS of the AVR hospitalization was 7.2 days for stage 0 and showed significant increases of 1.0, 1.1, and 2.4 days for cardiac damage stages 2, 3, and 4, respectively (all p<0.01) • Number of heart failure hospitalizations per patient was 0.12 for stage 0 and increased by 0.07, 0.18, 0.20, and 0.25 for stages 1, 2, 3, and 4, respectively (all p<0.01) (2x greater for stage 4 vs. stage 0) • Total costs increased by $2,746 in stage 1, $19,511 in stage 2, $19,198 in stage 3, and $35,663 in stage 4, compared with stage 0; p<0.01)
Vemulapalli (2025) [32] Optum Database N = 4,069 patients: 2,051 (50.4%) received timely TAVR, 2,018 (49.6%) received delayed TAVR (>90 days post-diagnosis or urgent/emergent procedure)	2019-2023 Patients who underwent TAVR for AS	• Over 3 years following AVR, delayed TAVR was associated with a 50% higher mortality risk (19.5 vs. 13.7%; HR: 1.50; p< 0.01) and 59% higher risk of heart failure hospitalization (38.4 vs. 26.5%; HR: 1.59; p< 0.01) compared to timely intervention. • Delayed patients also incurred $36,740 higher health care costs over 3 years ($182,470 vs. $145,730; p<0.01), largely driven by increased heart failure hospitalizations ($22,127 difference).

First Author (Year); Patient Population	**Study Period; Interventions**	**Key Findings**
Ebinger (2025) [33] Medicare Limited Dataset (5% random sample of Medicare FFS claims) N= 15,305 patients: 2,407 (16%) had their procedure performed on an urgent/emergent basis, 12,898 (84%) underwent elective AVR	2017-2022 Patients who underwent AVR (TAVR/SAVR) for AS	• Delayed care contributed to increased urgent/emergent admissions, which were associated with a 2.8 times higher risk of post-AVR mortality (OR: 2.83; 95% CI: 2.21-3.61) and a 2.4 times higher risk of ICU admission (OR: 2.38; 95% CI:1.89-3.00) compared to elective, planned admissions. • Urgent/emergent AVR status was associated with an on average 8.42-day longer hospital LOS (95% CI: 8.12–8.73 days; p<0.0001) and $21,369 higher mean index hospitalization costs per patient (95% CI: $20,170–$22,567; p<0.0001) than elective admissions.
Stinis (2025) [6] Optum Database N = 14,225 patients: 5,993 (42%) underwent TAVR, 8,232 (58%) underwent SAVR	2016-2023 Patients who underwent AVR (TAVR/SAVR) within 2 years of AS diagnosis	• TAVR undergoing TAVR faced an average treatment delay of 59 days longer than those undergoing SAVR (157 vs. 98 days; RR = 1.77, 1.67–1.87). • Delay in time to AVR was largely driven by more extensive pre-procedural requirements for TAVR-83% of the delay in TAVR was explained by the higher frequency of cardiac specialist visits and imaging visits (2x more for TAVR vs. SAVR).

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