July 15, 2026
Submitted electronically to: CAGInquiries@cms.hhs.gov
Centers for Medicare & Medicaid Services (CMS)
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Edwards Lifesciences commends CMS for its proposed modernization of the National Coverage Determination (NCD) for Transcatheter Aortic Valve Replacement (TAVR). The draft policy reflects careful consideration of contemporary evidence, the evolving needs of Medicare beneficiaries with aortic stenosis (AS), and stakeholder feedback. Edwards supports CMS' efforts to modernize this policy that advances timely access for Medicare beneficiaries to appropriate treatment while preserving the quality safeguards for patients that have enabled TAVR to become one of the most rigorously studied and successful innovations in cardiovascular care.

Edwards urges CMS to finalize many of the proposed policy updates and also respectfully offers several recommendations, as summarized below. Detailed rationale, supporting evidence, and specific policy recommendations are provided in our full comments.

- **Finalize coverage of TAVR for symptomatic severe AS without CED**
- **Finalize coverage of TAVR for asymptomatic severe AS under § 1862(a)(1)(A)**
- **Finalize the Heart Team as the foundation of high-quality aortic stenosis care, while allowing flexible patient evaluation and the ability to determine the TAVR operator approach based on patient needs, preserving joint participation when appropriate**
- **Finalize removal of hospital volume thresholds while maintaining facility infrastructure, physician proficiency, and continuous quality improvement requirements**
- **Clarify that emergency TAVR is exempt from pre-procedure evaluation requirements that may be intended for elective procedures**
- **Cover moderate AS under § 1862(a)(1)(E)**

The success of TAVR in the United States has been a shared achievement of many acting in the best interest of patients – reflecting contributions of CMS, FDA, specialty societies, the multidisciplinary Heart Team, hospitals, industry partners, and patients themselves. The Heart Team, inclusive of both cardiac surgery and interventional cardiology, has been foundational to this progress. The proposed modernization is an opportunity to build on this shared foundation by preserving the Heart Team's central role in multidisciplinary shared decision-making while allowing programs the operational flexibility to determine the most appropriate evaluation pathway, procedural staffing model, and care-delivery workflow based on patient needs. In doing so, CMS can preserve the quality infrastructure these stakeholders jointly established while helping more Medicare beneficiaries receive timely, appropriate care.

Edwards appreciates CMS' leadership and its continued commitment to evidence-based, patient-centered coverage policy. If the experience of the past 15 years is a guide, a thoughtfully modernized NCD can preserve accountability and quality while reducing unnecessary barriers to care – allowing more patients with AS to benefit from timely treatment in the care of a Heart Team. Edwards looks forward to continuing this shared progress and thanks you for your consideration of our comments.

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Edwards' Comments on CMS' Proposed TAVR NCD Policy Updates

Introduction

Edwards commends CMS for proposing a meaningful modernization of the TAVR NCD that affirms the Heart Team while reducing barriers to timely care. If finalized with additional targeted refinements, this policy would advance coverage equipoise at the disease level by harmonizing Medicare coverage requirements for TAVR with other established AS therapies, including surgical aortic valve replacement (SAVR) and balloon aortic valvuloplasty (BAV), while maintaining appropriate safeguards for quality, patient selection, and outcomes monitoring.

Edwards believes CMS should finalize language in the draft NCD that continues to protect the core Heart Team principles of multidisciplinary review, shared decision-making, and patient-centered treatment selection, while allowing local Heart Teams – inclusive of cardiac surgeons and interventional cardiologists – to determine the most appropriate evaluation pathway, procedural staffing model, and care-delivery workflow based on patient needs.

The proposed updates preserve the essential safeguards that have supported high-quality TAVR care – including multidisciplinary Heart Team oversight, appropriate facility capabilities, physician proficiency, patient-centered evaluation, outcomes monitoring, and continuous quality improvement – while allowing local Heart Teams to operationalize those safeguards in a manner that reflects patient needs, program capabilities, and contemporary clinical practice. This approach can reduce avoidable delays, address workforce and geographic barriers, and support timely, high-quality treatment for Medicare beneficiaries with AS.

As CMS finalizes the TAVR NCD, procedural quality safeguards should be preserved, but Edwards also encourages CMS to balance these against the equally important need for timely, practical, and reliable access to care.

In contemporary AS care, delay is not simply an access issue – it is a quality issue. Coverage requirements designed to protect patients should not inadvertently place patients at risk by delaying lifesaving treatment. Empirical evidence now shows that patients undergoing TAVR wait substantially longer for treatment than patients undergoing SAVR for the same disease. In a real-world analysis of more than 14,000 AVR patients with clinically significant AS, TAVR patients waited an average of 157 days from diagnosis to treatment compared with 98 days for SAVR patients; after adjustment, the TAVR pathway remained 65 days longer.[1]

Importantly, this delay appears closely linked to potentially modifiable pre-procedural requirements. TAVR patients had nearly twice as many cardiac specialist encounters and imaging events as SAVR patients, and after accounting for those encounters, the adjusted TAVR-SAVR treatment gap narrowed from 65 days to 11 days.[1] These findings suggest that well-intended process requirements, including multiple specialist evaluations and sequential testing, may contribute to treatment delays in a capacity-constrained health care system.

These delays are not benign. Among patients recommended for AVR, mortality while waiting was 3.7% at 1 month and 11.6% at 6 months, supporting the view that patients with symptomatic AS should be treated on a semi-urgent rather than purely elective basis.[2] In addition, delayed TAVR beyond 90 days has been associated with substantial downstream consequences, including higher 3-year mortality, more heart failure hospitalizations, and $36,740 in excess health care costs.[3]

Delayed or missed treatment also leaves patients vulnerable to stroke or other preventable cardiovascular events. Patients treated only after developing acute or advanced valve syndrome experience three times higher mortality and four times more heart-failure hospitalizations compared with patients treated earlier while stable.[3] The burden of delay also falls unevenly across the Medicare population. Geographic access gaps, "no-TAVR" zones, and socioeconomic disadvantage compound barriers for rural and underserved beneficiaries, increasing the risk that patients most vulnerable to disease progression are also the least likely to receive timely treatment.[4,5]

The final TAVR NCD should evaluate coverage requirements not only by whether they maintain procedural safety, but also by whether they unintentionally delay or limit access to lifesaving care.

Coverage of TAVR for Symptomatic Severe AS Without CED

Evolution of CED Policy

Edwards applauds CMS for proposing to end Coverage with Evidence Development (CED) for TAVR in patients with symptomatic severe aortic stenosis (AS), a meaningful step toward recognizing TAVR as a well-established, evidence-supported treatment for AS. This proposed update represents an important milestone in the progression of the TAVR NCD and demonstrates the success of CMS' evidence-based coverage framework. Through the original CED policy, CMS created a pathway that enabled Medicare beneficiaries to access a transformative therapy while simultaneously supporting the development of a national evidence base, real-world outcomes infrastructure, and quality improvement framework for TAVR. CMS' proposal reflects the successful execution of its CED principles, demonstrating how an evidence generation framework can support patient access while resolving evidence gaps.

CMS' leadership in establishing the TAVR CED program has had a profound impact on AS patients. At the time TAVR was first covered, it was an emerging therapy with unanswered questions about patient selection, procedural outcomes, durability, long-term survival, and program requirements. CMS' decision to pair coverage with structured evidence development helped ensure that Medicare beneficiaries could benefit from innovation while the field continued to generate the data needed to guide high-quality care. As a result, more than half a million Americans have received lifesaving TAVR treatment under a national framework that advanced access, evidence generation, and procedural quality.

TAVR Evidence

More than a decade later, the TAVR CED program should be recognized as a major policy achievement. The questions that justified CED for TAVR have been substantially answered through randomized controlled trials, long-term follow-up, national registry analyses, real-world clinical experience, and continued evidence submitted to CMS through Edwards' prior letters, communications, and the public comment process (**Appendix C** & **Appendix D**). The depth and breadth of this evidence base is reflected in more than 12,000 peer-reviewed publications on TAVR, underscoring the maturity of the science supporting its use in patients with AS.

Recent evidence further strengthens the evidence base for TAVR with SAPIEN 3 valves, demonstrating excellent long-term durability and clinical outcomes in intermediate and low risk patients and directly addressing CED requirements related to valve durability, long-term effectiveness, and adverse events. (**Appendix A, Table 1** [6,7,8,9,10]) Edwards agrees with CMS' assessment that TAVR has a "convincing, meaningful clinical benefit," and supports the draft policy's conclusion that the original evidence generation objectives have been achieved and that TAVR now meets the standard for Medicare coverage as reasonable and necessary.

Recommendations: **Edwards urges CMS to finalize its proposal to end CED for TAVR in symptomatic severe AS and to recognize TAVR as reasonable and necessary for Medicare beneficiaries.**

Expanded Coverage of TAVR for Asymptomatic Severe AS

Edwards commends CMS for expanding coverage of TAVR for patients with asymptomatic AS, a population for whom the clinical evidence has matured considerably and for whom delays in intervention may result in irreversible cardiac damage and adverse clinical outcomes.[11,12,13,14,15]

While Edwards commends CMS for proposing coverage expansion, the totality of evidence justifies coverage under § 1862(a)(1)(A) as reasonable and necessary for patients with FDA-approved indications for TAVR in asymptomatic severe AS.

The evidence base supporting earlier intervention in asymptomatic severe AS has expanded substantially over the past several years, with randomized data,[16,17,18,19] multiple contemporary meta-analyses,[20,21,22,23,24,25,26,27,28,29,30,31] and a robust body of real-world observational data,[32,33,34,35,36,37,38,39,40,41,42,43,44,45,46] each demonstrating that timely intervention with TAVR reduces clinically meaningful events compared with surveillance. Together, this body of evidence establishes a consistent, reproducible signal favoring timely intervention across trial and real-world settings, patient phenotypes, and analytic methods.

Risks of Watchful Waiting for Asymptomatic AS Patients

The EARLY TAVR trial, now reinforced by five-year follow-up results presented at New York Valves 2026, provides the highest level of evidence to date in this population. Among 901 patients with asymptomatic severe AS, early TAVR significantly reduced the composite endpoint of death, stroke, or unplanned cardiovascular hospitalization compared with guideline-recommended surveillance (median follow-up, 3.8 years: 26.8% vs 45.3%; HR: 0.50; 95% CI: 0.40–0.63; p<0.001; median follow-up, 5.0 years: 15.2% vs 24.2%; HR: 0.58; 95% CI: 0.43–0.78; p<0.001).[16,47] Kaplan-Meier estimates showed that 95.2% of patients assigned to surveillance had converted to AVR by five years, and 40% did so with advanced symptoms.[16,47] This high crossover rate reflects the natural progression of severe AS rather than a limitation of the trial. Even after most patients in the surveillance group eventually received treatment, those treated with TAVR earlier had better outcomes, including reduced mortality, stroke and heart failure hospitalizations, suggesting that waiting for treatment may not fully offset the consequences of disease progression during watchful waiting.[47,48]

These findings likely understate the risks of watchful waiting in routine clinical practice, where the intensity and timeliness of surveillance achieved in EARLY TAVR is unlikely to be replicated. Asymptomatic patients in EARLY TAVR underwent rigorous, protocol-mandated follow-up, including frequent clinical assessments, serial echocardiography, and predefined triggers for intervention, which substantially exceeds what is typical in real-world care. All patients had also completed a comprehensive pre-TAVR evaluation prior to randomization, enabling a short window from symptom onset to conversion to AVR in the surveillance arm (32 days).[16] By contrast, a recent AHA Target: AS registry analysis found that approximately 40% of patients with echo-confirmed severe AS did not receive an annual surveillance echocardiogram in 2024.[49]

TAVR Evidence for Asymptomatic AS

The evidence supporting coverage for TAVR in asymptomatic severe AS is comprehensive, consistent, and multidimensional. A rapidly expanding body of real-world data confirms that the treatment benefit of AVR observed in randomized trials is reproducible in broader, contemporary populations reflective of the Medicare beneficiary experience. These analyses consistently show that surveillance patients remain

vulnerable to adverse events, delayed presentation, and mortality.[32,33,34,35,36] Consistent signals of the association between timely intervention and improved outcomes across randomized and real-world settings also continue to be synthesized in a rapidly expanding body of meta-analytic evidence.[20,21,22,23,24,25,26,27,28,29,30,31,50,51,52,53,54,55,56,57,58,59,60,61,62] Across every category of clinical, mechanistic, real-world, health-economic, and patient-centered evidence, the case for timely intervention is not only well-established but continues to strengthen with each new analysis. [48,63,64,65,66,67,68]

Appendix B, Table 2 [17,20,21,22,23,26,32,33,34,35,36,47,48,63,67,68,69] summarizes key evidence on asymptomatic AS, including studies published since Edwards' January 2026 comment letter.

- **Randomized trial evidence:** Four randomized controlled trials (EARLY TAVR, AVATAR, EVOLVED, RECOVERY) each demonstrate a benefit of early intervention over watchful waiting. EARLY TAVR five-year follow-up shows a sustained and growing treatment effect (HR: 0.58; p<0.001), and 10-year RECOVERY data show a 90% reduction in cardiovascular death with early surgical intervention.[17,18,19,47]
- **Meta-analytic evidence:** Across recent RCT-level meta-analyses of the four trials (1,427 patients), timely intervention has been consistently associated with significant reductions in unplanned cardiovascular or heart failure hospitalizations and stroke, and, in several analyses, all-cause mortality.[26,27,28,29,30,31] Meta-analyses integrating randomized and observational evidence (spanning over 7,000 patients) have reinforced these findings, with directionally aligned and often larger effect estimates.[20,21,22,23,25,52,53,54,55,56,57,58,59,60,61,62]
- **Real-world evidence:** Real-world evidence spanning more than 19,000 patients, including a nationally representative Medicare-linked cohort, document that the treatment benefit of AVR observed in randomized trials is reproducible in contemporary US practice and that surveillance patients remain vulnerable to delayed treatment, adverse events, and mortality.[32-46]
- **Mechanistic sub-studies:** Prespecified EARLY TAVR analyses demonstrate that delayed intervention causes measurable, often only partially reversible, LV deterioration.[63,66]
- **Health economic evidence:** Cost-effectiveness modeling using EARLY TAVR outcomes demonstrates that early TAVR is economically dominant compared with surveillance, yielding both improved outcomes and reduced lifetime costs.[68]
- **Patient-centered evidence:** Emerging qualitative data confirm that early intervention aligns with patient values and preferences, with patients broadly favoring timely intervention when clinical evidence supports it.[69]
- **Guideline recognition:** The 2025 ESC/EACTS Guidelines endorse a more proactive approach and recommend AVR earlier in the treatment pathway for asymptomatic severe AS.[70]
- **Regulatory determination:** FDA premarket approval for TAVR in asymptomatic severe AS provides an independent, rigorous determination of safety and effectiveness for this indication.

The 2019 CED questions established under the current TAVR NCD have been answered: real-world outcomes in the TVT Registry[71,72,73] are clinically similar to those from the pivotal PARTNER trials[74,75,76,77]; long-term outcomes and adverse events are well characterized[78,79,80]; valve durability has been demonstrated through 5-, 7-, and 10-year follow-up[81,82,83]; and a composite performance measure is now available to directly assess TAVR procedural quality.[84] The three newly proposed CED questions in the 2026 draft decision memo, if applied to asymptomatic severe AS, are similarly already substantially addressed by the current evidence base. **Appendix B, Table 3** summarizes the alignment between each CED question and the corresponding body of evidence.[85,86,87,88,89,90,91,92,93,94,95]

Recommendations: **Edwards respectfully urges CMS to finalize coverage for TAVR in asymptomatic severe AS under § 1862(a)(1)(A) as reasonable and necessary, aligned with the FDA-approved indication.**

Heart Team

Edwards supports CMS' recognition that the multidisciplinary Heart Team has been foundational to the therapy and continues to play an essential role in evaluating clinical appropriateness, treatment options, and patient preferences.

Today, Heart Teams foster collaboration between disciplines and are deeply embedded in TAVR program practice.[96] As patient needs evolve, the Heart Team model should also evolve and function as a patient-centered resource that tailors clinical expertise to each patient's needs and helps patients navigate the health care system efficiently to receive timely, appropriate treatment. This patient-centered model is particularly important in the treatment of AS, where fewer than half of indicated patients receive treatment and the consequences of delayed or missed treatment are deadly.[97,98]

The final NCD should continue to maintain the Heart Team's central role in multi-disciplinary shared decision-making while giving programs the operational flexibility needed to determine the most appropriate evaluation pathway, procedural staffing model, and care-delivery workflow based on patient needs. Edwards recognizes the importance of multidisciplinary participation in the Heart Team, including both cardiac surgery and interventional cardiology expertise, as well as other physicians, advanced practice clinicians, nurses, research personnel, and administrators. As programs adapt to the updated TAVR coverage framework, Edwards notes that adequately staffed care coordination roles will be essential to supporting the Heart Team's patient-navigation function and advancing efficient access to TAVR care.

Lastly, Edwards supports CMS' approach recognizing that Heart Team collaboration is important and not limited to TAVR. In contemporary valve care, lifetime management requires multidisciplinary collaboration across treatment modalities—including TAVR, SAVR, and BAV—and in the management of adjacent conditions such as atrial fibrillation, heart failure, pulmonary disease, and other structural heart abnormalities. This mirrors a broader pattern across medicine, where multidisciplinary collaboration has become standard practice not because it is mandated as a condition of coverage but because clinicians recognize its value to patients. Multidisciplinary tumor boards in oncology, multidisciplinary stroke teams, and transplant selection committees are all well-established examples of clinicians voluntarily convening the right expertise to guide complex, high-stakes decisions. The Heart Team reflects this same principle. CMS should therefore affirm the Heart Team as a flexible, patient-centered model that enables the right expertise to be applied where it is most clinically meaningful.

Recommendations: **Edwards urges CMS to finalize the draft policy affirming the Heart Team – inclusive of cardiac surgeons and interventional cardiologists – as a required element of TAVR care, while allowing flexible, modern, and patient-centered mechanisms for Heart Team participation.**

Patient Evaluation

Edwards believes that modernization of the evaluation process proposed by CMS preserves the Heart Team's accountability for patient selection, procedural planning, shared decision-making, and outcomes monitoring, while allowing the team to determine how best to operationalize those responsibilities for each patient. The final NCD should preserve this language to continue to support meaningful

participation by both the cardiac surgeon and interventional cardiologist while avoiding prescriptive process requirements that may inadvertently impede efficient care delivery.

As TAVR decision-making has evolved beyond surgical risk alone to incorporate broader considerations, including anatomical suitability, patient-specific treatment goals, lifetime management strategy, and Heart Team judgment, an experienced cardiac surgeon or interventional cardiologist can evaluate a patient's suitability for TAVR based on training, expertise, and role within the Heart Team. Edwards believes multiple evaluations should remain an option when clinically appropriate, including for patients with complex anatomy, younger age, bicuspid valves, uncertain symptom status, or challenging lifetime-management considerations, but should not be mandated for every patient as a condition of coverage, and supports the language in the draft NCD that strikes this balance.

Edwards believes the proposed evaluation updates, particularly through the removal of the requirement for two separate face-to-face evaluations, can reduce avoidable treatment delays that have meaningful clinical consequences for patients.

Our growing understanding of the prevalence and progression of AS reinforces the need for coverage policies that support timely diagnosis, efficient specialist evaluation, and access to appropriate treatment. The PREVUE-VALVE study provides important new evidence on the burden of AS among Medicare-aged adults. In this nationally representative cohort, the prevalence of moderate or greater AS was 3.1% overall and increased from 1.1% among adults aged 65–69 years to 7.0% among those aged 80–85 years, underscoring the strong relationship between aging and aortic valve disease.[99]

Recommendations: **Edwards supports CMS' proposed revisions to the pre-procedural evaluation requirements permitting asynchronous evaluation and an independent, in-person evaluation by a TAVR Operator.**

Intra-Operative Requirements

Operator Flexibilities

Edwards commends CMS for proposing to empower Heart Teams with the flexibility to determine the most appropriate procedural approach for each patient. The draft policy appropriately recognizes that TAVR procedures vary in complexity and that the Heart Team is best positioned to determine the TAVR operator approach based on patient anatomy, clinical circumstances, institutional capabilities, and procedural considerations, including whether a single- or dual-operator approach best supports patient care. Edwards supports preserving this choice for Heart Teams and institutions, including the option for joint participation when the Heart Team determines that approach is important for patient care.

Experience gained during the Public Health Emergency (PHE), together with broader contemporary and international clinical experience, has demonstrated that strong patient outcomes can be maintained under more flexible care delivery models and that local teams can responsibly match procedural staffing to patient need.[114]

Finalizing the proposed operator flexibilities would also make the TAVR NCD more consistent with CMS' approach across other established cardiovascular NCDs. For example, the NCDs for Transcatheter Tricuspid Valve Replacement (TTVR), Transcatheter Edge-to-Edge Repair (TEER), Left Atrial Appendage Closure (LAAC), Ventricular Assist Device (VAD), and Percutaneous Transluminal Angioplasty (PTA) use a range of approaches to address procedural expertise, facility capability, multidisciplinary evaluation, and quality oversight, but they generally do so without imposing the same mandatory dual-operator specialty requirements that remain embedded in the current TAVR policy.

Implementation of Operator Flexibilities

Edwards requests CMS issue clear provider education and coding guidance to align billing and claims processing with the modernized NCD operator requirements. In particular, current CPT coding requirements and physician payment processes were developed around a two-operator TAVR model and rely on modifier -62 for co-operator billing. Misalignment between coverage requirements, coding, and reimbursement policies could inadvertently create administrative burden, confusion, or barriers to adoption.

To support successful implementation, Edwards respectfully requests that CMS issue timely implementation guidance and provider education following issuance of the final decision to address potential operational challenges arising from revised operator requirements. Clear and early guidance regarding coding, billing, and claims processing will be important to ensure that policy modernization translates into meaningful improvements in patient access without creating new reimbursement uncertainty or inappropriate denials for providers and hospitals.

It is our understanding that CMS has existing authority and established mechanisms to provide implementation guidance without requiring changes to CPT coding. CMS routinely issues claims-processing instructions and billing guidance through subregulatory communications, including Medicare Learning Network (MLN) Matters articles, Change Requests, and related implementation instructions. Similar guidance could be issued in conjunction with the final NCD to provide hospitals, physicians, MACs, and other stakeholders with adequate time to operationalize the revised requirements.

Specifically, Edwards requests CMS issue claims-processing instructions and billing guidance in alignment with the proposed policy that reiterates expectations for use of modifier -62 for dual-operator procedures, with continued use across operator specialties (e.g., interventional cardiologist + cardiac surgeon, interventional cardiologist + interventional cardiologist, or cardiac surgeon + cardiac surgeon), as well as expected use of existing TAVR CPT codes (e.g., 33361-33366) without modifier -62 for single-operator procedures. Issuing coding, billing, and claims-processing guidance concurrent with or shortly following publication of the final NCD will be critical to ensuring successful and timely implementation of the finalized policy.

Recommendations: **Edwards urges CMS to finalize the proposed operator flexibility framework so that Heart Teams and institutions may determine the TAVR operator approach that best supports individual patient care, while preserving joint participation when clinically appropriate. Edwards also requests that CMS address implementation considerations related to coding, billing, claims processing, and provider education immediately after the release of the final NCD.**

Facility and Physician Requirements

Elimination of Hospital Procedural Volume Thresholds

Edwards commends CMS for proposing to remove hospital volume requirements as a condition of TAVR coverage. This proposal maintains the appropriate balance between quality oversight and reducing access barriers for AS patients.

While any variation in mortality warrants continued monitoring and quality improvement, the patient-level risk of delayed or missed treatment is substantially greater than the observed mortality variation between low- and high-volume TAVR centers. For example, the observed 30-day TAVR mortality difference between the lowest- and highest-volume TAVR centers was 0.5% in a 2019 analysis.[100] In contrast, among patients recommended for AVR, mortality while waiting for treatment was 3.7% at 30

days, supporting the view that symptomatic AS should be treated on a semi-urgent rather than purely elective basis.[2] Among Medicare beneficiaries with medically managed severe symptomatic AS, mortality approached 50% at 1 year and reached 88% by 5 years, with 5-year mortality as high as 95% among high-risk patients.[101]

More contemporary evidence shows little meaningful hospital-level outcome variation by site volume, including similarly low in-hospital mortality across TAVR volume tertiles in the most recent hospital-level analysis from the STS/ACC TVT Registry (1.6% vs 1.7% vs 1.6%; p=0.11).[102] This evidence supports CMS' proposal to prioritize timely patient access while relying on ongoing outcomes monitoring, rather than rigid volume thresholds, to safeguard quality for a now mature, life-saving therapy.

Edwards anticipates that, by reducing volume-based site restrictions, this proposed policy will advance patient access, especially for patients in underserved or geographically constrained areas who may otherwise face delays in receiving timely, life-saving treatment. Since the 2019 NCD update for TAVR, new centers established under the revised volume criteria were smaller, more community-oriented institutions with substantially lower procedural volumes and greater rural representation (8.1% vs 1.5%) compared to existing centers in Medicare fee-for-service data. Despite entering the TAVR landscape with lower procedural volumes and distinct institutional profiles, new centers demonstrated no significant differences in clinical outcomes compared with established programs at both 30 days and 1 year (1-year all-cause mortality HR: 1.00; 95% CI: 0.94–1.06).[103] By enabling existing SAVR programs to establish TAVR capabilities without rigid volume-based barriers, the proposed policy can promote greater parity across the AVR treatment landscape and help ensure that patients with AS have access to both surgical and transcatheter treatment options based on clinical need and Heart Team evaluation, rather than geography or site-based restrictions.

Facility Criteria

Edwards supports CMS' proposed facility criteria requiring TAVR programs to maintain on-site structural heart interventional cardiology and cardiac surgery programs, as well as a post-procedure intensive care unit with personnel experienced in managing patients who have undergone open-heart procedures. Edwards supports CMS' evolution from heart valve surgery requirements to a broader cardiac surgery capability, which maintains appropriate access to surgical expertise while providing qualified facilities greater flexibility to establish TAVR programs.

Operator Volume Thresholds

Edwards supports the proposed updates to operator volume criteria that streamline requirements while recognizing the importance of maintaining procedural proficiency, without undermining the broader goal of improving access.

Quality Improvement

Edwards believes the proposed policy appropriately recognizes that quality for TAVR is best supported through ongoing program monitoring and continuous improvement, which programs may satisfy through voluntary participation in established registries or other meaningful quality oversight activities.

This approach is consistent with the precedent CMS set in October 2023 with the reconsideration of NCD 20.7 for percutaneous transluminal angioplasty (PTA) of the carotid artery concurrent with carotid artery stenting (CAS), where CMS expanded coverage and moved away from prescriptive procedural volume thresholds in favor of institutional and physician standards that support a dedicated program.[104] As CMS acknowledged in that decision, evolving clinical practice guidelines and a maturing evidence base had

established a standard of care that no longer required volume-based restrictions to safeguard quality. The same rationale applies to TAVR today, and Edwards believes CMS' proposed removal of volume thresholds is a similarly well-timed and evidence-based modernization.

Importantly, the CAS experience also demonstrates that removing volume requirements and decoupling registry participation from mandatory coverage conditions can strengthen quality infrastructure and sustain voluntary registry engagement outside of a CED framework. Following finalization of NCD 20.7, participation in national quality registries such as the Society for Vascular Surgery Vascular Quality Initiative (SVS VQI) has remained the primary mechanism through which facilities establish and maintain institutional and physician standards, track outcomes against national benchmarks, and demonstrate a commitment to continuous quality improvement, even though registry participation is no longer a coverage prerequisite.[105]

This precedent extends well beyond CAS. In 2013, CMS ended CED and the associated National Oncologic PET Registry data-collection requirement for fluorodeoxyglucose positron emission tomography (FDG-PET) across all oncologic indications under NCD 220.6.17, recognizing that the evidence base had matured to the point where prospective, coverage-linked data collection was no longer necessary to support appropriate use.[106] Similarly, in its 2022 reconsideration of NCD 210.14 for Lung Cancer Screening with low-dose computed tomography (LDCT), CMS removed the requirement that radiology imaging facilities participate in a CMS-approved registry as a condition of coverage, streamlining facility eligibility while preserving expectations for standardized reporting and quality infrastructure.[107] Across each of these NCDs, national quality infrastructure and voluntary data collection continued, reinforcing that CMS can confidently modernize the TAVR NCD by decoupling registry participation from mandatory coverage, while trusting the field to sustain robust, voluntary quality reporting through established mechanisms.

Edwards anticipates the same dynamic for TAVR. The STS/ACC TVT Registry, ACC's Transcatheter Valve Certification program, and public reporting infrastructure are now deeply embedded in how U.S. TAVR programs operate, benchmark performance, and demonstrate quality to patients, payers, and referring clinicians. Today, TAVR program quality is publicly reported in ways that enable patient choice and mirror the quality transparency already in place for SAVR procedures, including voluntary hospital and program procedure scores and star ratings through the TVT Registry, as well as US News & World Report recognition of high-performing TAVR hospitals based on patient outcomes. Registry-based quality reporting and available quality measures can continue to evolve their value and contributions to the TAVR evidence base by linking existing 1-year outcomes measures with Medicare claims data, further strengthening the field's ability to evaluate long-term durability, longitudinal outcomes, and national trends over time.

By pairing the removal of volume requirements with a clear expectation that facilities maintain an ongoing quality improvement program, CMS' proposed policy preserves a meaningful role for voluntary registry participation as a practical pathway for hospitals to demonstrate adherence without tying patient access to coverage-mandated CED.

Recommendations: **Edwards supports the proposed removal of site volume thresholds for both starting and maintaining a TAVR program, consistent with contemporary evidence. Edwards also believes the proposed minimum transcatheter valve operator volume requirements are appropriate to support ongoing proficiency without relying on site volume thresholds. In addition, Edwards supports the proposed requirement that programs maintain ongoing quality improvement processes and believes this proposal appropriately empowers programs to use established**

registries, public reporting, accreditation, benchmarking, or other meaningful quality oversight activities to monitor outcomes and improve care.

Other Uses of TAVR

TAVR in Emergency Scenarios

Edwards supports CMS' clarification that this NCD does not apply to the use of TAVR in emergency scenarios. This exception is essential to ensuring that patients requiring urgent or emergent TAVR can receive immediate care without being delayed by evaluation requirements intended for elective cases, including requirements that evaluation occur "prior to the day of the procedure."

A recent Medicare analysis of 15,305 AVRs showed that a notable 16% were performed urgently/emergently, were disproportionately Black, Hispanic, and Medicare-Medicaid dually eligible beneficiaries, and were associated with significantly higher in-hospital mortality (OR: 2.83; 95% CI: 2.21–3.61; p<0.0001), increased ICU admission, 8.42-day longer length of stay, and $21,369 higher index hospitalization costs. Among TAVR patients, 14.2% of procedures were urgent/emergent and associated with $16,109 higher index hospitalization costs. Timely AS diagnosis was associated with 88% lower odds of urgent/emergent AVR, reinforcing the value of minimizing delays to evaluation and treatment.[108]

Preserving this emergency-use flexibility could therefore help accelerate intervention, improve outcomes, reduce avoidable resource use, and support immediate access for patients who present late or deteriorate rapidly.

Medicare Administrative Contractor (MAC) Discretion

Edwards supports CMS' proposed language preserving MAC discretion to make reasonable and necessary determinations under section § 1862(a)(1)(A) for other beneficiaries seeking coverage for TAVR for AS. This flexibility is important to ensure that the NCD does not inadvertently create access barriers for patients whose clinical circumstances may fall outside the NCD, but for whom TAVR may nevertheless be appropriate. This language also provides an important pathway to coverage for future TAVR indications without requiring CMS to undertake an NCD reconsideration.

Investigational Device Exemptions (IDE) Coverage

Edwards supports CMS' proposed clarification that nothing in the TAVR NCD precludes coverage of TAVR for AS through NCD 310.1, the Clinical Trial Policy, or through IDE regulations. Preserving these pathways is important to ensure continued Medicare beneficiary access to TAVR in appropriately designed clinical studies and to avoid disrupting ongoing research that is generating evidence in evolving areas of structural heart disease.

In addition, Edwards appreciates CMS' proposal to preserve coverage for ongoing studies that were previously approved under CED in the TAVR NCD. This approach will help ensure continuity of access for patients already enrolled in clinical trials, avoid unnecessary disruption to ongoing evidence generation, and provide clarity to investigators, sponsors, sites, and MACs as studies transition under the finalized policy. Edwards also believes that aligning clinical trial coverage criteria for investigational TAVR uses with the existing IDE NCD will create a predictable, more consistent, and more navigable coverage pathway for future clinical trial requests.

Coverage of Moderate AS Under CED

As the evidence base and FDA-approved indications for TAVR continue to evolve, Edwards recommends that CMS consider for national coverage within the final NCD uses that may be FDA-approved in the future. In particular, requiring "severe" disease within the covered indication criteria does not address future moderate AS indications, even if supported by FDA approval. Edwards believes the TAVR NCD should permit coverage for FDA-approved indications for AS. A forward-looking NCD that supports coverage to label would promote national consistency, reduce variability in local coverage decisions, and ensure that Medicare beneficiaries have timely access to appropriate innovations as understanding of structural heart disease advances. Durable, transparent, and predictable coverage pathways are essential to sustaining innovation in structural heart disease and ensuring that coverage policy keeps pace with clinical evidence and patient need.

If CMS believes additional evidence generation is needed within the broader AS treatment landscape, moderate AS would be well-suited to CED study criteria and future data collection. Moderate AS remains an evolving clinical area where the optimal timing of intervention, patient selection criteria, and longitudinal outcomes are still being defined. Moderate AS is prevalent in 1.5% of individuals over the age of 65 and comprises a heterogenous population.[99] Approximately 50% of patients exhibit clinical or echocardiographic high-risk features, including symptoms, reduced LVEF, or evidence of cardiac damage, that are associated with increased mortality and/or faster disease progression.[109,110,111,112] To date, no large, randomized controlled trial has evaluated the impact of early TAVR in patients with moderate AS; however, the ongoing PROGRESS trial is designed to address this evidence gap.

In the PROGRESS Trial (NCT04889872), 744 older adults with moderate AS and at-risk features were randomized to TAVR with a SAPIEN 3/Ultra/RESILIA valve or to surveillance with deferred guideline-recommended AVR across 74 sites (n=60 US sites) from October 2021 to January 2024.[113] The primary effectiveness endpoint is the composite of death or heart failure events (with or without hospitalization) at 2 years, with annual follow-up planned through 10 years.[109] Baseline characteristics of the randomized PROGRESS population were recently presented at New York Valves. Patients had a mean age of 78 ± 6 years and a mean KCCQ score of 64 ± 24, with a broad distribution of surgical risk. Nearly all patients were symptomatic (96%), more than 70% had multiple at-risk features, and most (91%) had preserved left ventricular ejection fraction. Compared with the populations enrolled in PARTNER 3 and EARLY TAVR, PROGRESS enrolled an older cohort with poorer baseline health status, as reflected in higher STS scores, a larger proportion of NYHA Class III/IV symptoms, and lower KCCQ scores.[113]

Given the absence of definitive randomized evidence and the clinical complexity of patients enrolled in the ongoing PROGRESS trial, a CED approach would allow CMS to support national access to potentially life-saving technology while generating prospective evidence on clinical outcomes, patient selection, and value to the Medicare program. Such a framework could accelerate learning in an area of high unmet need and provide real-world evidence to complement forthcoming data from PROGRESS. CMS should therefore consider incorporating moderate AS into the CED framework using the proposed CED questions, rather than applying additional evidence-generation requirements to asymptomatic severe AS where randomized clinical evidence, FDA review, and Heart Team evaluation already support coverage for the Medicare population.

Recommendations: **Edwards recommends that CMS finalize the proposed provision clarifying that the NCD does not apply to emergency use cases. Edwards further recommends that CMS preserve MAC discretion to make reasonable and necessary determinations for other beneficiaries seeking coverage for TAVR for AS. CMS should also maintain access through NCD 310.1, the Clinical Trial**

Policy, and the IDE pathway. Finally, Edwards recommends that CMS extend coverage to FDA-approved TAVR indications for moderate AS under § 1862(a)(1)(E), and believes the proposed CED questions for asymptomatic AS are well suited to moderate AS.

Conclusion

The success of TAVR in the United States has been a shared achievement. CMS, FDA, specialty societies, cardiac surgeons, interventional cardiologists, imaging specialists, anesthesiologists, advanced practice clinicians, nurses, hospital leaders, industry partners, and patients have all contributed to building one of the most evidence-based and closely monitored innovations in cardiovascular medicine. The Heart Team model – including the essential contributions of both cardiac surgery and interventional cardiology – has been foundational to this success and should remain as Medicare coverage policy evolves.

Edwards supports finalizing the following proposals as drafted:

- Ending CED and recognizing TAVR for symptomatic severe AS as reasonable and necessary;
- Affirming the Heart Team – inclusive of cardiac surgeons and interventional cardiologists – as the foundation of high-quality AS care and empowering the Heart Team to determine the most appropriate TAVR operator approach, while preserving joint participation when clinically appropriate;
- Permitting asynchronous Heart Team evaluation and an independent, in-person evaluation by a TAVR operator;
- Removing hospital procedural volume thresholds while maintaining facility capabilities, physician proficiency, outcomes monitoring, and continuous quality improvement; and
- Preserving MAC discretion, IDE and clinical-trial coverage pathways, and the exemption for emergency TAVR.

To build on this strong foundation, Edwards respectfully recommends the following targeted refinements:

- Cover TAVR for asymptomatic severe AS under § 1862(a)(1)(A) as reasonable and necessary, consistent with the FDA-approved indication;
- Extend coverage to future FDA-approved TAVR indications for AS, including coverage of moderate AS under § 1862(a)(1)(E); and
- Issue timely coding, billing, and claims-processing guidance to support the modernized operator requirements.

The proposed NCD modernization builds on the quality infrastructure that CMS, specialty societies, clinicians, hospitals, and other stakeholders have helped establish, including the Heart Team, appropriate facility capabilities, physician proficiency, outcomes monitoring, and continuous quality improvement. Importantly, this reflects a broader evolution across medicine, where multidisciplinary collaboration has become standard practice not because it is mandated as a condition of coverage, but because clinicians recognize its value to patients. Edwards supports the overall direction of the proposed NCD and believes the targeted refinements described above would make an already strong policy even stronger, honoring the collaborative progress that has made TAVR a transformative therapy and helping extend that progress to save more lives in the years ahead.

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Appendices

Appendix A. Symptomatic AS Newly Published Evidence

Table 1. Recently Published Evidence Supporting Coverage of TAVR for Symptomatic AS without CED [6,7,8,9,10]

Study	Cohort & Setting	N	Key Findings
Nazif 2026 – PARTNER 2 S3i 10-year outcomes	Prospective, multicenter study of TAVR vs SAVR in propensity-matched patients at intermediate surgical risk (TAVR patients from the PARTNER 2 S3i Registry; SAVR patients from the PARTNER 2A RCT)	**1566** (783 propensity matched pairs); mean age 82; 74.5% NYHA class III/IV (TAVR)	At 10-year follow-up in the PARTNER 2 SAPIEN 3 Intermediate-risk (P2S3i) Registry study, propensity-matched TAVR and SAVR patients had similar rates of all-cause mortality (83.4% TAVR vs 82.3% SAVR; HR: 1.01; 95% CI: 0.91–1.13; p=0.82). Durability outcomes were similar for TAVR and SAVR patients, with low cumulative incidence rates of aortic valve reintervention with death as a competing risk (2.0% TAVR vs 1.9% SAVR; p=0.47) and similar hemodynamic outcomes (i.e., stable mean gradients and sustained improvements in effective orifice area) through 10 years.
Leon 2025 – PARTNER 3 7-year outcomes	Prospective, multicenter RCT of TAVR with SAPIEN 3 vs SAVR in patients at low surgical risk	**950** as-treated (TAVR n=496; SAVR n=454); mean age 73; 31.2% NYHA class III/IV (TAVR)	Among low-risk patients from the PARTNER 3 Randomized Controlled Trial, there was no significant difference in the individual and composite 7-year rates of death, stroke, and rehospitalization related to the procedure, the valve, or heart failure for TAVR and SAVR patients (composite endpoint rate: 34.6% TAVR vs 37.2% SAVR; HR: 0.87; 95% CI: 0.70–1.08).
Ternacle 2026 – PARTNER 3 7-year durability	Prospective, multicenter RCT of TAVR with SAPIEN 3 vs SAVR in patients at low surgical risk	**948** valve-implant population (TAVR n=495; SAVR n=453); mean age 73; 31.3% NYHA class III/IV (TAVR)	At 7 years, the cumulative incidence rates of valve reintervention with death as a competing risk were similarly low for TAVR and SAVR (6.0% vs 5.5%; HR: 1.09; 95% CI: 0.62–1.90; p=0.77).

Study	Cohort & Setting	N	Key Findings
Vemulapalli 2026 – Low-risk 7-year BEV outcomes	Retrospective registry study; Medicare FFS and MA-linked STS/ACC TVT Registry cohort of low-risk patients treated with balloon-expandable valves (2015-2024)	**68,071** CMS-linked low-risk transfemoral patients; mean age 76.5; 50.6% NYHA class III/IV	A recent real-world study of Medicare beneficiaries from the STS/ACC TVT Registry corroborates the durability of the SAPIEN 3 platform. In a real-world cohort of 68,071 low risk Medicare patients who underwent TAVR with a balloon expandable valve between 2015 and 2024, the 7-year mortality rate was 45.1%, while the 7-year cumulative incidence of reintervention remained low at 2.2% when accounting for death as a competing risk. Reintervention rates were similarly low among the youngest patients in the sample (65–74 years), with a 5-year cumulative incidence of 2.5%, supporting the long-term durability of the SAPIEN platform.
Alabbadi 2026 – TAVR reintervention outcomes	Retrospective claims study; Medicare analysis of patients undergoing transcatheter or surgical reintervention after TAVR (2013–2022)	**324,701** TAVR recipients (mean age 81); 2,387 reinterventions	Contemporary evidence demonstrates a simultaneous improvement in outcomes after failed TAVRs, with a significant decrease in the adjusted risk of 1-year mortality, corresponding to an approximate 4% relative reduction in mortality risk per year between 2013 and 2022 (HR: 0.96; 95% CI: 0.93–0.99).

Appendix B. Asymptomatic AS Published Evidence

Table 2. Recently Published Evidence Supporting Timely AVR in Asymptomatic Severe AS[17,21,22,23,20,26,32,33,34,35,36, 47,48,63,67,68,69]

Study	Cohort & Setting	N (Asymp)	Key Findings	Effect Size
Randomized Trial, Follow-up, Subgroup, and Mechanistic Analyses				
Généreux 2026 – EARLY TAVR 5 yr outcomes	Prospective, multicenter RCT of asymptomatic severe AS in patients ≥65 yrs with STS ≤10% and LVEF ≥50%; TAVR (SAPIEN 3/S3 Ultra) vs surveillance; asymptomatic status confirmed by negative treadmill stress test (or detailed clinical history if unable); median follow-up 5.0 years (IQR 4.1–5.0); all eligible patients reached 3-year follow-up; 95.2% of surveillance arm converted to delayed AVR by 5 yrs	**901** (455 TAVR; 446 surveillance); mean age 76, STS 1.8%, 83.5% low-risk per Heart Team; mean LVEF 67%, AVA 0.9 cm^2, peak velocity 4.3 m/s	Early TAVR sustained superiority over surveillance for the composite of death, stroke, or HF hospitalization (HFH) at 5 years, with an early HFH-driven benefit in the first 2 years (20.9% vs 41.7%; HR: 0.43; 95% CI: 0.33–0.55) and a death/stroke-driven benefit beyond 2 years (HR: 0.61; 95% CI: 0.40–0.94; p=0.02) a pattern consistent with the progressive myocardial remodeling and clinical deterioration documented during surveillance. Mortality curves diverged with longer follow-up, and stroke rates remained numerically lower with early TAVR.	• **Death, stroke, or HFH:** 15.2% vs 24.2%; HR: 0.58; 95% CI: 0.43–0.78; p<0.001 • **Death, stroke or HFH (2-yr landmark):** HR: 0.65; 95% CI: 0.43–0.98; p=0.04 • **All-cause death (incl. vital status sweep):** 10.3% vs 12.3%; HR: 0.84; 95% CI: 0.57–1.24; p=0.38 • **Stroke:** 4.8% vs 7.6%; HR: 0.63; 95% CI: 0.37–1.07; p=0.09 • **Death or stroke:** HR: 0.74; 95% CI: 0.53–1.04; p=0.08 — 2-yr landmark: HR: 0.61; 95% CI: 0.40–0.94; p=0.02 • **HF hospitalization:** 3.5% vs 10.3%; HR: 0.32; 95% CI: 0.18–0.57; p<0.001
Généreux 2026 – Secondary Analyses from EARLY TAVR	Prespecified subgroup analyses of the EARLY TAVR ITT population stratified by baseline NT-proBNP tertile, age (65–69/70–74/75–79/80+), cardiac damage stage (0/1/2/3–4), integrated LV health status (GLS + LAVi + LVMi), and guideline indication status (Class IIa/IIb/no recommendation); also evaluated clinical presentation at surveillance arm AVR conversion (Acute, Progressive, or Silent Valve Syndrome) and outcomes of delayed AVR vs early TAVR	**901** ITT (NT-proBNP tertiles n=266 each; cardiac damage assessable n=631; LV health n=833; guideline: 22.4% IIa, 7.0% IIb, 70.6% no recommendation)	Early TAVR benefit was consistent across every subgroup evaluated — including ≥80 yrs, Stage 3/4 cardiac damage, abnormal integrated LV health, elevated NT-proBNP, and Class IIa indication, with no interaction p-value reaching significance. Worse absolute outcomes in higher-risk subgroups reflected greater baseline disease burden, not attenuated TAVR benefit. 95.2% of surveillance patients converted to AVR by 5 yrs (median 11.1 months); at conversion, ~40% presented with Acute Valve Syndrome (NYHA III/IV, syncope, HFH, LVEF drop, or arrhythmia), and delayed AVR	**Death, stroke, or HFH** — HRs (NNT): • **NT-proBNP T1/T2/T3:** 0.54 (0.25–1.19)/0.51 (0.27–0.95)/0.64 (0.41–1.02); p-int=0.79 • **Age 65–69/70–74/75–79/80+**: 0.24 (0.07–0.85)/0.66/0.64/0.62 (0.37–1.02); p-int=0.53 • **Cardiac damage Stage 0/1/2/3–4**: 0.20/0.26 (0.10–0.69)/0.75/0.39; p-int=0.13 • **LV health Normal/Abnormal:** 0.44 (0.19–1.00)/0.63 (0.44–0.92); p-int=0.40 • **Guideline:** Class IIa 0.72/IIb 0.30/No GR 0.61 (0.40–0.92); p-int=0.41 • **Delayed AVR with AVS vs early TAVR (adjusted, 2-yr):**

Study	Cohort & Setting	N (Asymp)	Key Findings	Effect Size
			in Acute Valve Syndrome (AVS) patients carried significantly worse 2-yr outcomes than early TAVR.	Death/stroke/HFH HR: 2.14; 95% CI: 1.21–3.79; p=0.009; Death or stroke HR: 2.14 95% CI: 1.17–3.92; p=0.013
Kang 2026 – RECOVERY 10 yr outcomes	Multicenter, open-label RCT of asymptomatic very severe AS patients [(AVA ≤0.75 cm^2 with peak aortic jet velocity ≥4.5 m/s or mean gradient ≥50 mm Hg) and preserved LVEF (≥50%)]; early SAVR vs surveillance; median follow-up: 144 months (12 yrs early SAVR; 11.2 yrs surveillance)	**145** (73 early SAVR; 72 surveillance)	Early SAVR sustained a substantial long-term reduction in operative mortality/CV death and all-cause mortality over 10 years, with no HFH and no operative mortality in the early SAVR group; 85% of surveillance patients ultimately crossed over to AVR (median 1,048 days), and delayed AVR was associated with higher CV mortality than early SAVR; Kaplan–Meier curves did not converge, underscoring durable benefit.	• **Primary composite (operative mortality or CV death):** HR: 0.10; 95% CI: 0.02–0.43; p=0.002 (competing-risk); HR: 0.12; 95% CI: 0.03–0.46 (proportional hazards) • **All-cause mortality:** HR: 0.42; 95% CI: 0.21–0.86 • **HF hospitalization:** HR: 0.03; 95% CI: 0.00–0.49 (0 events in early-surgery group) • **10-yr cumulative incidence — primary endpoint:** 1% early SAVR vs 19% surveillance; all-cause death: 11% vs 25% • NNT = 6 to prevent 1 **CV death**; NNT = 7 to prevent 1 **all-cause death** at 10 yrs

Study	Cohort & Setting	N (Asymp)	Key Findings	Effect Size
Lindman 2025 – Biomarker substudy	Prespecified biomarker subgroup analysis of EARLY TAVR; core lab measurement of NT-proBNP and hs-cTnT at baseline; patients stratified by tertiles, elevated vs normal (per assay-defined age/sex thresholds), and count of elevated biomarkers (0/1/2)	**798** of 901 randomized (89%; 414 TAVR, 384 surveillance); median NT-proBNP 287 pg/mL, median hs-cTnT 14.6 ng/L	Higher NT-proBNP and hs-cTnT were associated with higher event rates across most endpoints, but the relative benefit of early TAVR was consistent across all biomarker tertiles and, contrary to the study hypothesis, was numerically greater among patients with the lowest baseline values. A natriuretic peptide threshold of >3× normal (the basis for the ACC/AHA Class IIa recommendation) did not identify a subgroup with greater benefit. A single biomarker measurement has limited value to guide the timing of TAVR; when elevated, findings support even greater urgency to intervene given higher absolute event rates and larger absolute risk reduction for HFH.	• **NT-proBNP** (per 1 SD log-transformed, adjusted HRs, ITT): **death, stroke, or HFH:** HR:1.45; 95% CI: 1.16–1.80; p<0.001; **HFH alone**: HR 2.24; 95% CI: 1.55–3.23; p<0.001; **CV death**: HR 1.65; 95% CI: 1.07–2.56; p=0.02 • **Treatment × NT-proBNP tertile interaction**: NS for primary/most secondary endpoints; HFH **NNT:** 32 (T1) → 11 (T3) • **hs-cTnT (elevated vs normal) × treatment interaction**: significant for death or HFH (p=0.04) and HFH alone (p=0.03) — greater relative early-TAVR benefit in patients with normal hs-cTnT • **Time to delayed AVR in surveillance arm shorter with elevated biomarkers** (NT-proBNP: 315 vs 397 days; hs-cTnT: 306 vs 347 days)

Study	Cohort & Setting	N (Asymp)	Key Findings	Effect Size
Lindman 2026 – LV health substudy	Prespecified secondary endpoint analysis of EARLY TAVR (effect-modification testing exploratory); echo core lab; integrated LV health = composite of GLS ≥15%, LVMi <115 g/m^2 (M)/<95 g/m^2 (W), LAVi ≤34 mL/m^2; longitudinal echo at baseline, 1 yr, and 2 yrs; also assessed each individual component (LVMi, LAVi, GLS)	**901 ITT** (833 with complete integrated LV health data); at baseline 27% normal integrated LV health, 73% abnormal; 88% normal GLS, 64% normal LVMi, 42% normal LAVi	Abnormal integrated LV health and each of its components were associated with higher event rates for the primary and secondary composites, but the benefit of early TAVR was consistent regardless of baseline LV health (integrated or by individual measure). At 2 years, patients randomized to early TAVR were substantially more likely to have normal LV health than those under surveillance. Among surveillance patients who converted to delayed AVR, LV health tended to decline from randomization to pre-procedure, but baseline LV health did not predict timing of conversion or severity of presentation at conversion.	• **Log-rank comparisons, abnormal vs normal LV health (5-yr KM rates):** Death, stroke, or unplanned CV hosp: 45.5% vs 33.0%; p<0.001; Death, stroke, unplanned CV hosp, or intervention with advanced signs/sx: 48.6% vs 39.6%; p=0.02 • **Treatment × integrated LV health interaction:** NS across primary and secondary composites — early TAVR benefit preserved in both normal and abnormal LV health strata • **2-year normal integrated LV health:** 48.1% early TAVR vs 35.9% surveillance; p<0.001 • **Baseline characteristics of abnormal LV health group:** higher STS score, more AF, prior MI, higher NT-proBNP (371 vs 171 pg/mL), higher hs-cTnT (15.6 vs 13.1 ng/L), higher mean gradient (all p<0.001–0.04)

Study	Cohort & Setting	N (Asymp)	Key Findings	Effect Size
Goel 2026 – Age-stratified analysis	Post-hoc, age-stratified analysis of EARLY TAVR across 4 groups: 65–69, 70–74, 75–79, and ≥80 years; primary composite (death, stroke, or unplanned CV hosp), composite of death/stroke/HFH, and individual components examined with treatment × age interaction testing; median follow-up 3.8 years	**901 ITT:** 141 (15.6%) 65–69 yrs; 263 (29.2%) 70–74 yrs; 250 (27.7%) 75–79 yrs; 247 (27.4%) ≥80 yrs	The clinical advantage of early TAVR was preserved across every age stratum (65–69, 70–74, 75–79, and ≥80 years), with no significant interaction between age and treatment effect. Absolute reductions in stroke were most pronounced in the youngest (65–69 years; absolute risk reduction [ARR]: 13%) and oldest (≥80 years; ARR: 12.3%) patients, while the largest absolute reduction in HFH was observed among those ≥80 years. Time to conversion in the surveillance group was similar across ages (median ~11 mo), and ~1/3 of even the youngest surveillance patients presented with acute valve syndrome at conversion (trend toward higher AVS with age, p=0.06).	• **P-interaction for treatment × age:** primary composite p=0.47; death/stroke/HFH p=0.53; death p=0.81; stroke p=0.17; HFH p=0.52 — all NS • **Stroke:** – 65–69 yrs: 0 events (TAVR) vs 7/69 (surveillance); ARR 13%; p=0.008 – ≥80 yrs: ARR: 12.3%; p=0.029 • **HFH 2-yr absolute risk reduction** (TAVR vs surveillance): 65–69 yrs 4.4%; 70–74 yrs 5.1%; 75–79 yrs 5.9%; ≥80 yrs 9.1% (NNT 11) • **Surveillance arm — median time to delayed AVR:** 65–69 yrs 13.0 mo; 70–74 yrs 11.0 mo; 75–79 yrs 9.6 mo; ≥80 yrs 11.7 mo; p=0.73 • **2-yr integrated LV health normal (65–69):** 63.9% early TAVR vs 28.3% surveillance; p=0.0002
Généreux 2026 – Cost Effectiveness Analysis	Literature-based CEA (Markov model, 30-day cycles, lifetime horizon) from US health care payor perspective; inputs from EARLY TAVR (up to 5-yr follow-up) and US Medicare reimbursement; WTP threshold $100,000/QALY; deterministic + probabilistic (5,000 iterations) sensitivity analyses + 7 scenario analyses	**Model cohort reflecting EARLY TAVR baseline population**: mean age 75.8 yrs; 69.1% male; low-surgical-risk, transfemoral-eligible	Early TAVR was economically dominant vs surveillance — 0.21 additional life years and 0.24 additional quality-adjusted life years (QALYs) while reducing lifetime costs by $8,812 per patient. Cost savings were driven primarily by downstream reductions in heart failure hospitalizations, strokes, and acute decompensation events associated with delayed intervention. In probabilistic sensitivity analysis, 95.9% of iterations were cost-effective and 90.3% demonstrated dominance, confirming that timely intervention is both clinically superior and economically favorable from a US healthcare system perspective.	• **Incremental LYs:** +0.21 (Early TAVR vs surveillance) • **Incremental QALYs:** +0.24 • **Incremental lifetime cost:** –$8,812 (eTAVR $58,863 vs surveillance $67,674 per patient) • **ICER:** Early TAVR dominant (better outcomes, lower cost) • **Cost savings drivers:** AVR procedure –$4,576; stroke –$1,432; HFH –$1,504 • **Probabilistic sensitivity analysis:** 95.9% of 5,000 iterations cost-effective at $100K threshold; 90.3% dominant • **Break-even year:** ~year 3 (year 5 in most conservative scenario)

Study	Cohort & Setting	N (Asymp)	Key Findings	Effect Size
Allmark 2026 – EASY AS substudy	Nested longitudinal qualitative substudy of the UK EASY-AS RCT (NCT04204915) of early AVR vs surveillance in asymptomatic severe AS; 73 semi-structured interviews across 6 UK sites (2022–2024); framework analysis with patient advisory group input; interviews at ≤8 weeks post-recruitment, 4–6 weeks post-AVR, and 12 months post-recruitment/AVR	**41** participants across 4 groups: 14 randomized to early intervention (11 SAVR, 3 TAVR), 11 randomized to surveillance, 7 who declined RCT participation, and 9 next-of-kin; mean age of trial participants 75 yrs (range 54–83); 56% male	Patients with asymptomatic severe AS broadly found early AVR acceptable; no participant objected in principle, and most favored early intervention based on the serious nature of AS, preference to intervene while still fit, and trust in clinicians. Decliners cited personal or social reasons rather than opposition to early AVR. Longitudinal interviews showed no unequivocal regret in the early-intervention group, and patients valued choice of intervention type and shared decision-making resources.	Descriptive findings on **acceptability** only: • Early AVR acceptable: 24/41 (58.5%) yes; 1/41 (2.4%) no; 11/41 (26.8%) equivocal; 5/41 (12.2%) unclear • Among 25 trial participants: 17 yes / 0 no / 5 equivocal / 3 unclear • EASY-AS UK screening log (n=1,391 eligible): 28% of men and 33.7% of women declined RCT participation; the most common documented reason (~101 patients) was "does not want early SAVR/TAVR" — but interview data indicated this typically reflected personal timing/circumstances rather than principled objection
Meta-analyses				
Huang 2026	Systematic review and meta-analysis of **4 RCTs and 9 observational studies;** asymptomatic severe AS through June 2025; ~15,000 patient-years follow-up	**3,960** (1,868 early AVR; 2,092 surveillance)	Early AVR was associated with lower all-cause mortality (RR: 0.51), cardiovascular mortality (RR: 0.50), and HFH (RR: 0.40) compared with surveillance. Natural history analysis showed 44% of asymptomatic patients developed symptoms during a median/mean follow-up of ~4-6 years. One-third of asymptomatic patients in the surveillance group died over a median follow-up of 5.6 years.	• **All-cause mortality:** RR: 0.51; 95% CI: 0.35–0.75; p<0.001 • **CV mortality:** RR 0.50; 95% CI: 0.37–0.67; p<0.001 • **HF hospitalization:** RR 0.40; 95% CI: 0.20–0.82; p=0.012 • **Longer-follow-up RCT subgroup (RECOVERY + AVATAR):** all-cause mortality RR: 0.44; 95% CI: 0.27–0.72; p=0.001

Study	Cohort & Setting	N (Asymp)	Key Findings	Effect Size
Ma 2026	Systematic review of **4 RCTs and 14 observational studies** through April 2025; median age 71.3 years; median follow-up 5 years	**5,764** (2,601 early AVR; 3,163 surveillance)	Early AVR was associated with ~50% lower risk of mortality, stroke, and unplanned cardiovascular hospitalization vs surveillance. The most robust benefit was a reduction in cardiovascular hospitalization, with low heterogeneity across studies (I^2=5.2%). While a mortality benefit was observed, the effect was attenuated after excluding studies at high risk of bias.	• **Composite (death + stroke + unplanned CV hosp)**: IRR: 0.51; 95% CI: 0.44–0.59; p<0.001 • **All-cause mortality:** HR: 0.41; 95% CI: 0.30–0.56; p<0.001 • **CV mortality:** HR: 0.58; 95% CI: 0.39–0.86; p=0.013 • **Unplanned CV hospitalization**: HR: 0.29; 95% CI: 0.15–0.56; p=0.006 • **Stroke:** HR: 0.80; 95% CI: 0.44–1.43; p=0.34
Adamu 2026	Systematic review of **4 RCTs and 4 propensity-matched observational studies** through August 2025	**3,086** (1,539 early AVR; 1,547 surveillance)	Early AVR was associated with substantial reductions in MACE, all-cause mortality, cardiovascular mortality, heart failure hospitalization, and sudden cardiac death compared with surveillance. No significant differences were observed for myocardial infarction, stroke, or permanent pacemaker implantation.	• **MACE:** OR: 0.41; 95% CI: 0.29–0.59; p<0.001 • **All-cause mortality:** OR: 0.59; 95% CI: 0.39–0.88; p=0.011 • **CV mortality:** OR: 0.49; 95% CI: 0.35–0.69; p<0.001 • **HF hospitalization:** OR: 0.36 95% CI: 0.20–0.65; p<0.001 • **Sudden cardiac death:** OR: 0.51; 95% CI: 0.29–0.88; p=0.015 • **Major vascular bleeding:** OR: 1.75 95% CI: 1.05–2.92; p=0.032
Awad 2026	Systematic review of **4 RCTs and 13 observational studies** through September 2025; reconstructed individual patient data with Kaplan-Meier analysis	**7,338** (2,896 AVR; 4,656 surveillance)	Early AVR was associated with lower rates of mortality and cardiovascular events compared with conservative management in asymptomatic severe AS. Reconstructed KM analysis showed durable survival benefit through 12 years across both SAVR and TAVR subgroups.	• **All-cause mortality:** IRR: 0.43; 95% CI: 0.32–0.57; p<0.001 • **CV mortality:** IRR 0.47; 95% CI: 0.29–0.75; p<0.01 • **HF hospitalization:** IRR: 0.39; 95% CI: 0.22–0.67; p<0.01 • **Sudden cardiac death:** IRR: 0.13; 95% CI: 0.04–0.48; p<0.01 • **MI:** IRR: 0.11; 95% CI: 0.04–0.31; p=0.03

Study	Cohort & Setting	N (Asymp)	Key Findings	Effect Size
				• **Reconstructed KM long-term survival:** HR: 0.32; 95% CI: 0.28–0.36; p<0.0001
Song 2025	Systematic review of **4 RCTs** (RECOVERY, AVATAR, EVOLVED, EARLY TAVR) through December 2024	**1,427** (719 early AVR; 708 surveillance)	Early AVR reduced the composite risk of death, HFH, and other major cardiovascular events compared with surveillance. Results demonstrated a consistent direction of benefit across RECOVERY, AVATAR, and EARLY-TAVR-era evidence. Early AVR superior to conservative management for the primary composite endpoint (all-cause mortality, CV hospitalization, stroke, MI); significant reductions in all-cause mortality, CV hospitalization, and stroke; no significant difference in cardiac-specific mortality.	• **Composite (mortality + CV hosp + stroke + MI):** RR:0.56; 95% CI: 0.49–0.64; I^2=60% • **All-cause mortality:** RR: 0.74; 95% CI: 0.55–0.99; I^2=58% • **CV hospitalization:** RR: 0.48; 95% CI: 0.39–0.58; I^2=26% • **Stroke:** RR: 0.62; 95% CI:0.40–0.95; I^2=0% • **Cardiac-specific mortality:** RR: 0.68; 95% CI: 0.40–1.16; NS • **MI:** RR 0.21; 95% CI: 0.04–1.19; NS
Real-World Observational Cohorts				
Braasch 2026	Retrospective STS-CMS linked analysis (2011–2022) of patients with severe AS and preserved LVEF undergoing isolated SAVR across 990 US centers, comparing outcomes in asymptomatic vs symptomatic patients	**1,399** (of 17,683)	Patients undergoing SAVR while asymptomatic had better 10-year survival than those treated after symptom onset (aHR 1.19; 95% CI 1.09–1.29). The survival advantage was most pronounced in patients ≥75 years, with LVEF ≥60%, and STS PROM <2%.	• **10-year survival:** aHR: 1.19; 95% CI: 1.09–1.29 • **LVEF ≥60%:** aHR: 1.20; 95% CI: 1.08–1.34 • **Age ≥75y:** aHR: 1.24; 95% CI: 1.11–1.39 • **STS PROM <2%:** aHR: 1.17; 95% CI: 1.01–1.34 • **Very severe AS:** aHR: 1.16; 95% CI: 1.01-1.35
Wasfy 2025	Retrospective, physician-adjudicated cohort study of asymptomatic patients with severe AS, preserved LVEF, and LVH identified from 1.2M echocardiograms across 12 Mass General Brigham hospitals (2000–2022), evaluating AVR vs no AVR	**607**	AVR was associated with a 63% lower risk of mortality among asymptomatic patients with severe AS, preserved LVEF, and LVH. Among 607 confirmed asymptomatic patients, 55% underwent AVR, including both SAVR and TAVR.	• **All-cause mortality:** HR: 0.37; 95% CI: 0.25–0.55; p<0.0001 • **TAVR subgroup:** HR: 0.34; 95% CI: 0.22–0.52; p<0.001 • **SAVR subgroup:** HR: 0.27; 95% CI: 0.14–0.54; p<0.001

Study	Cohort & Setting	N (Asymp)	Key Findings	Effect Size
Etiwy 2026	Retrospective multicenter echocardiography registry analysis (2000–2022) of asymptomatic patients with severe high-gradient AS and LVEF 50–54% (guideline-discordant range) identified from 1.2M echocardiograms across 7 Mass General Brigham hospitals, comparing AVR vs surveillance	**83**	In asymptomatic patients with severe high-gradient AS and LVEF 50–54%, AVR was associated with improved survival in those with more severe disease (AVA <0.9 cm^2: HR: 0.42; AVA ≤0.75 cm^2: HR: 0.33). Nearly 76% of patients who ultimately underwent AVR developed symptoms before intervention, despite being asymptomatic at diagnosis.	• **Overall:** HR: 0.56; 95% CI: 0.31–1.01; p=0.054 • **AVA <0.9 cm^2:** HR: 0.42; 95% CI: 0.21–0.84; p=0.01 • **AVA ≤0.75 cm^2:** HR: 0.33; 95% CI: 0.15–0.75; p=0.008
Mikami 2026	Retrospective single-center study of patients with asymptomatic severe AS and preserved LVEF treated at a quaternary-care center (2016–2024), comparing AVR before vs after symptom onset	**65** (of 160)	AVR performed before symptom onset reduced the risk of major adverse cardiovascular events by 73% compared with waiting until symptoms developed (aHR: 0.27; 95% CI: 0.12–0.63). Higher E/e', LV end-diastolic volume, and LV end-systolic volume were associated with worse outcomes.	• **Composite MACE:** aHR: 0.27; 95% CI: 0.12–0.63; p=0.002 • **Higher E/é (per 5 units)**: aHR: 1.39; 95% CI: 1.10–1.75; p=0.006 • **Higher LVEDVi (per 10 mL/m^2):** aHR: 1.22; 95% CI: 1.00–1.47; p=0.04 • **Higher LVESVi (per 10 mL/m^2):** aHR: 1.71; 95% CI: 1.00–2.93; p=0.05
Mao 2025	Multicenter retrospective cohort study of asymptomatic severe AS patients enrolled across 9 high-volume centers in China (2017–2018), comparing early TAVR, early SAVR, and surveillance	**476**	Early AVR was associated with better outcomes than surveillance, with lower all-cause mortality after TAVR (33.3% vs 46.4%) and lower MACE after SAVR (12.8% vs 22.3%). Among surveillance patients, those who later underwent AVR had significantly lower mortality (37.3% vs 60.4%) than those who never received AVR.	• **All-cause mortality** (TAVR vs surveillance): 33.3% vs 46.4%; p=0.023 • **MACE (SAVR vs conservative):** 12.8% vs 22.3%; p=0.047 • **Converters vs non-converters:** mortality 37.3% vs 60.4%, p<0.001; stroke 19.0% vs 40.7%, p<0.001

Study	Cohort & Setting	N (Asymp)	Key Findings	Effect Size
Vemulapalli 2026	Retrospective analysis of untreated severe asymptomatic AS patients from Optum Market Clarity (2016–2021) who developed symptoms within 3 years of diagnosis	**1,158** untreated severe asymptomatic AS patients who subsequently developed symptoms	Most asymptomatic patients (86.6%) became symptomatic within the first year of their diagnosis. Symptom onset was associated with a five-fold increase in cardiac hospitalization costs ($4,004 to $20,795), excluding AVR costs. Hospital admissions nearly quintupled (0.22 to 1.10 per patient-year), and ED visits more than doubled (0.30 to 0.72 per patient-year).	• **Total health care costs:** Cost ratio: 3.61; 95% CI: 2.09–6.24; p<0.01 • **Cardiac hospitalization costs:** Cost ratio: 5.19; 95% CI: 2.48–10.86; p<0.01 • **All-cause admissions:** IRR: 4.94; 95% CI: 3.06–7.96; p<0.01 • **Cardiac admissions:** IRR: 6.78; 95% CI: 3.99–11.51; p<0.01 • **ED visits:** IRR: 2.44; 95% CI: 1.67–3.57; p<0.01

Table 3. Summary of Evidence Addressing the 2019 CED Questions and Newly Proposed 2026 CED Questions for TAVR in Asymptomatic Severe Aortic Stenosis

2019 CED Questions	Summary
When performed outside a controlled clinical study, how do outcomes and adverse events compare to the pivotal clinical studies?	• STS/ACC TVT Registry analyses across all surgical risk levels demonstrate that 30-day TAVR outcomes achieved in real-world practice are consistent with those reported in pivotal randomized trials of symptomatic severe AS patients.[71,72,74,75,76,77] • Asymptomatic patients in the EARLY TAVR trial had lower rates of 30-day all-cause mortality (0.2%) than low-risk patients in recent TVT registry data.[16,47,72] • Real-world observational data in asymptomatic severe AS, including cohorts with TAVR-treated patients, demonstrate outcome trends directionally consistent with EARLY TAVR, with AVR associated with lower mortality in physician-adjudicated asymptomatic cohorts and similar signals observed in TAVR-specific analyses.[33,34,25] • STS-CMS linked real-world analysis of 17,683 asymptomatic patients undergoing AVR demonstrated favorable early postoperative outcomes and superior risk-adjusted 10-year survival compared to symptomatic patients.[32]
What is the long-term durability of the device?	• Long-term durability evidence now extends through 5-, 7-, and 10 years across high-, intermediate, and low-risk populations in the PARTNER trials, with complementary evidence from real-world cohorts demonstrating low reintervention rates through 10 years.[6, 8,7, 9,10,78,82,83,88,89] • Although asymptomatic-specific durability follow-up is necessarily shorter because TAVR in asymptomatic severe AS is a newer indication, extensive durability evidence from the same balloon-expandable TAVR platform used in EARLY TAVR demonstrates sustained valve performance through 5-, 7-, and 10 years across low-, intermediate-, and high-risk populations. These findings provide the most relevant evidence regarding the expected long-term durability of TAVR in asymptomatic patients.[6,7,81,82,83,88]
What are the long-term outcomes and adverse events?	TAVR has excellent, well-evidenced long-term outcomes in the pivotal PARTNER trials.[7,76,78] Long-term follow-up from randomized and observational studies demonstrates sustained clinical benefit and favorable safety outcomes following early valve replacement in asymptomatic severe AS. • In the EARLY TAVR trial, patients randomized to early TAVR experienced sustained reductions in death, stroke, or heart failure hospitalization through a median follow-up of 5.0 years compared with surveillance (15.2% vs 24.2%; HR: 0.58; 95% CI: 0.43-0.78; p<0.001). Importantly, no late safety signal emerged during follow-up, with similar all-cause mortality between groups and numerically lower stroke rates among patients treated with TAVR and significantly reduced death or stroke rates with early TAVR in the 2-year landmark analysis (HR: 0.61; p=0.02).[16,47] • RECOVERY 10-year data in asymptomatic severe AS demonstrated lower cardiovascular mortality, all-cause mortality, and heart failure hospitalization through 10 years (mortality 15% vs 32%; no HF hospitalizations with early AVR).[17] • Meta-analyses incorporating all randomized trials and more than 5,000 asymptomatic patients further demonstrate lower rates of heart failure hospitalization, unplanned cardiovascular hospitalization, and stroke with early valve replacement, with observational studies additionally showing consistent reductions in all-cause and cardiovascular mortality.[25,28]

2019 CED Questions	Summary
	• Real-world data demonstrated superior risk-adjusted 10-year survival among asymptomatic patients undergoing AVR before symptom onset (aHR: 1.19; STS ACSD linked to CMS claims).[32]
What morbidity and procedure-related factors contribute to TAVR patients' outcomes? Specifically, this must be addressed through a composite metric.	Validated STS/ACC TVT Registry composite metrics integrating mortality and major morbidity outcomes have been established for TAVR performance assessment, incorporated into national quality measurement and public reporting programs, and used to evaluate factors contributing to improvements in TAVR outcomes over time.[65,80,84,85,86,87]

2026 Proposed CED Questions	Summary

Does TAVR, SAVR, or close surveillance until symptom onset better improve health outcomes, particularly in patients with lower surgical risk, longer life expectancy, preserved LVEF, and bicuspid aortic valves?	Evidence directly addressing outcomes in these subgroups now includes:
	Low Surgical Risk & Preserved LVEF
	• Four randomized trials of early AVR vs surveillance (EARLY TAVR, RECOVERY, AVATAR, EVOLVED) in asymptomatic severe AS
	  • EARLY TAVR (mean age 76; STS <10; preserved LVEF; 8% bicuspid; 83.5% low-risk per Heart Team, mean STS 1.8%); reduced composite of death, stroke, or CV hospitalization (26.8% vs 45.3%; HR: 0.50) and sustained through five years;[16,47]
	  • RECOVERY (mean age 64; STS <4; 61% bicuspid); reduced CV mortality (3% vs 24%) and all-cause mortality (15% vs 32%); longest randomized follow-up available;[17]
	  • AVATAR (mean age 67; STS <8; preserved LVEF; mean STS 1.7%); reduced composite endpoint (23.1% vs 46.8%; HR: 0.42);[18]
	  • EVOLVED (mean age 73; high prevalence of myocardial fibrosis (81% of patients); reduced AS-related hospitalization (6% vs 17%; HR: 0.37; 95% CI: 0.16-0.88).[19]
	• Contemporary real-world evidence in asymptomatic severe AS
	  • STS-CMS linked, 17,683 patients; superior 10-year survival for asymptomatic AVR; benefit greatest in patients with LVEF ≥60% (aHR: 1.20) and STS PROM <2% (aHR: 1.17);[32]
	  • Physician-adjudicated cohort of asymptomatic patients with preserved LVEF and LVH; AVR reduced mortality (HR: 0.37); consistent in TAVR-specific subgroup (HR: 0.34);[33]
	  • Asymptomatic patients with LVEF 50%-54%; AVR associated with improved survival, particularly in more severe cases.[34]
	TAVR vs SAVR
	• Long-term follow-up from the PARTNER trials establishing durable TAVR performance across risk groups;[6,7,77,78,82]
	• Contemporary bicuspid-specific analyses.[91,92,93,94,95]
	Meta-analyses demonstrate consistent effect estimates across randomized and non-randomized populations.[20,25,27,28,30,31]

2026 Proposed CED Questions	Summary
What are the long-term valve re-intervention rates of TAVR vs SAVR, and does re-intervention impact health outcomes?	Long-term reintervention rates following TAVR and SAVR are low and comparable across risk populations. • In randomized trials of low-, intermediate-, and high-risk symptomatic populations using the same contemporary valve platforms evaluated in EARLY TAVR, reintervention rates have been consistently below 10% through 7 to 10 years and have not been associated with excess long-term mortality or clinical harm.[76,82,83] • Real-world data further confirm low reintervention rates following TAVR, with reintervention not associated with excess long-term clinical risk.[32] • In asymptomatic populations, RECOVERY 10-year follow-up demonstrated similar repeat valve surgery rates between groups, and EARLY TAVR reported low reintervention rates during 5-year follow-up.[16,17,47]
Can longer-term, risk-standardized, patient-centered health outcomes replace volume criteria for TAVR operators?	TAVR now has a validated, national, patient-centered, risk-standardized outcome measurement infrastructure that can replace volume-based operator and program criteria without compromising quality, and doing so is consistent with the approach CMS has taken in other NCDs where a mature evidence base and validated registry infrastructure supported the removal of volume-based facility requirements. • Validated composite metrics developed from the TVT Registry, incorporated into public reporting programs, provide a mature national infrastructure for risk-adjusted assessment of operator and program performance;[65,84] • National quality initiatives (Target AS) and ACC/AHA performance measures further support a shift from structural criteria to outcome-based quality measurement;[86,87] • TVT Registry analyses demonstrate that improvements in TAVR outcomes are driven primarily by patient selection, procedural technique, and program experience rather than volume alone;[71,73,85] • CMS precedent from PTA NCD 20.7, FDG-PET NCD 220.6.17, and Lung Cancer Screening with LDCT NCD 210.14, where volume-based facility requirements were replaced with voluntary registry-based quality assessment;[104,106,107] • For asymptomatic patients in whom timely intervention improves outcomes, outcome-based operator quality measures (rather than volume thresholds) best support both equitable access and clinical accountability.[71,73,85]

As shown in **Appendix B Table 3**, both the original 2019 CED questions and the newly proposed 2026 CED questions have been substantially or fully addressed by a comprehensive and consistent body of randomized, observational, and meta-analytic evidence. Continued CED in asymptomatic severe AS would therefore not resolve any remaining evidence gaps material to coverage decision-making and would instead perpetuate administrative burden, inequities in access, and delays in evidence-based care for Medicare beneficiaries.

Appendix C. Edwards Reconsideration Request Letter

1. Introduction

1.1 Background of disease and treatment

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

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

1.2 TAVR NCD reconsideration history

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

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

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

2. Rationale for Reopening the TAVR NCD

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

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

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

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

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

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

2.1 Updates are needed to include asymptomatic patients.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 1. 30-Day Registry & PARTNER Outcomes

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

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

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

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

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

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

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

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

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

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

All-cause mortality

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

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

Stroke

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

New permanent pacemaker implantation

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

Bleeding

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

Vascular complications

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

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

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

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

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

[†]Values reflect outcomes at 4 years

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

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

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

Procedure-related factors

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

Morbidity factors

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

Disease management quality measures

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

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

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

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

Survival

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

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

Stroke

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

New permanent pacemaker implantation

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

Bleeding

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

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

Vascular complications

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

Acute Kidney Injury (AKI)

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

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

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

*Significant difference at 1-year

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

Repeat Aortic Valve Procedures

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

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

Quality of Life

TAVR resulted in improved quality of life for all risk levels in 6 pivotal clinical studies, with short-term gains greater in TAVR patients than SAVR patients. In the TF TAVR subcohort of the PARTNER A RCT, patients who received TAVR experienced improvements from baseline in all QoL indicators, including the KCCQ-OS, physical limitations, total symptoms, QoL, and social limitation scores; SF-12 physical and mental scores; and EQ-5D utilities at 1 month, 6 months, and 1 year. Importantly, TF-TAVR patients experienced improvements earlier than SAVR patients, showing a significantly greater improvement in KCCQ-OS scores than SAVR patients at 1 month (+9.9-point increase, $p \leq 0.001$). This change corresponded to a moderate clinical improvement, although similar improvements were observed between patients who received SAPIEN or SAVR at 6 months and 1 year [92]. In the TA subcohort of PARTNER A, patients in the SAPIEN and SAVR groups experienced a significant improvement of KCCQ-OS scores at 30 days, 6 months, and 1 year compared with baseline [93]. Among high-risk patients in the CoreValve High-risk trial, patients who received the CoreValve had a mean 23.2-point increase in KCCQ-OS score from baseline to 1 year that was non-inferior to the increase observed in SAVR patients (+21.88 points). Analysis by access site revealed that CoreValve patients in the iliofemoral cohort experienced significant improvements from baseline earlier than SAVR patients across all health status measures. Specifically, health status improvements were significantly greater with the CoreValve than with SAVR at 1 month for KCCQ-OS (+16.7-point improvement), physical limitations (+17.8 points), total symptoms (+9.9 points), QoL (+19.0 points), and social limitation (+18.6 points) scores (all $p<0.001$) [94]. However, no differences in KCCQ-OS or SF-12 scores were observed between the CoreValve and SAVR groups at 6-month, 1-year, and 5-year follow-up [75].

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Paravalvular regurgitation

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

Permanent pacemaker implantation

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

Vascular events

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

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

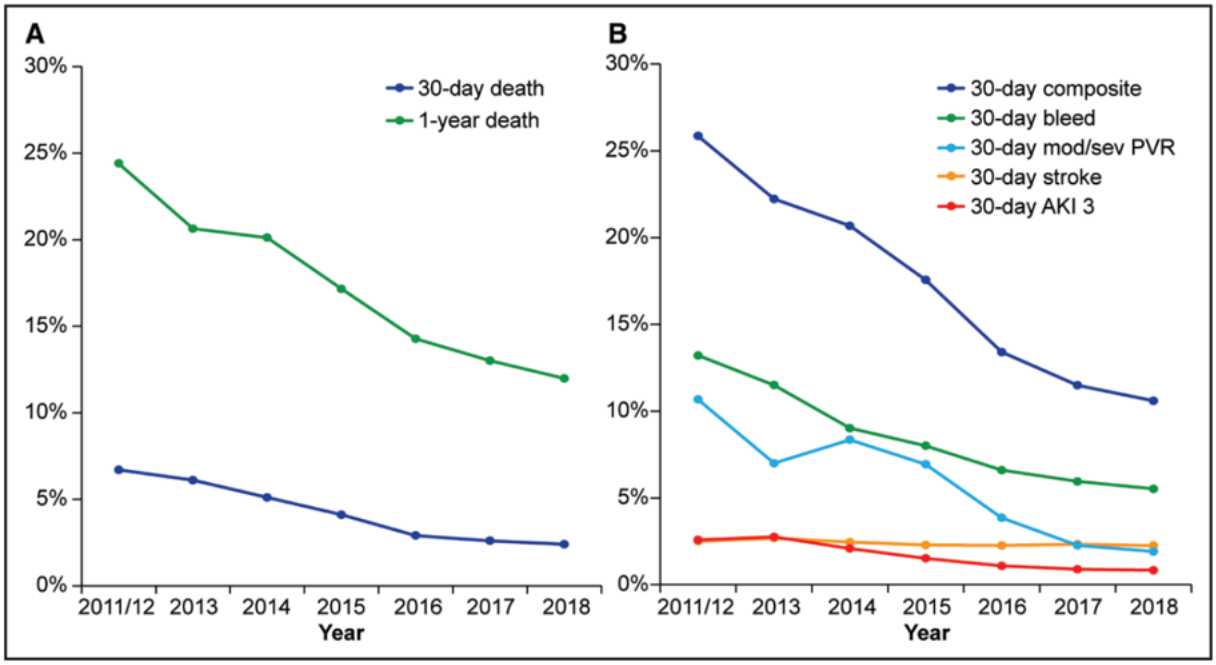
2.3 Updates are needed to remove outdated and burdensome requirements that create barriers to patient care.

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

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

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

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



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

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

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

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

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

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

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

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

2.3.3 Access barriers to TAVR are well-documented.

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

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

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

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

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

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

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

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

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

3. Summary of Request to Reconsider TAVR NCD 20.32

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

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

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

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

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

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

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

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

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

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

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

Relevant literature to support in asymptomatic patients with severe AS

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

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

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

Appendix Table A1. PICOS framework

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

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

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

Appendix Table A2. Search Strategy

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

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

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

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

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

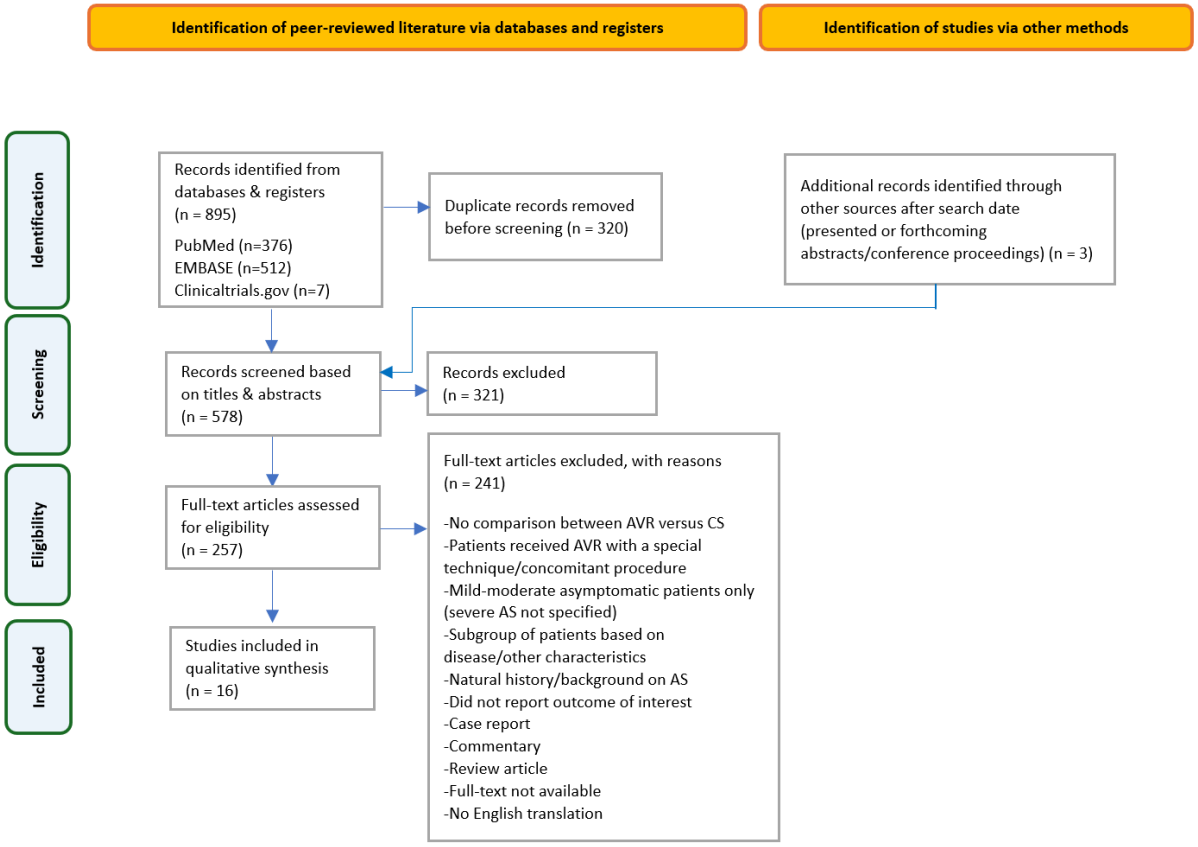
In addition to the 16 studies comparing AVR to CS noted above, two studies that did not meet full criteria for inclusion in the review were evaluated separately for the purpose of summarizing QoL data (in addition to EARLY TAVR): 1) Huded (2023) compared TAVR in minimally symptomatic versus moderate/severe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

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

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

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

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



Assessment of Study Quality/Risk of Bias

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

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

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

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

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

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

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

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

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

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

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

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

Overview of Studies

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

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

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

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

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

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

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

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

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

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

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

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

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

Clinical Outcomes Evaluated

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

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

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

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

Appendix Table A7: All-Cause Mortality Event Counts

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

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

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

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

Appendix Table A8: Primary Endpoint Event Counts by Study

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

AVR: aortic valve replacement; CS: clinical surveillance

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

Appendix Table A9: Cardiovascular Mortality Event Counts by Study

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

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

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

Appendix Table A10: HF Hospitalization Event Counts by Study

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

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

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

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

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

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

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

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

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

Appendix Table A12: Stroke Event Counts by Study

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

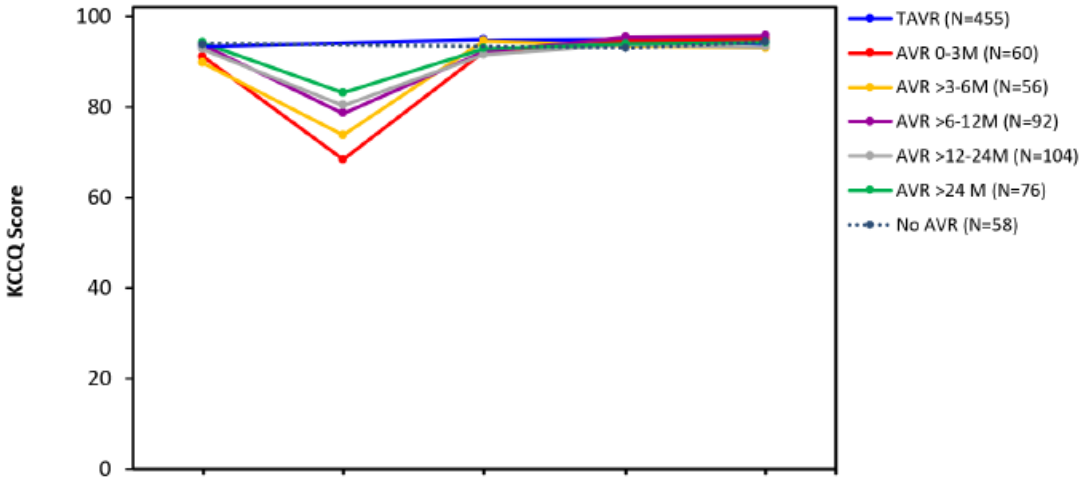
	First Author (Year)	Stroke Events (AVR vs CS)
Obs.	Kim (2019)	4/221 vs 2/247
	Taniguchi (2015)	23/291 vs 18/291

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

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

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

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



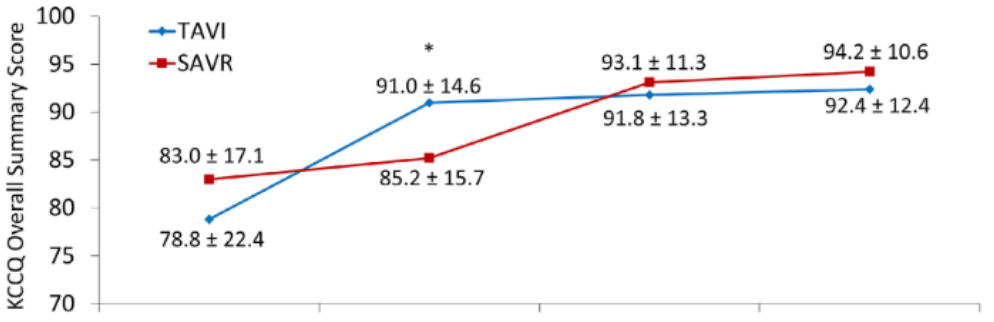
No. of Pts:					
TAVR	441	-	437	422	395
AVR 0-3M	60	56	58	54	50
AVR >3-6M	56	54	55	52	46
AVR >6-12M	91	89	90	85	79
AVR >12-24M	102	94	95	88	71
AVR >24M	76	74	73	55	29
No AVR	55	-	-	46	36

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

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

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

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



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

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

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

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

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

Key Conclusions & Recommendations

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

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

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

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

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Appendix D. Edwards Tracking Sheet Comment Letter

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.

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].

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

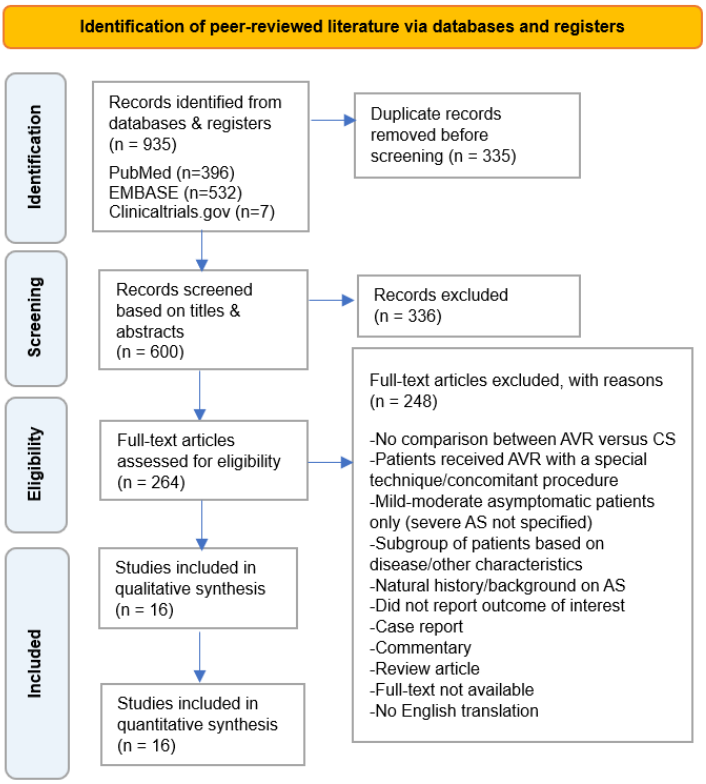
demographics, interventions, and outcomes of interest. Study quality was assessed using the Cochrane Risk of Bias 2 (RoB2) tool and the Newcastle-Ottawa Scale (NOS) for randomized and non-randomized studies, respectively [156, 157].

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

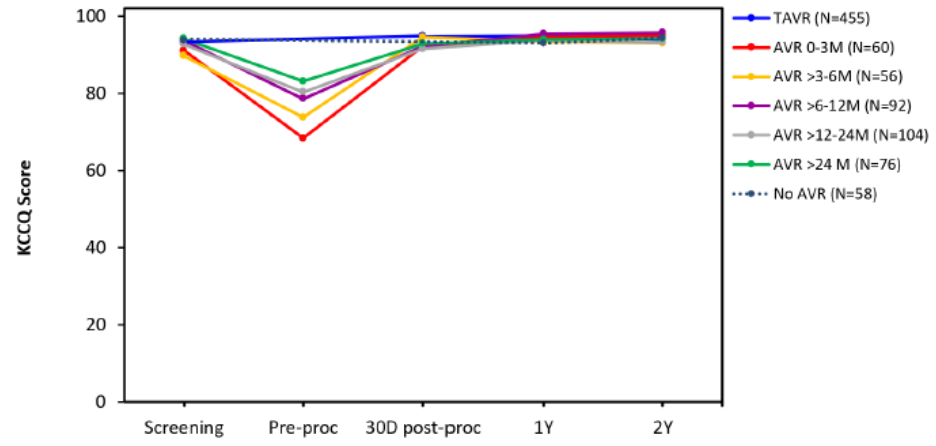
AVR: aortic valve replacement; CS: clinical surveillance; RCTs: randomized clinical trials

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

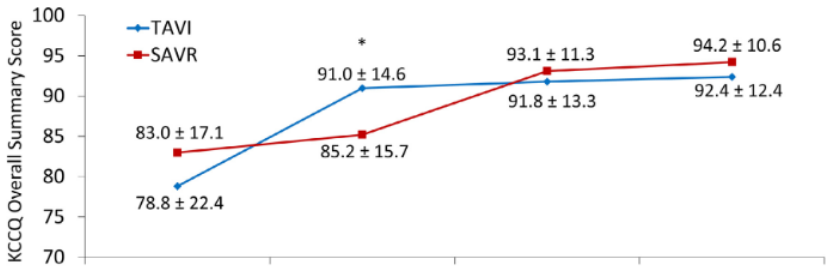


No. of Pts:					
TAVR	441	-	437	422	395
AVR 0-3M	60	56	58	54	50
AVR >3-6M	56	54	55	52	46
AVR >6-12M	91	89	90	85	79
AVR >12-24M	102	94	95	88	71
AVR >24M	76	74	73	55	29
No AVR	55	-	-	46	36

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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