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Transcatheter Aortic-Valve Implantation for Aortic Stenosis

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Related Policies (if applicable)
None

Disclaimer

Carefully check state regulations and/or the member contract.
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Coverage

Transcatheter aortic valve replacement with a U.S. Food and Drug Administration (FDA)-approved transcatheter heart valve system, performed via an approach consistent with the device's FDA-approved labeling, **may be considered medically necessary** for individuals with native valve aortic stenosis when **ALL** of the following conditions are present:

- Severe aortic stenosis (see Policy Guidelines section) with a calcified aortic valve; AND
- New York Heart Association (NYHA) heart failure class II, III, or IV symptoms; AND
- Individual does not have unicuspid or bicuspid aortic valves.

Transcatheter aortic valve replacement with a transcatheter heart valve system approved for use for repair of a degenerated bioprosthetic valve (valve-in-valve) **may be considered medically necessary** when **ALL** of the following conditions are present:

- Failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve; AND
- NYHA heart failure class II, III, or IV symptoms; AND
- Individual is:
  - Not an operable candidate for open surgery, as documented by at least two cardiovascular specialists (including a cardiac surgeon); or

- An operable candidate but is considered at increased surgical risk for open surgery as documented by at least 2 cardiac specialists (including a cardiac surgeon); or
- Considered at increased surgical risk for open surgery (e.g., repeat sternotomy) due to a history of congenital vascular anomalies AND/OR has a complex intrathoracic surgical history, as documented by at least 2 cardiovascular specialists (including a cardiac surgeon) (see Policy Guidelines section).

Transcatheter aortic valve replacement **is considered experimental, investigational and/or unproven** for all other indications.

Use of a cerebral embolic protection device (e.g., Sentinel) during transcatheter aortic valve replacement procedures **is considered experimental, investigational and/or unproven.**

3D predictive model generation for preplanning of a cardiac procedure, using data from cardiac computed tomographic angiography **is considered experimental, investigational and/or unproven** for all indications.

Policy Guidelines

The FDA definitions of risk for open surgery include:

- Extreme risk or inoperable: Predicted risk of operative mortality and/or serious irreversible morbidity 50% or higher for open surgery.
- High risk: Society of Thoracic Surgeons (STS) predicted operative risk score of 8% or higher; OR judged by a heart team, which includes an experienced cardiac surgeon and a cardiologist, to have an expected mortality risk of 15% or higher for open surgery.
- Intermediate risk: STS predicted operative risk score of 3% to 7%.
- Low risk: Individuals with STS predicted operative risk score of less than 3% or 4%.

Some individuals being considered for valve-in-valve transcatheter aortic valve replacement may be deemed at increased surgical risk for open surgery despite low-to-moderate STS risk scores. This may include individuals with advanced age, complex intrathoracic histories, congenital cardiac anomalies, liver disease, or other extreme comorbid conditions not accurately captured by STS risk scores as documented by at least 2 cardiovascular specialists, including a cardiac surgeon. (1, 2)

For the use of the FDA approved SAPIEN, CoreValve, or Portico device, severe aortic stenosis is defined by one or more of the following criteria:

- An aortic valve area of less than or equal to 1 cm^2; or
- An aortic valve area index of less than or equal to 0.6 cm^2/m^2; or
- A mean aortic valve gradient greater than or equal to 40 mm Hg; or
- A peak aortic-jet velocity greater than or equal to 4.0 m/sec.

Description

Aortic stenosis is narrowing of the aortic valve opening, resulting in obstruction of blood flow from the left ventricle into the ascending aorta. Patients with untreated, symptomatic severe aortic stenosis have a poor prognosis. Valve replacement is an effective treatment for severe aortic stenosis. Transcatheter aortic valve implantation (TAVI), also known as transcatheter aortic valve replacement (TAVR), is being evaluated as an alternative to open surgery for patients with aortic stenosis and to nonsurgical therapy for patients with a prohibitive risk for surgery.

Aortic Stenosis

Aortic stenosis is defined as narrowing of the aortic valve opening, resulting in obstruction of blood flow from the left ventricle into the ascending aorta. Progressive calcification of the aortic valve is the most common etiology in North America and Europe, while rheumatic fever is the most common etiology in developing countries. (3) Congenital abnormalities of the aortic valve, most commonly a bicuspid or unicuspid valve, increase the risk of aortic stenosis, but aortic stenosis can also occur in a normal aortic valve. Risk factors for calcification of a congenitally normal valve mirror those for atherosclerotic vascular disease, including advanced age, male gender, smoking, hypertension, and hyperlipidemia. (3) Thus, the pathogenesis of calcific aortic stenosis is thought to be similar to that of atherosclerosis (i.e., deposition of atherogenic lipids and infiltration of inflammatory cells, followed by progressive calcification).

The natural history of aortic stenosis involves a long asymptomatic period, with slowly progressive narrowing of the valve until the stenosis reaches the severe stage. At this time, symptoms of dyspnea, chest pain, and/or dizziness/syncope often occur, and the disorder progresses rapidly. Treatment of aortic stenosis is replacement of the diseased valve with a bioprosthetic or mechanical valve.

<u>Disease Burden</u>

Aortic stenosis is a relatively common disorder in elderly patients and is the most common acquired valve disorder in the United States. Approximately 2% to 4% of people older than 65 years of age have evidence of significant aortic stenosis, (3) increasing up to 8% of people by age 85 years. (4) In the Helsinki Aging Study (1993), a population-based study of 501 patients, ages 75 to 86 years, the prevalence of severe aortic stenosis by echocardiography was estimated to be 2.9%. (5) In the United States, more than 50,000 aortic valve replacements are performed annually due to severe aortic stenosis.

Aortic stenosis does not cause substantial morbidity or mortality when the disease is mild or moderate in severity. By the time it becomes severe, there is an untreated mortality rate of approximately 50% within 2 years. (6) Open surgical repair is an effective treatment for reversing aortic stenosis, and artificial valves have demonstrated good durability for up to 20 years. (6) However, these benefits are accompanied by perioperative mortality of approximately 3% to 4% and substantial morbidity, (6) both of which increase with advancing age.

Unmet Needs

Many patients with severe, symptomatic aortic stenosis are poor operative candidates. Approximately 30% of patients presenting with severe aortic stenosis do not undergo open surgery due to factors such as advanced age, advanced left ventricular dysfunction, or multiple medical comorbidities. (7) For patients who are not surgical candidates, medical therapy can partially alleviate the symptoms of aortic stenosis but does not affect the underlying disease progression. Percutaneous balloon valvuloplasty can be performed, but this procedure has less than optimal outcomes. (8) Balloon valvuloplasty can improve symptoms and increase flow across the stenotic valve but is associated with high rates of complications such as stroke, myocardial infarction, and aortic regurgitation. Also, restenosis can occur rapidly, and there is no improvement in mortality. As a result, there is a large unmet need for less invasive treatments for aortic stenosis in patients at increased risk for open surgery.

Treatment

Transcatheter aortic valve implantation, also known as transcatheter aortic valve replacement, has been developed in response to this unmet need and was originally intended as an alternative for patients for whom surgery was not an option due to prohibitive surgical risk or for patients at high risk for open surgery. The procedure is performed percutaneously, most often through the transfemoral artery approach. It can also be done through the subclavian artery approach and transapically using mediastinoscopy. Balloon valvuloplasty is first performed to open up the stenotic area. This is followed by passage of a bioprosthetic artificial valve across the native aortic valve. The valve is initially compressed to allow passage across the native valve and is then expanded and secured to the underlying aortic valve annulus. The procedure is performed on the beating heart without cardiopulmonary bypass.

3D Predictive Model Generation for Cardiac Procedure Preplanning

Precision TAVI (122)

DASI Simulations Precision TAVI is a computer simulation device that predicts implant frame deformation after implantation of a Transcatheter Heart Valve (THV) device. The simulation combines a predefined THV device model and size with a patient-specific model of the patient's anatomy thereby predicting the post deployment deformation of the THV and the anatomy. The simulation results are intended to be used by qualified clinicians as additional information for planning transcatheter aortic valve replacement (TAVR).

Precision TAVI is an optional, non-invasive, post processing software solution that is indicated for patient-specific simulations of TAVR during procedural planning. The software performs computer simulation to predict post TAVR in vivo valve frame deformation of clinician selected THV device types and sizes.

Regulatory Status

Multiple manufacturers have transcatheter aortic valve devices with U.S. Food and Drug Administration (FDA) approval. Regulatory status data for these devices are listed in Table 1.

Table 1. FDA-Approved Transcatheter Aortic Valve Device Systems

Device and Indication	Manufacturer	Date Cleared	PMA
Edwards SAPIEN Transcatheter Heart Valve System™ • Severe native aortic valve stenosis determined to be inoperable for open aortic valve replacement (transfemoral approach).	Edwards Lifesciences	11/11	P100041
• Edwards SAPIEN™ Transcatheter Heart Valve, Model 9000TFX. • Expanded to include high risk aortic stenosis (transapical approach).		10/12	P110021
• Edwards SAPIEN XT Transcatheter Heart Valve (model 9300TFX) and accessories. • Severe native aortic valve stenosis at high or greater risk for open surgical therapy.		07/14	P130009
• Expanded to include failure of bioprosthetic valve in high or greater risk for open surgical therapy.		10/15	P130009/S034
• Expanded to include severe aortic stenosis with intermediate surgical risk.		08/16	P130009/S057
• SAPIEN 3 THV System, a design iteration. • Severe aortic stenosis with high or greater risk for open surgical therapy.		06/15	P140031
• Expanded to include failure of a bioprosthetic valve with high or greater risk for open surgical therapy.		06/17	P140031/S028
• SAPIEN 3 Ultra THV System, a design iteration. NOTE: In August 2019, the FDA issued a recall for the Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System (Recall event ID: 83293) due to "reports of burst balloons which have resulted in significant difficulty retrieving the device into the sheath and withdrawing the system from the patient during procedures".		12/18	P140031
• Expanded to include severe aortic stenosis with low surgical risk.		08/19	P140031/S085

• Expanded to include failure of a bioprosthetic valve with high or greater risk for open surgical therapy.		09/20	P140031/S112
Medtronic CoreValve System™ • Severe native aortic stenosis at extreme risk or inoperable for open surgical therapy.	Medtronic CoreValve	01/14	P130021
• Expanded to include high risk for open surgical therapy.		06/16	P130021/S002
• Expanded to include intermediate risk for open surgical therapy.		07/17	P130021/S033
• Medtronic CoreValve Evolut R System™ (design iteration for valve and accessories).		06/15	P130021/S014
• Expanded to include intermediate risk for open surgical therapy.		07/17	P130021/S033
• Medtronic CoreValve Evolut PRO System™ (design iteration for valve and accessories, includes porcine pericardial tissue wrap).		03/17	P130021/S029
• Expanded to include intermediate risk for open surgical therapy.		07/17	P130021/S033
• Expanded to include severe aortic stenosis with low surgical risk.		08/19	P130021/S058
• Medtronic CoreValve Evolut PRO+ System™ (design iteration).		08/19	P130021/S059
• Medtronic Evolut™ FX System (design iteration).		8/21	P130021/S091
LOTUS Edge™ Valve System • Severe native aortic stenosis at high or greater risk for open surgical therapy. • See Note 3 below.	Boston Scientific Corporation	04/19	P180029
PORTICO™ with FLEXNAV™ • Severe native aortic stenosis at high or greater risk for open surgical therapy.	Abbott Medical	9/21	P190023
Navitor™ Transcatheter Aortic Valve Implantation System with FlexNav™ • Severe native aortic stenosis at high or great risk for open surgical therapy.	Abbott Medical	10/23	P190023/S016

FDA: Food and Drug Administration; PMA: pre-market approval.

NOTE 1: In January 2021, Boston Scientific Corporation announced a global, voluntary recall of all unused inventory of the LOTUS Edge™ Valve System due to complexities associated with the product delivery system. (9) There are no safety concerns for patents who have the LOTUS Edge™ Valve System currently implanted. Boston Scientific has chosen to retire the entire LOTUS product platform immediately rather than develop and reintroduce an enhanced delivery system. All related commercial, clinical, research and development, and manufacturing activities will cease.

Other transcatheter aortic valve systems are under development:

- JenaValve™ (JenaValve Technology); designed for transapical placement. The FDA granted breakthrough designation to this device system in January 2020.
- Acurate^{TM} aortic valve platform (Boston Scientific); designed for individuals with severe aortic stenosis indicated for transcatheter aortic valve replacement who are at low, intermediate, or high risk of operative mortality. The system received Conformité Européene (CE) mark approval in Europe as of 2020 but is not approved for non-investigational use in the U.S. The pivotal Acurate IDE trial will be completed in 2024 (NCT03735667).
- J-Valve™ Transfemoral System (Edwards Lifesciences; formerly JC Medical); self-expanding valve designed for transfemoral delivery in patients with severe aortic regurgitation. The FDA granted breakthrough device designation to this system in August 2023.

In June 2017, the Sentinel® Cerebral Protection System (Boston Scientific; previously Claret Medical, Inc.) was granted a de novo classification by the FDA (DEN160043; class II; product code: PUM). (10) The Sentinel system is a temporary catheter indicated for use as an embolic protection deice to capture and remove thrombus/debris while performing transcatheter aortic valve replacement procedures. The diameters of the arteries at the site of filter placement should be between 9 mm to 15 mm for the brachiocephalic and 6.5 mm to 10 mm in the left common carotid. The new classification applies to this device and substantially equivalent devices of this generic type.

On August 3, 2021, the FDA Circulatory System Devices Panel of the Medical Devices Advisory Committee met to discuss and make recommendations on the 510(k) submission for the TriGUARD 3™ Cerebral Embolic Protection Device (Keystone Heart). (11) With the Sentinel system serving as the predicate device, the panel expressed that the proposed indications for use of the TriGUARD 3 device were not supported by the safety and effectiveness data from the REFLECT II trial. Previously, the TriGUARD 3 device was granted Conformité Européene (CE) mark approval in Europe in March 2020. (11, 12)

On May 30, 2023, the FDA Office Cardiovascular Devices gave DASI simulations approval for Precision TAVI, a personalized computer simulation in the heart valve space. PrecisionTAVI is an optional, non-invasive, post processing software solution that is indicated for patient-specific simulations of Transcatheter Aortic Valve Replacement (TAVR) during procedural planning. DASI Simulations handles using the technology and then communicates the results with hospitals—reducing the need to train hospital staff and streamlining the process. (13)

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized control trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The literature evaluating transcatheter aortic valve implantation (TAVI), also known as transcatheter aortic valve replacement (TAVR), has reported on 4 main potential populations: 1) patients who are not surgical candidates, 2) patients who are at high risk for surgery but still considered to be surgical candidate, 3) patients who at intermediate risk for surgery, and 4) patients who are at low risk for surgery. This medical policy concludes with an assessment of the literature evaluating patients with valve dysfunction and aortic stenosis or regurgitation after aortic valve repair who are treated with transcatheter aortic “valve-in-valve” implantation.

Transcatheter Aortic Valve Implantation (TAVI) Outcomes in Patients at Prohibitive Risk for Open Surgery

Clinical Context and Therapy Purpose

The purpose of TAVI is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as medical management, in individuals with severe symptomatic aortic stenosis who are at prohibitive risk of open surgery.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with severe symptomatic aortic stenosis at prohibitive risk for open surgery. Many in this population are elderly and may have multiple medical comorbidities.

The U.S. FDA definition of extreme risk or inoperable for open surgery is a predicted risk of operative mortality and/or serious irreversible morbidity 50% or higher for open surgery.

Interventions
The therapy being considered is TAVI, which is performed percutaneously—most often through the transfemoral artery approach or through the subclavian artery approach. It can be performed transapically using mediastinoscopy.

Comparators
The main comparator of interest is medical management, including lipid-lowering therapy, anti-hypertensive drugs, and anti-calcific therapy.

Outcomes
The general outcomes of interest are overall survival (OS), symptoms, morbid events, treatment-related mortality, and treatment-related morbidity. Symptoms may include heart murmur, angina, dizziness or syncope, shortness of breath, fatigue, and heart palpitations. In adolescents with aortic stenosis, symptoms may also include cyanosis, poor feeding, and poor weight gain. Morbid events may include stroke, coronary obstruction, vascular complications, conduction disturbance, valve malpositioning and sizing, mitral valve injury, annular rupture, aortic dissection, myocardial trauma, low cardiac output, cardiogenic shock, and cardiac arrest.

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a tool for measuring health-related QOL. The KCCQ is self-administered, with 23-items across 5 health status domains (physical limitation, heart failure symptoms, self-efficacy, social interference, and QOL). The KCCQ summary scores range from 0 to 100 with higher scores indicating better health status. Differences of at least 5 points have been shown to be clinically important. (14)

The existing literature evaluating TAVI as a treatment for severe symptomatic aortic stenosis in individuals who are at prohibitive risk for open surgery has varying lengths of follow-up, with many following patients for 3 years after TAVI was performed.

<u>Study Selection Criteria</u>
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews

Systematic reviews assessing whether TAVI improves outcomes for patients who are not suitable candidates for open surgery consist of summaries of case series. An Agency for Healthcare Research and Quality sponsored systematic review (2010; archived) evaluated 84 publications (N=2375 patients). (4) Implantation was successful in 94% of patients overall, with higher success rates reported in more recent publications. The aggregate 30-day survival was 89% across all studies. Adverse event rates were reported in the larger case series, with an estimated 30-day rate of major cardiovascular adverse event and stroke of 8%.

A second systematic review was published by Figulla et al. (2011). (15) It included studies that enrolled symptomatic patients with severe aortic stenosis who had a mean age of 75 years or older, reported on 10 or more patients, and had a follow-up duration of 12 months or more. Twelve studies met these criteria and were compared with a group of 11 studies that treated severe aortic stenosis with nonsurgical therapy. The procedural success in these studies ranged from 86% to 100%, and the 30-day mortality ranged from 5.3% to 23%. The combined mean survival rate at 1 year was 75.9% (95% confidence interval [CI], 73.3% to 78.4%). This 1-year survival rate compared favorably with medical therapy, which was estimated to be 62.4% (95% CI, 59.3% to 65.5%).

Randomized Controlled Trials

SAPIEN and SAPIEN XT

The Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve (PARTNER) trial was a pivotal multicenter RCT of TAVI performed in the United States, Canada, and Germany, using the SAPIEN system. Leon et al. (2010) reported on trial results for patients with severe aortic stenosis who were not candidates for open surgery, referred to as the PARTNER B trial. (16) To be classified as unsuitable for open surgery, patients had to have a predicted probability of 50% or higher for death or a serious irreversible condition at 30 days post-surgery. This probability was determined by 2 surgeon investigators using clinical judgment and the Society of Thoracic Surgery (STS) Risk Score. The executive committee of the PARTNER trial reviewed all patient selection decisions and approved the classification of patients as unsuitable for surgery. A total of 3105 patients were screened for aortic valve surgery, and 12% of them were included in the cohort of patients deemed unsuitable for surgery.

A total of 358 patients were randomized to TAVI or usual care. TAVI was performed by the transfemoral approach under general anesthesia. Standard therapy was determined by treating clinicians. In most cases (83.8%), standard treatment included balloon valvuloplasty of the aortic valve. A small number of patients (6.7%) underwent open surgical valve replacement, despite the high risk, and another 2.2% of patients underwent TAVI at a center outside the United States not participating in the trial. The primary outcome was death from any cause during the trial (median follow-up, 1.6 years). A coprimary endpoint was the composite of time to death from any cause or time to repeat hospitalization related to aortic stenosis or TAVI. Secondary endpoints were cardiovascular mortality, New York Heart Association (NYHA)

functional class, the rates of hospitalizations due to aortic stenosis or TAVI, the 6-minute walk test (6MWT), valve performance as measured by echocardiography, and procedural complications (e.g., myocardial infarction [MI], stroke, acute kidney injury [AKI], vascular complications, bleeding).

The mean age of enrolled patients was 83.2 years. Some baseline imbalances in the patient population indicated that the standard therapy group might have had a higher severity of illness. Standardized scores of surgical risks were higher in the standard therapy group. The logistic EuroSCORE was significantly higher in the standard therapy group (30.4) than in the TAVI group (26.4; p=0.04), and the STS score was numerically higher but was not statistically significant (12.1 vs. 11.2, respectively; p=0.14). Significantly more patients in the standard therapy group had chronic obstructive pulmonary disease (52.5% vs. 41.3%, p=0.04) and atrial fibrillation (48.8% vs. 32.9%, p=0.04), and there was a nonsignificant trend for more patients in the standard therapy group having a lower ejection fraction (51.1% vs. 53.9%) and frailty, as determined by prespecified criteria (28.0% vs. 18.1%), all respectively.

Death from any cause at 1 year after enrollment was lower for the TAVI group (30.7% versus 49.7%, p<0.001). This represents a 19% absolute risk reduction, a 38.2% relative risk (RR) reduction, and a number needed to treat of 5.3 to prevent 1 death over a 1-year follow-up. Most secondary outcomes also favored the TAVI group. Cardiovascular death was lower in the TAVI group (19.6% vs. 44.1%, p<0.001). The composite of all-cause mortality and repeat hospitalizations was reached by 42.5% of the patients in the TAVI group compared with 70.4% in the standard therapy group. Symptoms and functional status were also superior in the TAVI group. The percentage of patients in NYHA class I or II at 1 year was higher for the TAVI group (74.8% vs. 42.0%, p<0.001), and there was a significant improvement in the 6MWT for the TAVI group but not for the standard therapy group (between-group comparisons not reported). Subgroup analysis did not report any significant differences in outcomes according to clinical and demographic factors.

Complication rates were higher for the TAVI group. Stroke or transient ischemic attack (TIA) at 1-year was more than twice as frequent for the TAVI group (10.6% vs. 4.5%; p=0.04). Major bleeding and vascular complications occurred in a substantial percentage of patients undergoing TAVI (22.3% vs. 11.2%; p=0.007) and were significantly higher than in the standard therapy group (32.4% vs. 7.3%; p<0.001).

Quality of life outcomes from this trial were reported by Reynolds et al. (2011). (17) QOL outcomes were evaluated using the KCCQ summary score, the 12-Item Short-Form Health Survey (SF-12), and the EuroQoL (EQ-5D). The number of participants who completed the QOL measures was not clearly reported; estimates from graphical representation show that between 149 and 170 patients in the TAVI group and 138 and 157 patients in the medical therapy group completed baseline QOL measures. At follow-up time points of 30 days, 6 months, and 12 months, change in the QOL scores was greater for the TAVI group. At 30 days, the mean difference in the KCCQ score was 13.3 points (95% CI, 7.6 to 19.0; p<0.001). This mean difference increased at later time points to 20.8 points (95% CI, 14.7 to 27.0; p<0.001) at

6 months and to 26.0 points (95% CI, 18.7 to 33.3; p<0.001) at 12 months. Changes in the SF-12 and EQ-5D measures showed similar patterns.

Two-year outcomes were reported from the PARTNER trial by Makkar et al. (2012). (18) Mortality at 2 years was 43.3% in the TAVI group compared with 68.0% in the medical therapy group (hazard ratio [HR], 0.58; 95% CI, 0.36 to 0.92; p=0.02). Cardiovascular mortality was also lower with TAVI (31.0%) than with medical therapy (62.4%; p<0.001). The rate of hospitalization over the 2-year period was lower with TAVI (35.0%) than with medical therapy (72.5%; p<0.001).

Svensson et al. (2014) reported detailed mortality outcomes for both arms of the PARTNER trial: the PARTNER B RCT (previously described), which compared surgical repair with TAVI in prohibitive surgical risk patients, and the PARTNER A RCT, which compared surgical repair with TAVI in high surgical risk patients (described next). (19) For the 358 patients considered inoperable and enrolled in the PARTNER B RCT, at last follow-up, 237 patients had died. Those randomized to standard therapy exhibited an early peak in mortality that was higher than those randomized to TAVI, and that persisted beyond 6 months. Compared with standard therapy, the estimated net lifetime benefit added by transfemoral TAVI was 0.50 years (90% CI, 0.30 to 0.67).

Kapadia et al. (2014) reported on 3-year outcomes for 358 prohibitive-risk patients randomized to standard therapy or TAVI in the PARTNER trial, along with all outcomes (early and long term) for randomized inoperable PARTNER patients, including 91 subjects in the randomized PARTNER continued-access study. (20) Analysis of the pooled randomized patients was anticipated in the study protocol. At the 3-year follow-up for the pivotal trial subjects, all-cause mortality was 54.1% in the TAVI group and 80.9% in the standard therapy group (HR=0.53; 95% CI, 0.41 to 0.68; p<0.001). The incidence of stroke was higher in the TAVI group (15.7%) than in the standard therapy group at 3 years (5.5%; HR=3.81; 95% CI, 1.26 to 6.26; p=0.012). However, at 3 years, the incidence of the composite of death or stroke was significantly lower in the TAVI group (57.4% vs 80.9%; HR=0.60; 95% CI, 0.46 to 0.77; p<0.001). Survivors at 3 years who had undergone TAVI were more likely to have NYHA class I or II symptoms than those who had received standard therapy. In the pooled sample, at the 2- and 3-year follow-ups, mortality was lower for patients who had undergone TAVI than in those who had standard therapy (2 years: 44.8% vs 64.3%; 3 years: 54.9% vs 78.0%; all p<0.001).

Webb et al. (2015) reported on a multicenter RCT comparing a newer-generation SAPIEN XT system with the original SAPIEN system in 560 patients with severe, symptomatic aortic stenosis considered at prohibitive risk for open surgery. (21) The trial used a noninferiority design; for its primary end point, a composite of all-cause mortality, major stroke, and rehospitalization at 1 year in the intention-to-treat population, the RR between the SAPIEN and SAPIEN XT groups was 0.99 (p<0.002), which met the criteria for noninferiority.

Kapadia et al. (2019) reported an analysis of stroke risk and its association with QOL after surgical aortic valve replacement (SAVR) versus TAVR from a propensity-matched study of 1204

pairs of patients in the PARTNER trials. (22) The analysis focused only on as-treated SAVR and transfemoral TAVI. The incidence of stroke by 30 days was 5.1% in SAVR versus 3.7% in TAVI; incidence of 30-day major stroke was 3.9% versus 2.2% (p=0.018). In both groups, risk of stroke peaked in the first post-procedure day but then remained low out to 48 months. Major stroke was associated with a decline in QOL as measured by the KCCQ at 1 year.

Huded et al. (2022) reported on rehospitalization rates from the PARTNER trial, finding no effect modification by transcatheter versus surgical aortic valve replacement (AVR). (23)

Case Series and Cohort Studies

Many case series of TAVI have been published in the last 10 years, most of which have included patients not candidates for open surgery. However, the selection process for TAVI has largely been subjective, with the expert opinion of the surgeons and/or cardiologists as the main factor determining suitability for open surgery. As a result, there may be overlap in these series with patients who are surgical candidates, but the distinction cannot be gleaned easily from the reported studies.

Some of the larger and/or prospective case series are discussed next. Included are the series reporting on the pivotal trials leading to the devices' approvals (i.e., Popma et al. [2014] [24] and Reardon et al. [2014] [25]) or on post approval registries (i.e., Mack et al. [2013] [26]).

CoreValve Extreme Risk Study

Popma et al. (2014) published results of the CoreValve Extreme Risk Study pivotal trial, which was designed to evaluate the CoreValve self-expanding valve among patients with severe aortic stenosis who were considered to be at extreme risk (NYHA class ≥II) for SAVR. (24) A patient was judged to be at extreme risk if 2 cardiac surgeons and 1 interventional cardiologist at the clinical site estimated a 50% or greater risk for mortality or irreversible morbidity at 30 days with surgical repair. The study's primary endpoint was the 12-month rate of all-cause mortality or major stroke in the "attempted implant" population. This population included all patients who underwent a documented valve implant via an iliofemoral approach. The study defined an objective performance goal of 43% for all-cause mortality or major stroke at 12 months post procedure. This goal was based on 2 sources: 1) a weighted meta-analysis of 7 balloon aortic valvuloplasty studies, which yielded a rate of 12-month all-cause mortality or major stroke of 42.7% (95% CI, 34.0 to 51.4); and 2) an adjusted estimate based on the lower 95% confidence bound of 43% in the standard therapy arm of inoperable patients in the PARTNER trial.

Four hundred eighty-nine patients were included in the attempted implant analysis population of 506 patients recruited (11 of whom exited the study before treatment, 6 of whom did not complete the procedure with iliofemoral access). The Kaplan-Meier estimate of the primary endpoint (all-cause mortality or major stroke) was 26.0% (upper bound of 95% CI, 29.9%), which was lower than the prespecified performance goal of 43% (p<0.001). The rate of all-cause mortality at 1year following enrollment was 24.3%, while the rate of major stroke at 12 months was 4.3%. These rates are comparable or better than those seen in the TAVI arm of

the PARTNER pivotal trial, although patients in the PARTNER pivotal trial had a higher baseline STS score (12.1% in the PARTNER trial vs. 10.3% in the CoreValve Extreme Risk trial).

Two-year results from the CoreValve study were reported by Yakubov et al. (2015). (27) The Kaplan-Meier estimate of all-cause mortality or major stroke was 38.0% (upper bound of 95% CI, 42.6%). The incremental rates between years 1 and 2 were 12.3% for all-cause mortality, 7.9% for cardiovascular mortality, and 0.8% for stroke. Baron et al. (2017) reported on 3-year results of the QOL data. The QOL improvements following TAVR were largely sustained through 3 years with clinically meaningful (≥10 points) improvements in the KCCQ overall summary score at 3 years observed in greater than 83.0%. (28) At 5 years of follow-up, the Kaplan-Meier rate of death or major stroke was 72.6%, and the KCCQ remained improved compared with pre-TAVI scores. (29)

Osnabrugge et al. (2015) reported on health status outcomes for the 471 patients who underwent TAVI via the transfemoral approach. (30) On average, general and disease-specific QOL scores both showed substantial improvements after TAVI. However, 39% of patients had a poor outcome at 6 months (22% death, 16% very poor QOL, 1.4% QOL declined).

Reardon et al. (2014) reported on outcomes for the group of patients enrolled in the CoreValve study who received the device through an approach other than the iliofemoral. (25) Inclusion criteria and procedures were the same as for the primary CoreValve Extreme Risk Trial. One hundred fifty patients with prohibitive iliofemoral anatomy were included and received the CoreValve device through an open surgical approach via the subclavian artery (n=70) or a direct aortic approach via a median hemisternotomy or right thoracotomy (n=80). Included patients were elderly (mean age, 81.3 years) and significantly symptomatic, with 92% of subjects having NYHA class III or IV heart disease. At 30 days post procedure, 23 (15.3%) patients met the primary endpoint of all-cause mortality or major stroke; of the 23 patients, 17 (11.3%) died, and 11 (7.5%) experienced a major stroke. At 12 months post procedure, 59 (39.4%) patients met the primary endpoint; of those, 54 (36%) died, and 13 (9.1%) experienced a major stroke. The 30-day mortality of 11.3% was higher than that reported in the studies of TAVI using a transfemoral or an iliofemoral approach (PARTNER B RCT and the CoreValve Extreme Risk Pivotal Trial) but similar to the 30-day mortality reported by the patients treated with a transapical approach (PARTNER A trial).

Postapproval Registries

Mack et al. (2013) reported on outcomes after TAVI from 224 hospitals participating in the Edwards SAPIEN device post-FDA approval registry. (26) From November 2011 to May 2013, the registry included 7710 patients who underwent TAVI placement, of whom 1559 (20%) patients were considered inoperable and 6151 (80%) were considered high risk but operable. Of those considered inoperable, 1139 underwent device placement via transfemoral access, while 420 underwent device placement via nontransfemoral access. In-hospital mortality was 5.4% and 7.1% for the inoperable patients who underwent TAVI via transfemoral and nontransfemoral access, respectively. Thirty-day clinical outcomes were reported for 694 inoperable patients; of

those, 30-day mortality was 6.7% and 12.6% for patients who underwent TAVI via transfemoral and nontransfemoral access, respectively.

Additional Case Series

The prospective nonrandomized Treatment of Aortic Stenosis with a Self-Expanding Transcatheter Valve: The International Multi-Centre ADVANCE study had central adjudication of endpoints and adverse events to evaluate the CoreValve implants in individuals with severe symptomatic aortic stenosis who were considered inoperable or at higher risk for SAVR. (31) The study enrolled 1015 patients, of whom 996 were implanted, most (88.4%) by the iliofemoral approach, with 9.5% and 2.1% by the subclavian and direct aortic approaches, respectively. For the study's primary endpoint of major adverse cardiac and cerebrovascular events (MACCE; a composite of all-cause mortality, MI, stroke, or reintervention), rates were 8.0% (95% CI, 6.3% to 9.7%) at 30 days and 21.2% (95% CI, 18.4% to 24.1%) at 12 months. The all-cause mortality rate was 4.5% (95% CI, 3.2% to 5.8%) at 30 days and 17.9% (95% CI, 15.2% to 20.5%) at 12 months. Overall, strokes occurred in 3.0% (95% CI, 2.0% to 4.1%) at 30 days and in 4.5% (95% CI, 2.9% to 6.1%) at 12 months. A new permanent pacemaker was implanted in 26.3% (95% CI, 23.5% to 29.1%) and in 29.2% (95% CI, 25.6% to 32.7%) of patients at 30-day and 12-month follow-ups, respectively. Patients were grouped into 3 categories of surgical risk based on logistic EuroSCORE values (≤10%, >10% but ≤20%, and >20%). Thirty-day survival did not differ significantly across risk groups, but 12-month rates of MACCE, all-cause mortality, cardiovascular mortality, and death from any cause or major stroke were higher for higher surgical risk patients.

The 2 largest series included in the Agency for Healthcare Research and Quality review (4) (described previously) reported on 646 patients treated with the CoreValve (32) and 339 patients treated with the SAPIEN valve. (33) The CoreValve study by Piazza et al. (2008) was notable in that it used more objective patient selection criteria than is common in this literature. Their criteria for eligibility included: 1) logistic EuroSCORE of 15% or higher, 2) age of 75 or older, or 3) age of 65 or older with liver cirrhosis, pulmonary insufficiency, pulmonary hypertension, previous cardiac surgery, porcelain aorta, recurrent pulmonary emboli, right ventricular insufficiency, previous chest burns, or radiation precluding open surgery, or body mass index of 18 kg/m^2 or less. Procedural success was 97%, and 30-day survival was 92%. The 30-day combined rate of death, MI, or stroke was 9.3%. The Canadian study by Rodes-Cabau et al. (2010) used the SAPIEN valve. This study had subjective inclusion criteria, relying on the judgment of the participating surgeons to determine eligibility for TAVI. The procedural success rate was 93.3%, and the 30-day mortality was 10.4%. The authors also reported a mortality rate of 22.1% at a median follow-up of 8 months.

Additional series have described experiences with TAVI in European centers. Zahn et al. (2011), in a large case series from Germany, reported on 697 patients treated with the CoreValve system. (34) Procedural success was 98.4%, and 30-day mortality was 12.4%. Another large case series (2011) from Italy included 663 patients treated with the CoreValve device. (35) Procedural success was 98%, and mortality at 1 year was 15%.

Section Summary: TAVI Outcomes in Patients at Prohibitive Risk for Open Surgery

Numerous case series have demonstrated the feasibility and short-term efficacy for TAVI in patients who are not surgical candidates. In the PARTNER B trial, there was a large decrease in all-cause mortality and cardiovascular mortality at 1 year for TAVI compared with standard therapy. Subsequent publications from this same trial reported that the mortality benefit was maintained at 2 years and that QOL was improved for the TAVI group. Baseline between-group differences were present, indicating that the TAVI group may have been healthier. While these differences are unlikely to account for the degree of mortality benefit reported, they may have resulted in an overestimation of the mortality benefit. The CoreValve Extreme Risk Study pivotal trial also demonstrated mortality rates much lower than the prespecified performance goal and comparable or better than those seen in the TAVI arm of the PARTNER pivotal trial.

The benefit in mortality was accompanied by an increased stroke risk as well as substantial increases in vascular complications and major bleeding. There is also uncertainty concerning the generalizability of these results because patient selection was primarily determined by the cardiovascular surgeons and/or cardiologists. It is not known whether this type of decision making is reliable across the range of practicing clinicians.

Transcatheter Aortic Valve Implantation (TAVI) Outcomes in Patients at High Risk for Open Surgery

Clinical Context and Therapy Purpose

The purpose of TAVI is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as surgical aortic valve repair, in individuals with severe symptomatic aortic stenosis who are at high risk of open surgery.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with severe symptomatic aortic stenosis at high risk for open surgery. Many in this population are elderly and may have multiple medical comorbidities.

The STS maintains an online calculator for risk stratification models for hospital mortality following cardiac surgery. The FDA definition of high risk for open surgery is an STS predicted operative risk score of 8% or higher or judged by a heart team, which includes an experienced cardiac surgeon and a cardiologist, to have an expected mortality risk of 15% or higher for open surgery. The FDA definition of intermediate risk is STS predicted operative risk score of 3% to 7%. In the PARTNER 3 trial, low-risk was defined as STS predicted operative risk score of less than 4%.

Interventions

The therapy being considered is TAVI, which is performed percutaneously—most often through the transfemoral artery approach or through the subclavian artery approach. It can be performed transapically using mediastinoscopy.

Comparators
The main comparator of interest is surgical aortic valve repair, which is performed through sternotomy. The decision to repair a damaged aortic valve depends on severity of the symptomatic aortic stenosis and individual age and overall health.

Outcomes
The general outcomes of interest are OS, symptoms, morbid events, treatment-related mortality, and treatment-related morbidity. Symptoms and morbid events are detailed in the first PICO above.

The KCCQ is a tool for measuring health-related QOL. The KCCQ is self-administered, with 23-items across 5 health status domains (physical limitation, heart failure symptoms, self-efficacy, social interference, and QOL). The KCCQ summary scores range from 0 to 100 with higher scores indicating better health status. Differences of at least 5 points have been shown to be clinically important. (14)

The existing literature evaluating TAVI as a treatment for severe symptomatic aortic stenosis in individuals who are at high risk for open surgery has varying lengths of follow-up, with many following patients for 5 years or more after TAVI was performed.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
A meta-analysis of 4 RCTs was published by Panoulas et al. (2018) to determine whether sex differences had any impact on mortality rates for TAVI and SAVR. (36) The 4 RCTs comprised of 3758 patients (2052 men, 1706 women); all patients had severe aortic stenosis. The study revealed that among women undergoing TAVI, a significantly lower mortality rate was found than in women undergoing SAVR at the 1-year mark; in fact, women undergoing TAVI were found to have a 31% lower mortality rate than women undergoing SAVR, again at the 1-year mark (odds ratio, 0.68; 95% CI, 0.50 to 0.94). There was no statistical difference in mortality in men undergoing TAVR versus men undergoing SAVR. An updated meta-analysis by Dagan et al. (2021) identified 8 RCTs including 8040 patients (41.4% female). Similar results were found to the 2018 analysis with lower 1-year mortality and improved safety with TAVI compared with SAVR in women. (37)

Villablanca et al. (2016) reported on a meta-analysis and meta-regression of long-term outcomes (>1 year) of TAVI compared with SAVR for severe aortic stenosis. (38) Trial methods were described in the meta-analysis protocol, which was registered with PROSPERO. (38) The review was limited to studies comparing TAVI with surgical repair, with subgroup analyses for high- and intermediate risk patients. Overall, 4 RCTs (n=3806 patients) and 46 observational studies (n=40,441 patients) were included, with a median follow-up of 21.4 months. Two of the RCTs were conducted in high-risk patients and are described in detail below (PARTNER 1 [39] and the CoreValve High Risk Trial [40]). Results from the subgroup analyses focused on high-risk patients are shown in Table 2.

Table 2. Transcatheter Aortic Valve Implantation (TAVI) Versus Surgical Repair in High-Risk Patients

Outcomes	TAVI[a]	Surgical Repair[a]	RR for TAVI vs Surgical Repair (95% CI)	I^2, %
30-day post-procedure mortality	508/8552 (5.9%)	804/29,323 (2.7%)	1.02 (0.76 to 1.36)	72.3
All-cause mortality	3625/8803 (41.1%)	5438/29,450 (18.6%)	1.16 (0.87 to 1.53)	96.6
Stroke incidence	191/4293 (4.4%)	213/4348 (4.9%)	0.79 (0.66 to 0.95)	0
Myocardial infarction incidence	57/2820 (2.0%)	59/2746 (2.1%)	0.91 (0.64 to 1.29)	21.5
Vascular complication incidence	203/2489 (8.2%)	35/2682 (1.3%)	5.5 (2.42 to 12.4)	67.5
Residual regurgitation incidence	268/2831 (9.5%)	36/2823 (1.3%)	6.3 (4.55 to 8.71)	0
Requirement for permanent pacemaker incidence	527/3449 (15.3%)	236/3653 (6.4%)	1.68 (0.94 to 3.00)	83.2
New-onset AF incidence	165/1192 (13.8%)	376/1281 (29.4%	0.38 (0.26 to 0.55)	64.6
Major bleeding incidence	321/2074 (15.4%)	416/2298 (18.1%)	0.73 (0.65 to 0.83)	24.2
Acute kidney injury incidence	294/3446 (8.5%)	396/3528 (11.2%)	0.73 (0.53 to 1.01)	68.4

Adapted from Villablanca et al. (2016). (38)
AF: atrial fibrillation; CI: confidence interval; RR: relative risk; TAVI: transcatheter aortic valve implantation.
[a] Values are n/N (%).

Earlier systematic reviews focused largely on nonrandomized comparative studies because only 1 RCT had been published at the time of the reviews (the PARTNER trial). Panchal et al. (2013)

reported on results from a meta-analysis of 17 studies that included 4659 patients, 2267 treated with TAVI, and 2392 treated with open surgery. (41) Patients in the TAVI group were more severely ill, as evidenced by a EuroSCORE for predicted 30-day mortality, which was higher by a mean of 3.7 points compared with patients undergoing open surgery. On combined analysis, there were no differences between groups for 30-day mortality, mortality at longest follow-up, cardiovascular mortality, MI, stroke, or TIA. Patients in the open surgery group had a higher incidence of major bleeding complications (RR=1.42; 95% CI, 1.20 to 1.67; p<0.001). In a similar meta-analysis (2013) that included 17 studies reporting on 4873 patients, there were no differences between TAVI and open surgery in early mortality (OR=0.92; 95% CI, 0.70 to 1.2) or mid-term mortality, defined as between 3 months and 3 years (HR=0.99; 95% CI, 0.83 to 1.2). (42)

Randomized Controlled Trials

SAPIEN PARTNER A Trial

Smith et al. (2011) published results from the cohort of patients in the PARTNER trial of the SAPIEN valve who were at high risk for open surgery, but still suitable candidates. (43) The inclusion and exclusion criteria were generally the same as those for the prior cohort, except that these patients were classified as high risk for surgery rather than unsuitable for surgery. For high risk, patients had to have a predicted perioperative mortality of 15% or higher, as determined by a cardiac surgeon and cardiologist using clinical judgment. An STS Risk Score of 10 or higher was included as a guide for high risk, but an STS Risk Score threshold was not a required criterion for enrollment. The executive committee of the PARTNER trial reviewed all patient selection decisions and approved the classification of patients as high risk for surgery. A total of 3105 patients were screened for aortic valve surgery, and 22.5% of them were included in the cohort of patients deemed high risk for surgery.

A total of 699 patients were randomized to TAVI or surgical aortic valve repair. The primary hypothesis was that TAVI was noninferior to open AVR, using a one-sided noninferiority boundary of 7.5% absolute difference in mortality at one year. Patients were first evaluated to determine if they were eligible for TAVI via the transfemoral approach. Four hundred ninety-two patients were eligible for transfemoral TAVI; the remaining 207 were categorized as the transapical placement cohort. Within each cohort (transfemoral and transapical), patients were randomized to surgical aortic valve repair (n=351) or TAVI (n=348).

The primary outcome was death from any cause at one-year follow-up. A second powered endpoint was noninferiority at one year for patients undergoing TAVI by the transfemoral approach. Secondary end points were cardiovascular mortality, NYHA functional class, rehospitalizations, 6MWT, valve performance as measured by echocardiography, and procedural complications (MI, stroke, AKI, vascular complications, bleeding). Mean age of enrolled patients was 83.6 years in the TAVI group and 84.5 years in the open AVR group. Other baseline demographics and clinical characteristics were generally well-balanced, except for a trend toward an increased percentage of patients in the TAVI group with a creatinine level greater than 2.0 mg/dL (11.1% vs 7.0%, p=0.06).

Death from any cause at 1 year following enrollment was 24.2% for the TAVI group and 26.8% for the open AVR group (between-group difference, p=0.44). The upper limit of the 95% CI for the between-group difference was a 3.0% excess mortality in the TAVI group, which was well within the noninferiority boundary of 7.5%. Thus, the criterion of noninferiority was met (p=0.001). For the subgroup of patients who underwent TAVI by the transfemoral approach, results were similar, with 22.2% mortality in the TAVI group and 26.4% mortality in the open AVR group (p=0.002 for noninferiority). The secondary outcomes of cardiovascular mortality (14.3% vs 13.0%; p=0.63) and rehospitalizations (18.2% vs 15.5%; p=0.38) did not differ significantly between the TAVI and the open AVR groups, respectively. The percentage of patients in NYHA class I or II at 1 year was similar between groups at 1 year, as was an improvement on the 6MWT. On subgroup analysis, there was a significant effect for sex, with women deriving greater benefit than men (p=0.045), and a significant effect for prior coronary artery bypass graft, with patients who had not had prior coronary artery bypass graft deriving greater benefit in the TAVI group.

Certain complication rates showed significant differences between groups. Stroke or TIA at 1 year was higher for the TAVI group (8.3% vs 4.3%, respectively; p=0.04). Vascular complications occurred in 18.0% of patients undergoing TAVI compared with 4.8% in the open AVR group (p=0.01), and major vascular complications were also higher in the TAVI group (11.3% vs 3.5%, p=0.01). On the other hand, major bleeding was more common in the open group (25.7%) compared with the TAVI group (14.7%; p=0.01).

Five-year results from the PARTNER trial were reported by Mack et al. (2015). (39) At 5-year follow-up, in the intention-to-treat population, the risk of death from any cause did not differ significantly between patients treated with TAVI (67.8%) and those treated with surgical repair (62.4%; HR=1.04; 95% CI, 0.86 to 1.24; p=0.76). As reported in the original PARTNER trial findings, moderate or severe aortic regurgitation - primarily paravalvular regurgitation - was more common among TAVI-treated patients. Among TAVI-treated patients, the presence of aortic regurgitation was associated with increased 5-year mortality risk (72.4% for moderate or severe aortic regurgitation vs 56.6% for mild aortic regurgitation or less; p=0.003).

Reynolds et al. (2012) published QOL results from the PARTNER A trial. (44) QOL outcomes were evaluated using the KCCQ summary score, the SF-12, and the EQ-5D. Of 699 patients in the trial, 628 completed baseline QOL measures. Patients in both the TAVI group and the SAVR group demonstrated significant improvements in all QOL measures over the 12 months following treatment. The TAVI group had superior improvement at 1 month on the KCCQ (mean difference, 9.9; 95% CI, 4.9 to 14.9; p<0.001), but this difference was no longer present at 6 or 12 months. A similar pattern of results was reported for the SF-12 and EQ-5D measures.

Genereux et al. (2014) published a follow-up study from the PARTNER A trial reporting on bleeding complications. (45) Using an as-treated approach, this analysis included 313 patients treated with surgical repair, 240 patients treated with transfemoral TAVI, and 104 patients treated with transapical TAVI. Seventy-one (22.7%) patients treated with surgery had major

bleeding complications within 30 days of the procedure, compared with 27 (11.3%) of those treated with transfemoral TAVI and 9 (8.8%) of those treated with transapical TAVI (p<0.001).

U.S. CoreValve High Risk Study

Adams et al. (2014) published results of the U.S. CoreValve High Risk Study. (46) This RCT compared SAVR with TAVI using the CoreValve device in patients who had severe aortic stenosis and were considered at increased risk of death during surgery. The study randomized 795 patients in a 1:1 ratio to TAVI or open AVR. Patients were considered to be at "increased surgical risk" if 2 cardiac surgeons and 1 interventional cardiologist estimated that the risk of death within 30 days of surgery was 15% or more and that the risk of death or irreversible complications within 30 days after surgery was less than 50%. The primary analysis was based on the as-treated population, which included all patients who underwent attempted implantation. For the study's primary outcome, the rate of death from any cause at 1 year was lower in the TAVI group (14.2%) than in the surgical group (19.1%; absolute risk reduction, 4.9%; upper boundary of 95% CI, -0.4%, which was less than the predefined noninferiority margin of 7.5%-point difference between groups; noninferiority, p<0.001; superiority, p=0.04). Major vascular complications and permanent pacemaker implantations were significantly more frequent in the TAVI group than in the surgical group: at 30 days, major vascular complications occurred in 5.9% of the TAVI group compared with 1.7% of the surgical group (p=0.003), while permanent pacemaker implantation was required in 19.8% of the TAVI group compared with 7.1% of the surgical group (p<0.001). In contrast to the PARTNER trial, the TAVI group did not have a higher rate of any stroke at 1-year postprocedure (8.8%) than the surgical group (12.6%; p=0.10).

Two-year follow-up results from the U.S. CoreValve High Risk Study were published in 2015 by Reardon et al. (2015). (40) At that point, the mortality benefits seen with TAVI were maintained.

A 3-year follow-up analysis was reported by Deeb et al. (2016), which found sustained improvements in the TAVI-treated group for all-cause mortality, stroke, and MACCE compared with the surgical group. (47) At 3 years, 37.3% (n=142) of TAVI-treated patients experienced all-cause mortality or stroke, which was significantly less than the 46.7% (n=160) of surgical patients for the same outcome (p=0.006). In the TAVI group, MACCE was observed in 40.2% (n=153) of patients; in the surgical group, MACCE occurred in 47.9% (n=164) of patients (p=0.025). Other outcomes that were improved in the TAVI group compared with surgery were life-threatening or disabling bleeding, AKI, aortic valve area, and mean aortic valve gradient. More TAVI-treated patients required implantation of a pacemaker (28.0%) than did surgical patients (14.5%; p<0.001); also, more patients in the TAVI group (6.8%) had moderate atrial regurgitation than in the surgery group (0.0%) at 3 years. The authors noted the improvement in mean aortic valve gradient for both cohorts (TAVR, 7.62 mm Hg vs SAVR, 11.40 mm Hg; p<0.001).

Additional analyses of the U.S. CoreValve High Risk Study have focused on the impact of patient and prosthesis mismatch (48) and health status. (49)

Conte et al. (2017) analyzed both periprocedural and early complications (0-3 days and 4-30 days postoperative, respectively) in patients from the U.S. CoreValve High Risk Study. (50) There were no statistically significant differences in all-cause mortality, stroke, MI, or major infection in either the periprocedural period (0-3 days) or between 4- and 30-days post procedure. The major vascular complication rate within 3 days was significantly higher with TAVR (6.4% vs. 1.4%, p=0.003). Life-threatening or disabling bleeding (12.0% vs. 34.0%, p<0.001), encephalopathy (7.2% vs. 12.3%, p=0.02), atrial fibrillation (8.4% vs. 18.7% p<0.001), and AKI (6.1% vs. 15.0%, p<0.001) were significantly higher with SAVR.

Gleason et al. (2019) reported 5-year follow-up of the CoreValve High Risk Trial and estimated similar 5-year survival (55.3% for TAVR vs. 55.4% for SAVR) and stroke rates (12.3% for TAVR versus 13.2% for SAVR) in high-risk patients. Valve reinterventions were uncommon; freedom from valve reintervention was 97.0% for TAVR and 98.9% for SAVR. (51)

Portico Investigational device exemption (IDE)
The Portico Re-sheathable Transcatheter Aortic Valve System U.S. Investigational Device Exemption (PORTICO IDE) trial enrolled patients with severe aortic stenosis at high or extreme surgical risk. (52) Patients were randomized to a Portico valve (n=381) or another FDA-approved valve (n=369). The primary efficacy endpoint was a composite of all-cause mortality and stroke at 1 year, and the primary safety endpoint was a composite of all-cause mortality, disabling stroke, life-threatening bleeding, AKI, or major vascular complications. Overall, the mean age was 83 years with females comprising 52.7% of patients. Additional demographic characteristics were not reported. The primary efficacy endpoint at 1 year was similar between groups (14.8% in the Portico group vs. 13.4% with other valves; absolute difference 1.5%; 95% CI, -3.6 to 6.5). For the composite safety endpoint at 30 days, the event rate was higher with the Portico valve (13.8% vs. 9.6%; absolute difference 4.2%; 95% CI, -0.4 to 8.8). At 2 years, the rates of death or disabling stroke were similar between groups.

Nonrandomized Comparative Studies
Since the publication of the pivotal RCTs and systematic reviews described previously, a number of nonrandomized studies have compared surgical with transcatheter aortic valve repair. (53-55) Given the availability of RCT evidence, these studies provide limited additional information on the efficacy of TAVI.

Section Summary: TAVI Outcomes in Patients at High Risk for Open Surgery
The most direct evidence related to the use of TAVI compared to SAVR for aortic stenosis in patients who are at high but not prohibitive risk of surgery comes from 2 industry-sponsored RCTs. The PARTNER RCT in high-risk patients who were eligible for SAVR reported no differences between TAVI and open AVR in terms of mortality at 1 year and most major secondary outcomes. The noninferiority boundaries for this trial included an upper limit of 7.5% absolute increase in mortality. The reported mortality for the TAVI group was lower than that for the open group, although not significantly better. QOL was also similar at 1 year between the TAVI and AVR groups. Stroke and TIA were significantly more common for the TAVI group,

occurring at a rate of almost 2 times that reported for open surgery. Other secondary outcomes were similar between groups, except for higher rates of vascular complications in the TAVI group and higher rates of major bleeding in the open surgery group. As in the first PARTNER cohort, there is concern about the generalizability of results because the patient selection process relied largely on the judgment of surgeons and cardiologists participating in the trial. The U.S. CoreValve High Risk Study reported that TAVI was noninferior to open surgical repair. Although unlike the PARTNER A RCT, stroke rates were not higher in patients who underwent TAVI, a requirement for permanent pacemaker was more common in the TAVI group. Follow-up analyses of the U.S. CoreValve High Risk Study showed sustained improvements in the TAVI group for the outcome of all-cause mortality and a number of secondary outcomes. The incidence of pacemaker implantation continued to be higher in TAVI-treated patients.

The Portico valve was compared with other FDA-approved valves. Although more safety events were noted at 30 days, the valves had comparable outcomes at 2 years.

Transcatheter Aortic Valve Implantation (TAVI) Outcomes in Patients at Intermediate Risk or Low Risk for Open Surgery

Clinical Context and Therapy Purpose

The purpose of TAVI is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as surgical aortic valve repair, in individuals with severe symptomatic aortic stenosis who are at intermediate or low risk of open surgery.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with severe symptomatic aortic stenosis at intermediate or low risk for open surgery.

The STS maintains an online calculator for risk stratification models for hospital mortality following cardiac surgery. The FDA definition of high risk for open surgery is an STS predicted operative risk score of 8% or higher or judged by a heart team, which includes an experienced cardiac surgeon and a cardiologist, to have an expected mortality risk of 15% or higher for open surgery. The FDA definition of intermediate risk is STS predicted operative risk score of 3% to 7%. In the Study to Establish the Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low-Risk Patients Who Have Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement (PARTNER 3) trial, low risk was defined as STS predicted operative risk score of less than 4%.

Interventions

The therapy being considered is TAVI, which is performed percutaneously—most often through the transfemoral artery approach or through the subclavian artery approach. It can be performed transapically using mediastinoscopy.

Comparators

The main comparator of interest is surgical aortic valve repair, which is performed through sternotomy. The decision to repair a damaged aortic valve depends on severity of the symptomatic aortic stenosis and individual age and overall health.

Outcomes
The general outcomes of interest are OS, symptoms, morbid events, treatment-related mortality, and treatment-related morbidity. Symptoms and morbid events are detailed in the first PICO above.

The KCCQ is a tool for measuring health related QOL. The KCCQ is self-administered, with 23-items across 5 health status domains (physical limitation, heart failure symptoms, self-efficacy, social interference, and QOL). The KCCQ summary scores range from 0 to 100 with higher scores indicating better health status. Differences of at least 5 points have been shown to be clinically important. (14)

The existing literature evaluating TAVI as a treatment for severe symptomatic aortic stenosis in individuals who are at intermediate- or low risk for open surgery has varying lengths of follow-up, with many following patients for 2 years or more after TAVI was performed.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Early research on TAVI focused on its use as an alternative to open surgery in patients with at least a high-risk of surgery. Recent RCTs have evaluated the use of TAVI in patients at lower risk of open surgery. We discuss the intermediate- and low-risk groups as is consistent with the literature but summarize the efficacy of TAVI for both populations separately below.

Systematic Reviews
Several systematic reviews and meta-analyses were published in 2017 through 2023, (56-74) including many overlapping RCTs and observational studies.

In a Cochrane review, Kolkailah et al. (2019) evaluated the literature on TAVI versus SAVR for severe aortic stenosis in patients with low surgical risk. (75) The review included 4 studies (N=2818) and 1 ongoing study. Results revealed that there is probably little or no difference between TAVI and SAVR with regard to the following short-term outcomes: all-cause mortality (RR=0.69; 95% CI, 0.33 to 1.44), stroke (RR=0.73; 95% CI, 0.42 to 1.25), myocardial infarction (RR=0.82; 95% CI, 0.42 to 1.58), and cardiac death (RR=0.71; 95% CI, 0.32 to 1.56). TAVI may

potentially reduce the risk of short-term hospitalization as well (RR=0.64; 95% CI, 0.39 to 1.06) and result in an increased risk of permanent pacemaker implantation (RR=3.65; 95% CI, 1.50 to 8.87). TAVI reduces the risk of atrial fibrillation (RR=0.21; 95% CI, 0.15 to 0.3), AKI (RR=0.3; 95% CI, 0.16 to 0.58), and bleeding (RR=0.31; 95% CI, 0.16 to 0.62) compared to SAVR.

Garg et al. (2017) published a systematic review and meta-analyses that included RCTs and prospective observational studies comparing TAVI with SAVR published between January 2000 and March 2017 including low-to-intermediate surgical risk patients with severe aortic stenosis. (58) Five RCTs (n=4425 patients) were included and are discussed in the following section. The meta-analytic results pooling the RCTs are shown in Table 3.

Table 3. Transcatheter Aortic Valve Implantation (TAVI) versus Surgical Repair in Low- or Intermediate Risk Patients

Outcomes	TAVI	Surgical Repair	RR for TAVI vs Surgical Repair (95% CI)	p	I^2
30-day mortality	3.1	3.0	1.04 (0.73 to 1.47)	0.84	0
Stroke incidence	7.3	8.1	0.91 (0.74 to 1.11)	0.35	0
Acute kidney injury incidence	1.8	4.7	0.38 (0.26 to 0.54)	<0.001	0
Myocardial infarction incidence	3.1	3.1	1.00 (0.71 to 1.41)	1.00	0
Major vascular complication incidence	7.3	3.2	3.09 (1.51 to 6.35)	0.002	66
Requirement for permanent pacemaker incidence	20.0	7.9	3.10 (1.44 to 6.66)	0.004	92

Adapted from Garg (2017). (58)
Values are percent unless other noted.
CI: confidence interval; RR: relative risk; TAVI: transcatheter aortic valve implantation.

Zhou et al. (2016) reported on a meta-analysis comparing TAVI with surgical repair in patients at low or intermediate risk of open surgery. (76) Seven studies were included, 3 RCTs (NOTION [2015], [77] STACCATO [2012], [78] Leon et al. [2016] [79]), and 4 observational studies (total N=6214 patients; n=3172 [51.0%] treated with TAVI). The main meta-analytic results are summarized in Table 4. Importantly, this review included a meta-analytic result for mortality at 1 year.

Table 4. Transcatheter Aortic Valve Implantation (TAVI) Versus Surgical Repair in Low- or Intermediate Risk Patients

Outcomes	TAVI	Surgical Repair	OR for TAVI vs Surgical Repair (95% CI)	p	I^2
Short-term postprocedure mortality	2.59	3.94	0.63(0.37 to 1.08)	0.09	56
Short-term cardiovascular mortality	1.96	3.15	0.51 (0.23 to 1.15)	0.11	68

Acute kidney injury incidence	1.92	4.8	0.34 (0.17 to 0.67)	0.002	61
Stroke incidence	3.57	4.90	0.72 (0.56 to 0.92	0.01	42
Myocardial infarction incidence	0.7	1.7	0.51 (0.23 to 0.69)	<0.001	10
Major vascular complication incidence	7.2	3.6	3.54 (1.42 to 8.81)	0.006	86
Requirement for permanent pacemaker incidence	11.9	6.1	2.79 (1.49 to 5.23)	0.001	88
All-cause mortality (1 year)	10.1	12.2	0.82 (0.58 to 1.16)	0.26	67

Adapted from Zhou et al. (2016). (76)
Values are percent unless other noted.
CI: confidence interval; OR: odds ratio; TAVI: transcatheter aortic valve implantation.

Earlier systematic reviews came to similar conclusions. (80, 81) In 2016, Siemieniuk et al. also reported on a systematic review and meta-analysis comparing TAVI with surgical repair in patients at low or intermediate risk of open surgery, with the aim of evaluating valve durability and need for reinterventions. (82) Overall, the results suggest that for intermediate and low operative risk patients, periprocedural and short-term (1-year) mortality rates do not differ significantly between TAVI and open aortic valve repair. However, similar to the high- and prohibitive-risk populations, TAVI is associated with higher rates of major vascular complications, paravalvular regurgitation, and need for permanent pacemakers, but lower rates of major bleeding.

Randomized Controlled Trials

Eight RCTs including patients with severe aortic stenosis who were at low and/or intermediate risk for open surgery have been published. The RCTs are summarized in Tables 5a, 5b and 6 and the following paragraphs.

Table 5a. Characteristics of RCTs Comparing Transcatheter Aortic Valve Implantation (TAVI) With Surgical Aortic Valve Replacement (SAVR) in Patients at Low and Intermediate Surgical Risk

Study; Trial; Sponsor	Countries	Sites	Dates	Participants
Nielsen et al. (2012) (78); STACATTO Sponsored by Participating hospitals and Danish Heart Foundation	Denmark	2	Nov 2008-May 2011	• Mean age, 81 y • No significant coronary artery disease • Any surgical risk (mean STS PROM, 3.3)
Thyregod et al. (2015) (77); Søndergaard et al. (2016) (83); Thyregod et al. (2019) (84); Søndergaard et al.	Denmark, Sweden	3	Dec 2009-Apr 2013	• Mean age, 79 y • No significant coronary artery disease • Any surgical risk (mean STS PROM, 3.0; 82% low risk)

(2019) (85) NOTION (NCT01057173) Sponsored by Danish Heart Foundation				
Reardon et al. (2016) (86); CoreValv8e U.S. Pivotal (NCT01240902) Sponsored by Manufacturer	U.S.	45	Feb 2011-Sept 2012	• Mean age, 81 y • STS score <7a (median, 5.3) • Symptomatic class ≥II)
Leon et al. (2016) (79); PARTNER 2A (NCT01314313) Sponsored by Manufacturer	U.S., Canada	57	Dec 2011-Nov 2013	• Mean age, 82 y • Symptomatic (NYHA class ≥II) • STS PROM ≥4 and ≤8 or • STS PROM <4 with coexisting conditions (mean, 5.8)
Reardon et al. (2017) (87); Van Mieghem et al. (2022) (88) SURTAVI (NCT01586910) Sponsored by Manufacturer	U.S., Spain, Netherlands, Germany, UK, Canada, Switzerland, Sweden	87	NR	• Mean age, 80 y • STS PROM ≥4 and <15 (mean, 4.5) • Symptomatic class ≥II)
Popma et al. (2019) (89); Forrest et al. (2022) (90); Forrest et al. (2023) (91) Evolut Low Risk Trial (NCT02701283) Sponsored by Manufacturer	Australia, Canada, France, Japan, Netherlands, New Zealand, U.S.	86	Mar 2016-Nov 2018	• Mean age, 74 y • STS PROM ≤ 3 (mean, 1.9) • 90% NYHA class ≥ II (symptomatic); 10 NYHA class I (asymptomatic)
Mack et al. (2019) (92); Leon et al. (2021) (93); PARTNER 3 (NCT02675114) Sponsored by Manufacturer	U.S., Canada, Australia, New Zealand, Japan	71	Mar 2016-Oct 2017	• Mean age, 73 y • STS PROM <4 (mean, 1.9) • 28% NYHA III or IV
Toff et al. (2022) (94); UK TAVI (ISRCTN 57819173) Sponsored by NIHR HTA Programme; University of Leicester	UK	34	Apr 2014 to Apr 2018	• Mean age, 81 y • Median STS PROM 2.7[b] ○ 43% NYHA III or IV

Jørgensen et al. (2024); (95) NOTION 2 (NCT02825134)	Denmark, Norway, Sweden, Finland, and Iceland	9	June 2016 to Feb 2023	• Mean age, 71 y • Mean STS PROM, 1.1% • Mean EuroSCORE II, 1% • 25% NYHA III or IV
Blankenberg et al. (2024); (96) DEDICATE-DZHK6 (NCT03112980)	Germany	38	May 2017 to Sept 2022	• Mean age, 74 y • Median STS PROM, 1.8 • 46% NYHA III or IV

CPB: cardiopulmonary bypass; HTA: health technology assessment; ISRCTN: International Standard Randomised Controlled Trial Number; NIHR: National Institute for Health Research; NCT: National Clinical Trial; NYHA: New York Heart Association; SAVR: surgical aortic valve replacement; STS PROM: Society of Thoracic Surgeons predicted risk of mortality score; TAVI: transcatheter aortic valve implantation; THV: Transcatheter heart valve; UK: United Kingdom; US: United States; Y: year.
[a]Includes analysis of a subset of originally randomized patients.
[b]No specified risk threshold for trial inclusion.

Table 5b. Characteristics of RCTs Comparing Transcatheter Aortic Valve Implantation (TAVI) With Surgical Aortic Valve Replacement (SAVR) in Patients at Low and Intermediate Surgical Risk

	Interventions		
Study; Trial; Sponsor	**TAVR**	**SAVR**	**Sponsor**
Nielsen et al. (2012) (78); STACATTO Sponsored by Participating hospitals and Danish Heart Foundation	• n= 34 • Edwards Sapien THV	• n=36 • Conventional open-heart surgery with CPB	Participating hospitals and Danish Heart Foundation Danish Heart Foundation
Thyregod et al. (2015) (77); Søndergaard et al. (2016) (83); Thyregod et al. (2019) (84); Søndergaard et al. (2019) (85) NOTION (NCT01057173) Sponsored by Danish Heart Foundation	• n= 145 • Core-Valve	• n=135 • Conventional open-heart surgery with CPB	Manufacturer
Reardon et al. (2016) (86); CoreValv8e U.S. Pivotal (NCT01240902) Sponsored by Manufacturer	• n= 202 • Core-Valve	• n=181 • Conventional open-heart surgery with CPB	Manufacturer
Leon et al. (2016) (79); PARTNER 2A (NCT01314313) Sponsored by Manufacturer	• n=1011 • SAPIEN XT	• n=1021 • Conventional surgery	Manufacturer
Reardon et al.	• n=879	• n=867	Manufacturer

(2017) (87); Van Mieghem et al. (2022) (88) SURTAVI (NCT01586910) Sponsored by Manufacturer	• Core-Valve	• Conventional surgery with coronary revascularization if needed	
Popma et al. (2019) (89); Forrest et al. (2022) (90); Forrest et al. (2023) (91) Evolut Low Risk Trial (NCT02701283) Sponsored by Manufacturer	• n=734 • Core Valve, Evolut R, or Evolut PRO	• n=734 • Conventional surgery	Manufacturer
Mack et al. (2019) (92); Leon et al. (2021) (93); PARTNER 3 (NCT02675114) Sponsored by Manufacturer	• n=503 • SAPIEN 3	• n=497 • Conventional surgery	NIHR HTA Programme; University of Leicester
Toff et al. (2022) (94); UK TAVI (ISRCTN 57819173) Sponsored by NIHR HTA Programme; University of Leicester	• n=458 • SAPIEN 3 (45.1%)	• n=455 • Conventional surgery	
Jørgensen et al. (2024); (95) NOTION 2 (NCT02825134)	• n=187 • Any CE mark approved aortic bio-prosthesis	• n=183 • Conventional surgery	Manufacturer
Blankenberg et al. (2024); (96) DEDICATE-DZHK6 (NCT03112980)	• n=701 • Valve selection left to operator choice	• n=713 • Conventional surgery	German Center for Cardiovascular Research; German Heart Foundation

CPB: cardiopulmonary bypass; HTA: health technology assessment; ISRCTN: International Standard Randomised Controlled Trial Number; NIHR: National Institute for Health Research; NCT: National Clinical Trial; NYHA: New York Heart Association; SAVR: surgical aortic valve replacement; STS PROM: Society of Thoracic Surgeons predicted risk of mortality score; TAVI: transcatheter aortic valve implantation; THV: Transcatheter heart valve; UK: United Kingdom; US: United States; Y: year.
[a]Includes analysis of a subset of originally randomized patients.
[b]No specified risk threshold for trial inclusion.

Table 6. Randomized Controlled Trials (RCTs) Comparing Transcatheter Aortic Valve Implantation (TAVI) With Surgical Repair in Patients at Low and Intermediate Surgical Risk

Study	Primary Outcome	Results of Primary Outcomes, %				All-Cause Mortality (2 y), %			New Permanent Pacemaker (2 y), %		
		TAVI	Surg	TE (95% CI)	p	TAVI	Surg	p	TAVI	Surg	p
Neilsen et al. (2012) (78)	**Death from any cause,**										

STACATTO (78)	**stroke, or renal failure at 30 d**										
All patients		14.7	2.8	RD (NR)	0.07	NR	NR		NR	NR	
Thyregod et al. (2015) (77); Sondergaard et al. (2016) (83); Thuregod et al. (2019) (84); Sondergaard et al. (2019) (85) NOTION (NCT01057173)	**Death from any cause, stroke or MI at 1 y**										
All patients		13.1	16.3	RD= -3.2	0.43[a]	4.9	7.5	0.38	34.1	1.6	<0.001
Reardon et al. (2016) (86) CoreValve U.S. Pivotal (NCT01240902)	**Death from any cause at 2 y**										
STS score ≤ 7		26.3	15	HR (NR)	0.01	See previous columns			27.7	10.5	<0.001
Leon et al. (2016) (79) PARTNER 2A (NCT01314313)	**Death from any cause or disabling stroke at 2 y**										
All patients		19.3	21.1	HR = 0.92 (0.75 to 1.08)		16.7	18	0.45	11.8	10.9	0.29
Trans-femoral access		16.8	20.4	HR=0.79 (0.62		14.2	17.2	0.11	11.4	10.8	0.71

				to 1.00)							
Trans-thoracic access		27.7	23.4	HR=1.21 (0.84 to 1.74)		25.2	20.7	0.26	13.1	8.6	0.13
Reardon et al. (2017) (87); van Mieghem et al. (2022) (88) SURTAVI (NCT 01586910)	**Death from any cause or disabling stroke at 2 y**										
All patients at 2 years		12.6	14.0	RD = 1.4 (-5.2 to 2.3) [b]		11.4	11.6	-3.8 to 3.3[b]	25.9	6.6	15.9 to 22.7 [b]
All patients at 5 years		31.3	30.8	P= .085		30	28.7	.55	35.8	14.6	< .001
Popma et al. (2019) (89); Forrest et al. (2022) (90); Forrest et al. (2023) (91) Evolut Low Risk Trial (NCT02701283)	**Death or disabling stroke at 2 y**										
All patients at 2 years		5.3	6.7	RD = -1.4 (-4.9 to 2.1) [b]		4.3	6.3	NR	23.8	7.0	NR
All patients at 5 years		7.4	10.4	HR=0.7 (0.49 to 1); p= 0.051		6.3	8.3	.16	23.2	9.1	< .001

Mack et al. (2019) (92); Leon et al. (2021) (93) PARTNER 3 (NCT02675114)	**Death, stroke or rehospitalization at 1 year**										
All patients		8.5	15.1	RD = -6.6 (-10.8 to -2.5) [b]		11.5	17.4		NR		
Toff et al. (2022) (94); UK TAVI (ISRCTN 57819173)	**All-cause mortality at 1 year**								**New Permanent Pacemaker (1 y), %**		
All patients		4.6	6.6	RD=-2.0 (-∞ to 1.2)[c]	< .001	NR			14.2	7.3	<.001
Jørgensen et al. (2024); (95) NOTION 2 (NCT02825134)	All-cause mortality, stroke, or rehospitalization (related to the procedure, valve, or heart failure) at 1 year										
All patients		10.2	7.1	RD=3.1 (-2.7 to 8.8)[d]	.3	2.1	1.1	NS	15.1	8	.03
Blankenberg et al. (2024); (96) DEDICATE-DZHK6 (NCT03112980)	All-cause mortality, or fatal or nonfatal stroke at 1 year					At 1 year			At 1 year		

All patients		5.4	10	HR=.53 (.35 to.79)	<.001	2.6	6.2	NBR	11.8	6.7	NR

CI: confidence interval; HR: hazard ratio; RD: risk difference; MI: myocardial infarction; NR; not reported: Surg: surgical repair; TAVI: transcatheter aortic valve implantation; TE: treatment effect; y: year; STS: Society of Thoracic Surgery; d: days, ISRCTN: International Standard Randomised Controlled Trial Number.

[a] Superiority.

[b] Bayesian credible interval.

[c] Noninferiority with 97.5% confidence interval.

Mixed risk populations including intermediate- and low risk

A previous RCT, the STACCATO trial, was designed to compare transapical TAVI using the SAPIEN valve with surgical aortic valve repair in operable patients with isolated aortic stenosis, without selection based on the predicted risk of death after surgery. However, the trial was prematurely terminated due to an increase in adverse events in the TAVI arm. The available results were reported by Nielsen et al. (2012). (78) The trial was limited by a design that assumed a low event rate (2.5%). Also, operators' experience with the device and implantation techniques at the time of the trial might not be representative of current practice.

Reardon et al. (2016) reported on an analysis of patients from the U.S. Pivotal High-Risk Trial who had STS score less than 7.0% at baseline. (86) The trial was described in a previous section on high surgical risk. Of the 750 total patients in the trial, 383 (202 TAVR; 181 SAVR) had an STS PROM score of 7% or less, with a median STS PROM score of 5.3%. All-cause mortality at 2 years for TAVR vs SAVR in the subgroup with STS score less than 7.0 was 15% (95% CI, 9% to 20%) vs 26% (95% CI, 20% to 33%; p=0.01). The rates of stroke at 2 years for TAVR vs SAVR were 11% vs 15% (p=0.50).

Thyregod et al. (2015) reported on the results of the NOTION RCT, which compared TAVI with surgical repair in 280 patients with severe aortic stenosis who were 70 years or older, regardless of the predicted risk of death after surgery. (77) Patients randomized to TAVI underwent implantation of the CoreValve self-expanding prosthesis by the femoral (preferred) or subclavian route. The trial was powered to detect an absolute risk reduction of 10% or a RR reduction of 66.7% in primary outcome at 1 year. At baseline, 81.8% of the study population was considered to be at low risk (STS Risk Score <4). Some of the main findings from NOTION are summarized in Table 6. In addition, TAVI-treated patients had lower rates of major or life-threatening bleeding (11.3% vs 20.9%, p=0.03), cardiogenic shock (4.2% vs 10.4%, p=0.05), stage 2 or 3 AKI (0.7% vs 6.7%, p=0.01), and new-onset or worsening atrial fibrillation (16.9% vs 57.8%, p<0.001) than surgical repair patients, all respectively. Both groups showed improvements in NYHA functional class. However, more TAVI-treated patients were in NYHA functional class II at 1-year follow-up (29.5% vs 15.0%, p=0.01).

In a 2-year follow-up of the NOTION trial, Søndergaard et al. (2016) reported slight improvements in the TAVI-treated group (n=142) compared with the surgical repair group

(n=134), although between-group differences were almost exclusively not statistically significant. (83) For the composite rate of death at 2 years, the between-group difference was also statistically insignificant (18.8% of surgical repair patients vs 15.8% of TAVI-treated patients; p=0.43). A similar difference was observed for all-cause mortality (8.0% of patients treated with TAVI experienced all-cause mortality vs 9.8% of the surgical repair patients; p=0.54). Cardiovascular mortality rates, stroke rates, and MI were likewise marginally improved in the TAVI-treated patients, although the only significant difference was found for atrial fibrillation and permanent pacemaker implantation. For the former outcome, there were 60.0% of surgical patients, compared with 22.7% of TAVI patients (p<0.001); for the latter, only 4.2% of surgical patients received implantation vs 41.3% of the TAVI group (p<0.001). As a secondary outcome, moderate aortic regurgitation was improved at 2 years for the TAVI group (15.4%) compared with the surgical group (0.9%; p<0.001). The authors noted that the variety of risk levels observed in the patients limited their results, as did the exclusion of patients with coronary artery disease. Further, the trial was limited by its lack of power for subgroup analyses, and its inability to reveal any significant differences between groups with certainty. Overall, the results showed that TAVI-treated patients had comparable, if not improved, outcomes when treated alongside patients who received SAVR.

Results after 5 years of follow-up were reported by Thyregod et al. (2019). (84) There were no significant differences between TAVR and SAVR in the incidence of the composite primary outcome (38.0% vs. 36.3%, p=0.86) or any of the components of the composite. The incidence of moderate/severe total aortic regurgitation (8.2% vs. 0.0%, p<0.001) and a new pacemaker (43.7% vs. 8.7%, p<0.001) were both higher in the TAVR group. Four patients had prosthetic re-intervention. Søndergaard et al. (2019) compared the durability of TAVR versus SAVR after 6 years of follow-up from NOTION. At 6 years, the rates of all-cause mortality were similar for TAVR (42.5%) and SAVR (37.7%) patients. The rate of moderate to severe structural valve deterioration was higher for SAVR than TAVR (24.0% vs. 4.8%; p < 0.001) and there were no differences in nonstructural valve deterioration (57.8% vs. 54.0%), bioprosthetic valve failure (6.7% vs. 7.5%) or endocarditis (5.9% vs. 5.8%). (85) At 8 years of follow-up, Jørgensen et al. (2021) found no significant difference between TAVI and SAVR in the composite outcome of mortality, stroke, or MI. (95) At 10 years of follow-up, Thyregod et al. (2025) found no significant differences in the composite outcome of all-cause mortality, stroke, or myocardial infarction (TAVI 65.5% vs. SAVR 65.5%; HR 1.0; 95% CI, 0.7 to 1.3; p=.9), or in the individual components. (97) New permanent pacemaker implantation was significantly more frequent in the TAVI group (44.7% vs. 14.0%; p<.01), while new-onset atrial fibrillation occurred more often in the SAVR group (74.1% vs. 52.0%; p<.01). Severe structural valve deterioration was significantly less common with TAVI (1.5% vs. 10.0%; p=.02), and the rate of severe non-structural valve deterioration was also lower (20.5% vs. 43.0%; p<.001); however, more TAVI patients had moderate or severe paravalvular leakage (25.4% vs. 2.5%; p<.01). Rates of bioprosthetic valve failure (9.7% vs. 13.8%; p=.4), reintervention, and endocarditis were low and similar between groups.

Toff et al. (2022) published 1-year results from an investigator-initiated, publicly funded, pragmatic RCT in the United Kingdom (UK TAVI) that compared clinical outcomes for 913

patients aged ≥80 years, or aged ≥70 years with low-to-intermediate surgical risk, with severe, symptomatic aortic stenosis randomized to TAVI or SAVR. (94) For the primary outcome (all-cause mortality at 1 year), TAVI was noninferior to SAVR (4.6% vs. 6.6%; adjusted absolute risk difference, -2.0% [1-sided 97.5% CI, -∞ to 1.2%]; p<.001) based on a prespecified margin of 5%. The adjusted hazard ratio for death from any cause was 0.69 (95% CI, 0.38 to 1.26; p=.23). No significant differences in cardiovascular deaths or strokes (fatal or nonfatal) were found between groups. While TAVI was associated with significantly shorter hospital stay and fewer major bleeding events, it was also associated with more vascular complications (p<.001), conduction disturbances requiring pacemaker implantation (p=.01), and mild or moderate aortic regurgitation (p<.001). Trial follow-up is planned for 5 years.

Blankenberg et al. (2024) reported results of the DEDICATE-DZHK6 trial, a non-industry-sponsored, multicenter RCT comparing TAVR (n=701) with SAVR (n=713) in patients 65 years of age or older with severe, symptomatic aortic stenosis and low-to-intermediate surgical risk (median STS-PROM 1.8%). (96) The trial was conducted across 38 German centers and allowed operators discretion for valve and access selection. The primary outcome was a composite measure of death or stroke at 1 year which was found to be non-inferior between the TAVR and SAVR groups (5.4% vs. 10.0%; HR,.53; 95% CI, 0.35 to 0.79; p<.001 for noninferiority). Secondary outcomes favored TAVR: at 1 year, all-cause mortality was 2.6% vs. 6.2% (HR,.43; 95% CI, 0.24 to 0.73), cardiovascular death was 2.0% vs. 4.4% (HR, 0.47; 95% CI, 0.24 to 0.86), and disabling stroke occurred in 1.3% vs. 3.1% (HR,.42; 95% CI, 0.19 to.88). New-onset atrial fibrillation was lower in the TAVR group (12.4% vs. 30.8%; HR, 0.36; 95% CI, 0.28 to 0.46). No differences in the rate of stroke or CV rehospitalization rate were observed between groups. Major or life-threatening bleeding occurred less frequently with TAVR (4.3% vs. 17.2%; HR, 0.24; 95% CI, 0.16 to 0.35); however, vascular complications were more frequent with TAVR (7.9% vs. 0.7%; HR, 10.64; 95% CI, 4.84 to 28.94), as were new permanent pacemaker implantations. Moderate or greater AR at 1 year occurred more frequently after TAVR (2.8% vs. 1.0%), although events of valve thrombosis, endocarditis, and reintervention were rare and similar across groups

Including Intermediate-Risk Only

Reardon et al. (2017) published 2-year results from an RCT (SURTAVI trial) that compared clinical outcomes for 1746 patients at intermediate surgical risk randomized to transcatheter aortic valve replacement (TAVR) or SAVR. (87) For the primary outcome (composite death at 2 years), an improvement was observed in the TAVR-treated group, compared with surgery (12.6% of TAVR patients vs 14.0% of SAVR patients [95% credible interval, -5.2% to 2.3%]; posterior probability, >0.999). Rates of death, MI, and disabling stroke were comparable between groups, as were secondary outcomes that included echocardiographic measurement of aortic valve gradient and paravalvular regurgitation (data reported in the supplemental material). More patients were assigned to the CoreValve bioprosthesis (n=724) than received Evolut R bioprosthesis (n=137), which might have affected the results; also, a considerable number of patients withdrew consent before surgery, resulting in an as-treated population of 1660. Finally, the authors acknowledged a gap in knowledge of how baseline characteristics of patients who received surgery differed from those who did not. The authors noted the low 30-

day surgical mortality ratio (0.38; observed-to-expected) and the similarity of this rate between groups (2.2% of the TAVR patients vs 1.7% of surgical patients). Three-year follow-up of the SURTAVI trial reported by van Mieghem et al. (2023) showed no difference in disabling stroke or death from any cause between groups (31.3% of TAVI patients vs. 30.8% of SAVR patients; p=.85) but reported that the rate of new pacemaker implantation was significantly higher with TAVI than with SAVR (35.8% vs. 14.6%; p<.001). (88)

Leon et al. (2016) reported on results of a multicenter noninferiority RCT (PARTNER 2A) comparing TAVI with the Edwards SAPIEN XT valve system in patients with severe aortic stenosis who were at intermediate risk for open surgery, stratified by access route (transfemoral or transthoracic). (79) Eligible patients had degenerative aortic valve stenosis, with NYHA functional class II or higher, and were in STS PROM score of 4 or greater (or <4 if determined by a heart team to have an "intermediate risk patient profile with important comorbidities not represented in the STS Risk Calculator algorithm.") The trial used a noninferiority design, with a primary composite end point of death from any cause or disabling stroke (score of ≥2 on the modified Rankin Scale) at 2 years and a noninferiority margin of 1.2 (i.e., noninferiority was considered met if upper bound of 2-sided CI for the RR for the primary outcome was <1.2). A total of 2032 patients were randomized to TAVI (n=1011) or surgical repair (n=1021), with 1550 considered suitable for transfemoral placement (76.3%) and 482 (23.7%) requiring transthoracic access. At baseline, the mean STS Risk Score was 5.8%; 81.3% had a score between 4% and 8%. The primary outcome results and select additional results of the trial are summarized in Table 6. Also, similar to other TAVI trials, the frequency and severity of paravalvular regurgitation was higher after TAVI than in surgical repair. The presence paravalvular regurgitation was associated with all-cause mortality during follow-up (HR for moderate or severe paravalvular regurgitation vs none or trace, 2.85; 95% CI, 1.57 to 5.21; p<0.001). The 5-year outcomes from the PARTNER 2A study revealed no significant difference in the incidence of death from any cause or disabling stroke between the TAVI and surgical repair groups (47.9% vs. 43.4%; HR, 1.09; 95% CI, 0.95 to 1.25; p=0.21). (95) Overall, more patients in the TAVI group had at least mild paravalvular aortic regurgitation (33.3% vs. 6.3%), experienced repeat hospitalizations (33.3% vs. 25.2%), and underwent aortic valve reinterventions (3.2% vs. 0.8%). Improvement in health status at 5 years was similar between the groups.

Including Low-Risk Only

Popma et al. (2019) reported results of prespecified, interim analyses of the multinational Evolut Low Risk Trial, a noninferiority trial conducted from 2016 to 2018 comparing TAVR (n=734) to SAVR (n=734) in patients who had severe aortic stenosis and were at low surgical risk (STS-PROM ≤3%). (89) Patient's bicuspid aortic valves were excluded. Patients assigned to TAVR were treated with 1 of 3 Medtronic self-expanding, supra-annular bioprostheses (CoreValve, Evolut R, or Evolut PRO). Preliminary analyses were performed when 850 patients had reached 12-month follow-up. Long-term follow-up is scheduled to continue for 10 years. The primary outcome was a composite of death or disabling stroke at 24 months performed using Bayesian methods. At the time of the preliminary analysis, 149 patients had reached the 24 months visit. The 24-month estimated incidence of the primary outcome was 5.3% in the

TAVR group and 6.7% in the SAVR group (risk difference= −1.4%; 95% Bayesian credible interval, −4.9 to 2.1; posterior probability of noninferiority >0.999). Several 30-day outcomes were also reported. The incidence at 30 days of disabling stroke (0.5% vs. 1.7%), bleeding complications (2.4% vs. 7.5%), acute kidney injury (0.9% vs. 2.8%), and atrial fibrillation (7.7% vs. 35.4%) were lower in SAVR compared to SAVR. The incidence at 30 days of moderate or severe aortic regurgitation (3.5% vs. 0.5%) and pacemaker implantation (17.4% vs. 6.1%) was higher in TAVR compared to SAVR. There was not a statistically significant difference in the KCCQ overall summary score at 30 days (88.7±14.2 in the TAVR group vs. 78.6±18.9 in the SAVR group). In 2022, Forrest et al. published 2-year outcomes. (91) Follow-up data was available for 97.7% in the TAVI group and 92.3% in the SAVR group. The Kaplan-Meier estimate of all-cause mortality or disabling stroke at 2 years was 4.3% and 6.3% in the TAVI and SAVR groups, respectively (p=.084). The number of patients requiring new permanent pacemaker implantation was significantly higher with TAVI (23.8% vs. 7.0%). In 2023, Forrest et al. published 5-year outcomes that showed a non-significant difference in all-cause mortality or disabling stroke in the TAVI (7.4%) and SAVR (10.4%) groups (HR, 0.7; 95% CI, 0.49 to 1; p=.051). The rate of permanent pacemaker implantation remained higher with TAVI than with redo-SAVR (23.2% vs. 9.1%; p<.001). (91) At 5 years, no significant difference in the primary endpoint between TAVI (15.5%) and surgery (16.4%; p=.47) or in the rate of disabling stroke, all-cause mortality, or CV mortality; however, permanent pacemaker implantation was significantly more frequent after TAVI (27.0% vs 11.3%; p<.001) whereas the rate of atrial fibrillation was significantly greater in the SAVR group (41.2% vs. 16.3%; p<.001). (99)

Mack et al. (2019) reported results of the multinational PARTNER 3 randomizing patients with severe aortic stenosis and low surgical risk to either TAVR with the SAPIEN (n=503) or SAVR (n=497) in 2016 to 2017. (92) Patients' bicuspid aortic valves were excluded. The primary outcome was a composite of death, stroke, or rehospitalization at 1 year. Follow-up is designed to continue for at least 10 years. Primary analyses were performed and reported in the as-treated population (n=496 in the TAVR; n=454 in SAVR) but sensitivity analyses of the primary outcome performed in the intention-to-treat population with multiple imputations for missing data were reportedly consistent with the primary analysis. The number of participants that did not receive the assigned treatment was higher in the SAVR group (7 vs.43). The most common reported reason was refusal to undergo surgery or the choosing to undergo surgery at a nontrial site. The estimated incidence of the primary outcome at 1 year was significantly lower in TAVR versus SAVR (8.5% vs. 15.1%; risk difference= −6.6%; 95% CI, −10.8 to −2.5; p<0.001 for noninferiority). All components of the composite (death, stroke, and hospitalization) individually favored TAVR at 30 days and 1 year. At 30 days, the rate of stroke (0.6% vs. 2.4%; HR=0.25 (95% CI, 0.07 to 0.88); p = 0.02) and new-onset atrial fibrillation (5.0% vs. 39.5%; HR=0.10 (95% CI, 0.06 to 0.16); p<0.001) was lower in TAVR than SAVR and index hospitalization time was shorter (3 days vs. 7 days, p<0.001). There were no significant differences at 30 days in major vascular complications, new permanent pacemaker insertions, or moderate or severe paravalvular regurgitation. The incidence of mild paravalvular regurgitation at 1 year was higher with TAVR (29.4% vs. 2.1%). In an analysis specific to the echocardiographic findings of the PARTNER 3 trial, Pibarot et al. (2020) reported that the percentage of moderate or severe aortic regurgitation was low and not statistically different

between the TAVR and SAVR groups at 30 days (0.8% vs. 0.2%; p=0.38); mild aortic regurgitation occurred more frequently after TAVR than SAVR (28.8% vs. 4.2%; p<0.001). (100) Mean transvalvular gradient (13.7±5.6 vs. 11.6±5.0 mmHg; p=0.12) and aortic valve area (1.72±0.37 vs. 1.76±0.42 cm^2; p=0.12) were similar between groups at 1 year. In another analysis specific to atrial fibrillation (N=781), Shahim et al. (2021) found lower early postoperative atrial fibrillation in patients following TAVI compared with SAVR (19.5% vs. 36.6%; p<.0001). (101) At 2-year follow-up, Leon et al. (2021) reported continued improvement of the composite primary endpoint with TAVI versus SAVR (11.5% vs. 17.4%; HR 0.63; 95% CI, 0.45 to 0.88; p=.007); however, there was no significant difference in death or stroke between TAVI and SAVR. (93) Mack et al. (2023) reported 5-year results, which found no statistically significant difference in the composite outcome of death, stroke, or rehospitalization between TAVR (22.8%) and surgery (27.2%) among low-risk patients with severe aortic stenosis (Hazard ratio [HR], 0.79; 95% CI, 0.61 to 1.02; p=.07), and valve durability and functional outcomes were similar in both groups. (92)

Jørgensen et al. (2024) reported results of the NOTION-2 trial, a multicenter randomized trial comparing TAVI (n=187) with SAVR (n=183) in low-surgical-risk patients aged 75 years of age or older with severe symptomatic aortic stenosis. (95) The primary endpoint was a composite of all-cause mortality, stroke, or rehospitalization related to the procedure, valve, or heart failure at 1 year. In the intention-to-treat analysis, the composite outcome occurred in 10.2% of TAVI patients and 7.1% of SAVR patients (HR 1.4; 95% CI, 0.7 to 2.9; p=.3). At 1 year, TAVI was associated with significantly lower rates of new-onset atrial fibrillation (3.2% vs. 41.7%; HR.06; 95% CI, 0.03 to 0.2; p<.001) and major or life-threatening bleeding (4.8% vs. 17.5%; HR 0.3; 95% CI, 0.1 to 0.5; p<.001), but higher rates of permanent pacemaker implantation (15.1% vs. 8.0%; HR 2.0; 95% CI, 1.1 to 3.8; p=.03), and non-disabling stroke (3.7% vs. 0.5%; HR 7.0; 95% CI, 0.9 to 56.5; p=.03). Moderate or greater paravalvular regurgitation occurred more often in TAVI patients (4.7% vs. 0%; p=.005), particularly in those with bicuspid AS. Both groups experienced similar improvements in valve hemodynamics and health status by KCCQ score, though TAVI patients had more rapid early gains.

The purpose of the study limitation tables (Tables 7 and 8) is to display notable limitations identified in each study. This information is synthesized as a summary of the body of evidence following the tables and provides the conclusions on the sufficiency of evidence supporting the position statement.

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Nielsen et al. (2012) (78) STACATTO	4: Included patients with any surgical risk, not limited to patients requiring	4: Transapical TAVI, multi-detector computed tomography was not			1, 2: Terminated early

	alternative access	performed before procedure			
Thyregod et al. (2015) (77) NOTION	4: Included patients with any surgical risk				
Reardon et al. (2016) (86) CoreValve U.S. Pivotal	4: Subgroup analysis included patients at low/intermediate risk by STS-PROM but deemed at high surgical risk based on screening committee assessment despite their STS scores				
Leon et al. (2016) (79) PARTNER 2A	4: 12% of the population had an STS risk score >8				
Reardon et al. (2017) (87) SURTAVI					
Popma et al. (2019) (89) Evolut Low Risk Trial					
Mack et al. (2019) (92) PARTNER 3				4: Rehospitalization was included in the composite primary outcome	
Toff et al. (2022) (94); UK TAVI	1: Proportion of patients with low versus				

	intermediate risk unclear; median STS risk score 2.7				
Jørgensen et al. (2024); (95) NOTION 2 (NCT02825134)					
Blankenberg et al (2024); (96) DEDICATE-DZHK6 (NCT03112980)	1. Included a small proportion of intermediate risk patients				

STS: Society of Thoracic Surgeons; STS PROM: Society of Thoracic Surgeons predicted risk of mortality score; TAVI transcatheter aortic valve implantation.

The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 8. Study Design and Conduct Limitations

Study	Allocation [a]	Blinding [b]	Selective Reporting [c]	Data Completeness [d]	Power [e]	Statistical [f]
Nielsen et al. (2012) (78) STACATTO		1: Patients and study staff not blinded		1: Study terminated early with only 70 participants		
Thyregod et al. (2015) (77) NOTION		1: Patients and study staff not blinded 2,3: Unclear if outcome				

		adjudication was blinded				
Reardon et al. (2016) (86) CoreValve U.S. Pivotal		1: Patients and study staff not blinded			2: Post-hoc analysis of RCT: not powered to detect differences in the low/ intermediate risk population	
Leon et al. (2016) (79) PARTNER 2A		1: Patients and study staff not blinded		1: High frequency of withdrawals in patients assigned to undergo surgery		
Reardon et al. (2017) (87) SURTAVI		1: Patients and study staff not blinded 2,3: Unclear if outcome adjudication was blinded		1: High frequency of withdrawals in patients assigned to undergo surgery		
Popma et al. (2019) (89) Evolut Low Risk Trial		1: Patients and study staff not blinded		1: High frequency of withdrawals in patients assigned to undergo surgery		3: Incomplete reporting of confidence intervals and/or p-values
Mack et al. (2019) (92) PARTNER 3		1: Patients and study staff not blinded 2,3: Unclear if outcome adjudication was blinded		1: High frequency of withdrawals in patients assigned to undergo surgery		
Toff et al. (2022); (94)		1: Patients and study				

UK TAVI		staff not blinded				
Jørgensen et al. (2024); (95) NOTION 2 (NCT02825134)		1: Patients and study staff not blinded				
Blankenberg et al (2024); (96) DEDICATE-DZHK6 (NCT03112980)		1: Patients and study staff not blinded 2,3: Outcome adjudication not blinded				

RCT: randomized controlled trial.
The study limitations stated in this table are those notable in the current literature review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.
[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: Transcatheter Aortic Valve Implantation (TAVI) Outcomes in Patients at Intermediate or Low Risk for Open Surgery

Intermediate Risk

Most participants in 6 RCTs were intermediate risk, and two RTCs included only intermediate surgical risk patients. The primary outcomes were generally a composite of death and stroke; most RCTs were noninferiority studies. The rates of the primary outcome were noninferior for TAVI compared with SAVR and numerically lower, although not statistically significantly lower in 4 of the 6 RCTs including the 2 RCTs exclusively enrolling intermediate risk patients. The rates of adverse events differed between groups, with bleeding, cardiogenic shock, and AKI higher in patients randomized to open surgery and permanent pacemaker requirement higher in patients randomized to TAVI. Subgroup analyses of meta-analyses and the transthoracic arm of the Leon RCT suggested that the benefit of TAVI may be limited to patients who are candidates for transfemoral access. Two-year follow-up results were published for NOTION, PARTNER 2A,

CoreValve U.S. Pivotal and SURTAVI trials, but reported outcomes did not include rates of reoperation. A number of recently completed meta-analyses evaluated mortality for TAVR vs SAVR at the 30-day mark. Mortality rates were found to be comparable between the 2 procedures.

Low Risk
The NOTION and UK TAVI trial was predominantly low surgical risk patients; the Evolut Low Risk Trial and PARTNER 3 were only low risk patients. The STACCATO trial also included some patients at low surgical risk. In the NOTION trial, the risk of the composite outcome of death from any cause, stroke, or MI at 1 year was numerically, but not statistically significantly, lower in the TAVI group compared to SAVR and, after 5 years of follow-up, there were still no significant differences between TAVI and SAVR in the incidence of the composite outcome (38.0% vs. 36.3%, p=0.86) or any of the components of the composite. Ten-year follow-up from NOTION showed less structural valve deterioration in TAVI than SAVR. In the publicly sponsored UK TAVI trial, TAVI was noninferior to SAVR with respect to all-cause mortality at 1 year. In the Evolut Low Risk Trial, TAVI was noninferior to SAVR with respect to the composite outcome of death or disabling stroke at 24 months. At 30 days, TAVI was associated with a lower incidence of disabling stroke, AKI, bleeding events, and atrial fibrillation but with a higher incidence of aortic regurgitation and permanent pacemaker use. In the PARTNER 3 trial, the rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVI than SAVR. At 30 days, TAVI was associated with a lower rate of stroke, death or stroke composite, new-onset atrial fibrillation, and shorter index hospitalization. The NOTION-2 trial found no significant difference between TAVI and SAVR groups in the composite primary outcome of death, stroke, or valve-related rehospitalization at 1 year. TAVI was associated with lower risks of bleeding and atrial fibrillation but higher rates of pacemaker implantation, non-disabling stroke, and paravalvular regurgitation.

There were no significant between-group differences in major vascular complications or new permanent pacemaker insertions at 30 days. The age of participants in the low-risk RCTs was markedly lower than that in previous TAVI trials and therefore life expectancy is longer. Extended follow-up will be needed to address the long-term advantages and disadvantages of TAVI versus SAVR and valve durability. Both of the low-risk RCTs have planned follow-up of 10 years and both excluded patients with bicuspid aortic valves.

TAVI Outcomes for "Valve-in-Valve" Approach
Clinical Context and Therapy Purpose
The purpose of transcatheter aortic "valve-in-valve" (ViV) implantation is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as surgical aortic valve repair and medical management, in individuals with valve dysfunction and aortic stenosis or regurgitation after aortic valve repair.

The following PICO was used to select literature to inform this policy.

Populations

The relevant populations of interest are individuals with valve dysfunction and aortic stenosis or regurgitation after aortic valve repair.

Interventions
The therapy being considered is transcatheter aortic ViV implantation, a minimally invasive surgical procedure that repairs the aortic valve without removing the old, damaged valve by wedging a replacement valve into the place of the aortic valve.

Comparators
The first comparator of interest is surgical aortic valve repair, which is performed through sternotomy. The decision to repair a damaged aortic valve depends on severity of the symptomatic aortic stenosis and patient age and overall health. Medical management, including lipid-lowering therapy, anti-hypertensive drugs, and anti-calcific therapy, is the second comparator of interest in this policy.

Outcomes
The general outcomes of interest are OS, symptoms, morbid events, treatment-related mortality, and treatment-related morbidity. Symptoms may include heart murmur, angina, dizziness or syncope, shortness of breath, fatigue, and heart palpitations. In adolescents with aortic stenosis, symptoms may also include cyanosis, poor feeding, and poor weight gain. Morbid events may include stroke, coronary obstruction, vascular complications, conduction disturbance, valve malpositioning and sizing, mitral valve injury, annular rupture, and aortic dissection, myocardial trauma, and low cardiac output, cardiogenic shock, and cardiac arrest.

The existing literature evaluating transcatheter aortic “valve-in-valve” implantation as a treatment for valve dysfunction and aortic stenosis or regurgitation after aortic valve repair has varying lengths of follow-up, with many following patients for at least 1 year after the ViV approach was performed.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:
- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Reviews
Comentale et al. (2025) conducted a systematic review and meta-analysis of 27 studies comparing ViV TAVI to rSAVR in 20,339 patients with failed bioprosthetic valves, which included 10627 patients (52%) treated with ViV TAVI and 8663 patients (43%) treated with rSAVR (PROSPERO ID: CRD42023490612). (102) ViV-TAVI was associated with a significantly lower risk

of 1-year all-cause mortality (RR, 0.74; 95% CI, 0.57 to 0.96; p=.02; I^2=17%), but no difference was observed between groups in procedural, 30-day mortality of CV mortality (p>.05). ViV TAVI was also associated with a lower rate of acute kidney injury (RR, 0.47; 95% CI, 0.32 to 0.70; p<.001; I^2=61.5%), major bleeding (RR, 0.44; 95% CI, 0.31 to 0.62; p<.001; I^2=93.8%), stroke or TIA (RR, 0.70; 95% CI, 0.51 to 0.96; p<.05; I^2=0%), and new pacemaker implantation (RR, 0.69; 95% CI, 0.48 to 0.99; p<.05; I^2=83.4%). However, redo-SAVR was associated with superior hemodynamic outcomes, including lower postoperative mean aortic valve gradients (mean difference, 2.59 mmHg; 95% CI, 0.86 to 4.31; p<.01) and lower rates of patient-prosthesis mismatch (RR, 3.23; 95% CI, 2.39 to 4.36; p<.001).

Aedma et al. (2022) conducted an umbrella or meta-meta-analysis evaluating the efficacy and safety of valve-in-valve (ViV) TAVI compared to redo-surgical aortic valve replacement (rSAVR). (103) Nine analyses were included for review. ViV TAVI was associated with a significantly lower risk of 30-day mortality (OR, 0.60; 95% CI, 0.53 to 0.68; p<.00001) and procedural mortality (OR, 0.52; 95% CI, 0.27 to 0.98; p=.04). No significant differences in long-term mortality (1 year follow-up) or hospital readmissions were identified. ViV TAVI was also associated with a lower risk several complications, including stroke (OR, 0.71; 95% CI, 0.59 to 0.84; p<.001), major bleeding (OR, 0.44; 95% CI, 0.35 to 0.57; p<.000001), acute kidney injury (OR, 0.57; 95% CI, 0.43 to 0.75; p<.0001), and pacemaker implantation (OR, 0.67; 95% CI, 0.52 to 0.86; p<.002). No association of acute myocardial infarction with ViV TAVI and redo-SAVR was found (OR, 1.15; 95% CI, 0.84 to 1.59; p=.38); however, ViV TAVI was associated with a higher risk of vascular complications (OR, 2.70; 95% CI, 1.58 to 4.62; p<.0003).

Raschpichler et al. (2022) published a systematic review and meta-analysis of nonrandomized studies comparing ViV TAVI with redo-SAVR. (104) A total of 15 studies including 8881 patients were identified for analysis, which included 4458 patients (50.2%) treated with ViV TAVI and 4423 patients (49.8%) treated with redo-SAVR. Short-term mortality (<30 days) was 2.8% in patients undergoing ViV TAVI compared with 5.0% in patients undergoing redo-SAVR (RR, 0.55; 95% CI, 0.34 to 0.91). Midterm mortality (up to 5 years) was not significantly different between groups (HR, 1.27; 95% CI, 0.72 to 2.25). The rate of acute kidney failure was lower following ViV (RR, 0.54; 95% CI, 0.33 to 0.88); however, prosthetic aortic valve regurgitation (RR, 4.18; 95% CI, 1.88 to 9.3; p=.003) and severe patient-prosthesis mismatch (RR, 3.12; 95% CI, 2.35 to 4.1; p<.001) were significantly more frequent. Additionally, the transvalvular gradient was significantly higher following ViV procedures (standard mean difference, 0.44; 95% CI, 0.15 to 0.72; p=.008). There were no significant differences between groups with respect to stroke (p=.26), myocardial infarction (p=.93), or pacemaker implantation (p=.21). The authors concluded that the early safety advantages of ViV should be weighed against a potential midterm benefit of redo-SAVR. The authors concluded that the early safety advantages of ViV should be weighed against a potential midterm benefit of rSAVR. The authors also noted that given the likely selection bias in individual studies, an adequately powered multicenter randomized trial with sufficiently long follow-up in patients with low-to-intermediate surgical risk is warranted.

A subsequent time-to-event analysis of all-cause mortality in ViV TAVI versus redo-SAVR in 10 studies conducted by Sá et al. (2023) similarly found a short-term protective effect with ViV TAVI in the first 44 days (HR, 0.67; 95% CI, 0.49 to 0.93; p=.017). (105) A HR reversal was observed after 197 days favoring redo-SAVR (HR, 1.53; 95% CI, 1.22 to 1.93; p<.001). Additionally, a statistically significant association of patient-prosthesis mismatch with all-cause mortality during follow-up for ViV TAVI was identified via Cox regression modeling (p<.001).

In 2019, the National Institute for Health and Care Excellence (NICE) prepared an interventional procedure overview on safety and efficacy of valve-in-valve TAVI for aortic bioprosthetic valve dysfunction based on a rapid review of medical literature including publications through August 2018 and specialist opinion. (106) The review included 3 systematic reviews and meta-analysis (107-109) and 8 case series (registries) totaling 4256 patients, although the authors note that there may be some overlap of patients in the global valve-in-valve register and other registries. There are no RCTs comparing valve-in-valve TAVI with redo SAVR. The available evidence is from observational studies and registry data with follow-up ranging from 1 month to 1 year. Two systematic reviews and meta-analysis compare valve-in-valve TAVI with redo SAVR reported similar favorable outcomes. One of the included systematic reviews of 15 studies (861 patients) reported a pooled technical success rate of 95% (95% CI, 94% to 97%). Another included systematic review of 6 observational studies reported no statistically significant difference between valve-in-valve TAVI and redo SAVR in perioperative mortality (5% vs. 6%; Risk Ratio=0.78; 95% CI, 0.33 to 1.84), late mortality (median 1-year follow-up, Incident Rate Ratio=0.93; 95% CI, 0.74 to 1.16), or perioperative stroke (2% vs. 3%; RR=0.73; 95% CI, 0.18 to 3.02), whereas, the rate of permanent pacemaker insertion was statistically significantly lower in the valve-in-valve TAVI group (8% vs. 15%; RR=0.57; 95% CI, 0.32 to 1.0) and the rate of mild or greater paravalvular regurgitation was statistically significantly higher in the valve-in-valve TAVI group (21% vs. 6%; RR=3.83; 95% CI, 1.2 to 12.22). In 2 registries (including 365 and 227 patients), the rate of conversion to surgery or surgical reintervention within 30 days was less than 1%.

Registries

Registries not included in the NICE review described above will be briefly summarized if they include longer follow-up than those already summarized.

Following the National Institute for Health and Care Excellence review, 3-year results from the PARTNER 2 valve-in-valve registry were published by Webb et al. (2019). (110) The registry included 365 patients who had ViV TAVI (108, 109) procedures with a mean age was 79 years (±10) and mean STS-PROM score of 9.1% (±4.7%). The estimated incidence of all-cause mortality at 3 years was 32.7%. Aortic valve re-replacement was performed in 1.9% by 3 years. From baseline to year 3, NYHA functional class improved; 90.4% of patients were in class III or IV at baseline and 14.1% were in class III or IV at 3 years (p < 0.0001). QOL as measured by the KCCQ overall score also increased from baseline to 3 years (43.1 to 73.1; p < 0.0001).

Hahn et al. (2022) published 5-year follow-up outcomes from the PARTNER 2 registry. (111) The Kaplan-Meier rates of all-cause mortality, any stroke, and all neurological events (all strokes

and TIAs) in patients with high surgical risk were 50.6%, 10.5%, and 13.8%, respectively. The incidence of structural valve deterioration, related hemodynamic valve deterioration, or bioprosthetic valve failure was 6.6%. Aortic valve re-replacement was performed in 14 patients (6.3%). Reasons for reintervention included stenosis (n=6) and combined aortic insufficiency/paravalvular regurgitation (n=3). Improvements in NYHA functional class and KCCQ overall score were maintained at 5 years. Patients receiving a 23-mm SAPIEN XT valve were found to have a significantly increased risk of mortality compared to patients who received a 26-mm SAPIEN XT valve (HR, 1.55; 95% CI, 1.09 to 2.20; p=.01).

Hirji et al. (2020) published a retrospective comparison of 30-day outcomes of ViV TAVI compared to rSAVR drawn from a large U.S. multicenter National Readmission Database. (112) The authors identified 6815 eligible patients who underwent ViV TAVI (n=3443) or rSAVR (n=3372), but this cohort varied significantly in mean age and the prevalence of co-morbid conditions at baseline. A matched cohort of 2181 participants per group was created, which was balanced across baseline patient characteristics and had a mean age of 73 years. In the unmatched analysis, ViV TAVI patients had significantly lower 30-day mortality (2.8% vs. 5.0%; OR, 0.55; 95% CI, 0.33 to 1.91), 30-day morbidity (66.4% vs. 79%; OR, 0.52; 95% CI, 0.41 to 0.66), and rates of major bleeding complications (35.8% vs. 49.9%; OR, 0.56; 95% CI, 0.44 to 0.71) than rSAVR. However, no between-group differences were noted in the rate of all-cause 30-day readmission, postoperative stroke, renal failure, permanent pacemaker placement, or complete heart block. Findings from the propensity-matched analysis were similar, with ViV TAVI having lower odds of 30-day mortality (OR, 0.41; 95% CI, 0.23 to 0.74), 30-day morbidity (OR, 0.53; 95% CI, 0.43 to 0.72), and major bleeding (OR, 0.66; 95% CI, 0.51 to 0.85).

Kaneko et al. (2021) evaluated the safety and efficacy of ViV TAVI amongst patients treated from 2015 to 2020 with SAPIEN 3 valves in the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies Registry. (113) A total of 145,917 patients from SAPIEN 3 were identified in the database, of which 3% (n=4276) underwent transfemoral ViV TAVI and had adequate baseline data. The mean age of this cohort was 73.9 years, with a mean STS score of 6.9. Overall, 30-day mortality was 2.4%, with cardiac death occurring in 1.2% of patients. At 1-year follow-up, mortality was 10.8%. Stroke occurred in 1.4% of patients, and major vascular complications occurred in 0.9%. New pacemaker implantation was required in 2.1% of patients. Moderate or severe aortic regurgitation was observed in 0.9% of patients at 30 days follow-up and 1.3% at 1-year post-ViV TAVI. When stratified based on STS score (low score, <4%; intermediate score, 4% to 8%; high score, >8%), 30-day mortality was 0.9% in the low score group, 2.2% in the intermediate score group, and 4.3% in the high-score group. A stratified analysis found that the lower and intermediate STS score groups had significantly lower mortality rates than the high score group (p<.0001). Similarly, 1 year mortality rates were also lower in the low score (5.7%) and intermediate score (9.3%) groups compared to the high score group (17.9%; p<.0001).

Tam et al. (2022) reported data from the CorHealth Ontario Cardiac Registry for patients undergoing ViV TAVI and rSAVR. A total of 558 patients (ViV TAVI, n=214 and rSAVR, n=344) were included in the unmatched analysis. A propensity-matched subset of patients with 131

individuals in each group was constructed based on 27 clinically relevant baseline characteristics that were not balanced in the unmatched population. (114) In the matched cohort, patients treated with ViV TAVI had better early outcomes for mortality (absolute risk difference, -7.5; 95% CI, -12.6% to -2.3%), permanent pacemaker implantation (absolute risk difference, -9.8%; 95% CI, -16.1% to -3.4%), and blood transfusion rate (absolute risk difference, -63.1%; 95% CI, -76.2% to -50.1%) than patients in the rSAVR group. No differences in all-cause hospital readmission rates at 30 days post-treatment were observed between groups. The median follow-up period was 3.2 years (interquartile range [interquartile range], 1.6 to 5.1 years), with a maximum follow-up of 10.4 years. At 5 years follow-up, survival was significantly higher for ViV TAVI (76.8%; 95% CI, 67.8 to 86.9%) than rSAVR (66.8%; 95% CI, 58.3% to 76.6%; p=.046) in the matched cohort, but no significant difference was observed in the unmatched cohort. No differences in the cumulative incidence of late all-cause readmission or freedom from late major adverse cardiac events (death, stroke, or aortic valve reintervention) were observed.

van Steenbergen et al. (2022) reported on outcomes of ViV TAVI and redo-SAVR via a propensity score-matched analysis of data from the Netherlands Heart Registry collected between 2014 and 2018 from 16 cardiac centers. (115) Patients with concomitant coronary procedures such as percutaneous coronary interventions or coronary artery bypass grafting were eligible for inclusion. A total of 653 high risk patients were identified, including 374 treated with ViV TAVI and 279 with redo-SAVR; following propensity score-matching, 165 pairs were included for analysis. EuroSCORE I surgical risk was significantly higher for ViV TAVI patients compared to redo-SAVR (19.4 [IQR, 13.3 to 27.9] vs. 13.8 [IQR, 8.3 to 21.9]; p<.01). The primary endpoint of composite 30-day all-cause mortality and in-hospital postoperative stroke was not significantly different for ViV TAVI and redo-SAVR (OR, 1.30; 95% CI, 0.57 to 3.02). Additionally, no significant differences in procedural, 30-day, and 1-year all-cause mortality rates or incidence of in-hospital post-operative stroke, pacemaker implantation, and redo procedures within 1 year were identified. Study interpretation is limited by its retrospective nature, small sample size, and possible selection bias.

Begun et al. (2023) published a retrospective analysis of ViV TAVI compared to TAVI in a native valve using the Danish National Patient Registry from 2008 to 2020. (116) A total of 5,823 patients with native valve TAVI and 247 with ViV TAVI were identified with a median age of 81 years. All-cause mortality was reported at 30 days, 1 year, and 5 years post-procedure with values of 2.4%, 9.7%, and 28.7% in the ViV TAVI group, respectively, and 2.7%, 10.3%, and 33.8% in the native valve TAVI group, respectively; no significant between group differences were observed for HRs at any follow-up assessment. The cumulative 5-year risk of death was similar with patients with ViV TAVI (42.5%; 95% CI, 34.2% to 50.6%) and patients who received native valve TAVI (44.8%; 95% CI, 43.2% to 46.4%). Overall, the number of rehospitalizations from any cause and from cardiovascular causes was not significantly lower in the group of patients with ViV TAVI compared with native valve TAVI at 30 days, 1 year, and 5 years postprocedure.

Section Summary: TAVI Outcomes for “Valve-in-Valve” Approach

For individuals who have valve dysfunction and aortic stenosis or regurgitation after open surgical aortic valve repair who receive transcatheter aortic ViV implantation, the evidence includes observational studies including registry data with follow-up ranging from 1 month to 5 years and systematic reviews. Relevant outcomes are OS, symptoms, morbid events, and treatment-related mortality and morbidity. Recent meta-analyses of observational studies have compared ViV TAVI to rSAVR and have reported a reduced risk of short-term mortality (<30 days) with ViV TAVI. Beyond 30 days, meta-analyses have reported mortality outcomes that were similarly favorable or improved with rSAVR. The PARTNER 2 registry reported a 50.6% rate of all-cause mortality after 5 years among patients with high surgical risk; patients who received a 23-mm SAPIEN XT valve had a significantly higher risk of mortality compared to those who received a 26-mm valve (HR, 1.55; 95% CI, 1.09 to 2.20; p=.01). The CorHealth Ontario Cardiac Registry reported that at 5 years after treatment, patients who underwent ViV TAVI had greater OS than patients who underwent rSAVR in a matched cohort of patients (absolute risk difference, -7.5%; 95% CI, -12.6% to -2.3%). An analysis using the Danish National Patient Registry data reported that ViV TAVI had similar mortality and rehospitalization rates compared to native valve TAVI at 1- and 5-years follow-up. Given that no RCTs are available, selection bias cannot be ruled out. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Cerebral Embolic Protection During Transcatheter Aortic Valve Implantation

Clinical Context and Therapy Purpose

The purpose of cerebral embolic protection is to provide an adjunct treatment option to improve outcomes in individuals who undergo TAVI compared to standard TAVI without cerebral embolic protection.

The following PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals with an FDA-approved indication for TAVI.

Studies of cerebral embolic protection have focused on individuals with severe aortic stenosis at various risk levels for open surgery.

Interventions

The therapy being considered is use of a cerebral embolic protection (CEP) device (e.g., Sentinel Cerebral Protection System) during TAVI. The device is a single-use percutaneous catheter system with blood filters designed to prevent embolic material from the transcatheter aortic valve implantation procedure from traveling towards the cerebral circulation. The Sentinel device has 2 filters, which are positioned in the brachiocephalic artery (proximal filter) and the left common carotid artery (distal filter) before the TAVI procedure. The diameters of the arteries at the site of filter placement should be between 9 mm to 15 mm for the brachiocephalic and 6.5 mm to 10 mm in the left common carotid arteries.

Comparators

The main comparator of interest is standard TAVI without cerebral embolic protection.

Outcomes
The general outcomes of interest are OS, symptoms, morbid events, treatment-related mortality, and treatment-related morbidity. Symptoms may include heart murmur, angina, dizziness or syncope, shortness of breath, fatigue, and heart palpitations. In adolescents with aortic stenosis, symptoms may also include cyanosis, poor feeding, and poor weight gain. Morbid events may include stroke, coronary obstruction, vascular complications, conduction disturbance, valve malpositioning and sizing, mitral valve injury, annular rupture, aortic dissection, myocardial trauma, low cardiac output, cardiogenic shock, and cardiac arrest. Studies of cerebral embolic protection devices have also reported on neuroimaging findings and neurocognitive outcomes.

The KCCQ is a tool for measuring health-related QOL. The KCCQ is self-administered, with 23-items across 5 health status domains (physical limitation, heart failure symptoms, self-efficacy, social interference, and QOL). The KCCQ summary scores range from 0 to 100 with higher scores indicating better health status. Differences of at least 5 points have been shown to be clinically important. (14)

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess longer-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Studies of cerebral protection devices without marketing clearance in the United States. (e.g., TriGUARD 3 [Keystone Heart]) were excluded. See the Regulatory Section for additional details.

Systematic Reviews
Zahid et al. (2023) conducted a meta-analysis evaluating the safety and efficacy of TAVI with CEP devices versus TAVI alone. (117) Six RCTs and 5 observational cohort studies with a total of 125,267 individuals with severe aortic stenosis who underwent TAVI with (n=13,453) CEP or without (n=111,814) were included for review. The rate of major adverse cardiac events (OR, 0.75; 95% CI, 0.70 to 0.81; p<.01), mortality (OR, 0.65; 95% CI, 0.76 to 0.93; p<.01), and stroke (OR, 0.84; 95% CI, 0.76 to 0.93; p<.01) was significantly lower in patients who had TAVI with CEP compared to TAVI with no CEP at 30 days follow-up. No significant differences were observed in the rate of vascular complications, AKI, or major or life-threatening bleeding between groups. Estimates of heterogeneity for these analyses were not reported. A stratified analysis by device found that the rate of major adverse cardiovascular events was significantly lower in patients

who had TAVI with the Sentinel device (OR, 0.74; 95% CI, 0.66 to 0.82; p<.01) but not different for other devices (Triguard or Embrella) compared to TAVI with no CEP.

Randomized Controlled Trials

CLEAN-TAVI

The Claret Embolic Protection and TAVI (CLEAN-TAVI) trial was s single-center, blinded, RCT performed at the Heart Center at the University of Leipzig, Germany. (118) Patients with symptomatic severe aortic stenosis were eligible for enrollment if they were considered at increased risk for open surgery. Patients were randomized to transfemoral TAVI with the Medtronic CoreValve with (n=50) or without (n=50) CEP using the Claret Montage Dual Filter System, a precursor to the Sentinel system. The study primary endpoint was the numerical reduction in positive postprocedure diffusion-weighted MRI lesions relative to baseline at 2 days following TAVI in potentially protected territories, with a 50% reduction in the number of positive brain lesions considered clinically significant. Secondary endpoints included serial volumetric and numerical reductions in brain lesions at 2 and 7 days, in addition to serial neurological and neurocognitive assessments. Study characteristics and results are summarized in Tables 9 and 10. The procedural success rate was 90%, defined as successful positioning and deployment of both filters in correct anatomical position, correct positioning of both filters during TAVI, and successful retrieval of both filters after TAVI. A significant reduction in both lesion number and volume was seen in potentially protected regions and in the entire brain in the CEP group at both 2 and 7 days. However, stroke incidence did not significantly differ between groups, with 5 (10%), 5 (10%), and 4 (8%) non-disabling strokes reported at 2, 7, and 30 days in both control and CEP groups. Patient outcomes were not stratified by baseline STS risk score. At 30 days, a lower proportion of patients treated with CEP exhibited an overall worsening of National Institute of Health Stroke Scale and modified Rankin Scale scores compared to TAVI alone, whereas a higher proportion exhibited an overall worsening on the Montreal Cognitive Assessment. It is unclear whether these differences were statistically significant. Study investigators additionally noted that the CEP device used in the study failed to protect the left vertebral circulation and that results may not be generalizable to broader populations. Study relevance, design, and conduct limitations are summarized in Tables 11 and 12.

MISTRAL-C

The MRI Investigation in TAVI with Claret (MISTRAL-C) multicenter, double-blind trial randomized patients with aortic stenosis to transfemoral TAVI with (n=32) and without (n=33) CEP with the Sentinel device at 4 study sites in the Netherlands. (119) The primary end point was the number of new cerebral lesions by diffusion-weighted MRI at 5 to 7 days after TAVI. Study characteristics and results are summarized in Tables 9 and 10. Twenty-eight patients did not undergo a follow-up MRI for various reasons, including: implantation of a non-MRI compatible pacemaker (n=10), patient refusal (n=6), unstable clinical condition/deceased (n=5), logistical challenges (n=4), and delirium (n=3). Of the 57% of patients with a follow-up MRI available, 78% had new brain lesions. Lesions were numerically fewer with a smaller total lesion volume in CEP versus control groups (95 mm^3 vs. 197 mm^3, respectively). In protected brain regions, no lesions were detected in 55% and 20% of patients in the CEP and control groups,

respectively (p=.04). While changes in neurocognitive performance were not significantly different at 5 days, neurocognitive deterioration was present in 1 (4%) patient in the CEP groups compared to 6 (27%) in the control group (p=.017). Two patients had a disabling stroke in the control group compared to none in the CEP group. Study relevance, design, and conduct limitations are summarized in Tables 11 and 12.

SENTINEL

The Cerebral Protection in Transcatheter Aortic Valve Replacement SENTINEL Study was a randomized, double-blind trial comparing TAVI with and without transcatheter CEP with the Sentinel device across 19 centers in the U.S. and Germany. (120) Individuals with severe symptomatic aortic stenosis and high surgical risk were randomized 1:1:1 into a safety arm (n=123; CEP only), a control imaging arm (n=119), and a CEP device imaging arm (n=121). Blinded diffusion-weighted MRI and neurocognitive function assessments were performed in the device and control arms, in addition to histopathologic evaluation of particulate debris from extracted CEP filters in the device arm. Post-procedure neurological evaluations were conducted at 30 and 90 days. MRI studies were conducted at baseline and 2 to 7 days to identify the formation of any new lesions. The primary safety endpoint was occurrence of MACCE at 30 days compared with a historical performance goal of 18.3% based on prior studies. MACCE was defined as all deaths, all strokes (disabling and non-disabling), and acute kidney injury (stage 3). The primary efficacy endpoint was reduction in median total new lesion volume in protected territories between the device and control arms as assessed by MRI at 2 to 7 days post-TAVI, with a pre-specified success criterion of 30% reduction. The correlation of lesion volume with neurocognitive function changes and histopathological evaluations was a prespecified secondary endpoint. Study characteristics and results are summarized in Tables 9 and 10. While the CEP device safety cohort met the noninferiority margin for 30-day MACCE rates (p<.001), the trial failed to meet the primary effectiveness superiority endpoint. No significant differences were noted between device and control cohorts in the efficacy population for any MACCE (p=.405), all cause death (p=.65), stroke (p=.25) or acute kidney injury (p=1.00). While the CEP device efficacy cohort met the 30% prespecified treatment effect success criterion with a reduction in median total new lesion volume of 42% in protected territories, this outcome was not significantly different in device versus control arms (p =.33). Additionally, no significant differences were noted between groups for median number of new lesions in protected or all territories, (p=.90 or .81, respectively) or median total new lesion volume in all territories (p=.77). Neurocognitive testing showed no difference in overall composite scores at baseline, 30 days, or 90 days between study arms. A post hoc analysis adjusting for valve type, baseline T_2/FLAIR lesion volume, and their interaction found significant reductions in new lesion volume in both protected and all territories in the device versus control arms (p=.025 and .050, respectively). Particulate debris, including acute thrombus, was found in filters from 99% of patients. The study investigators noted that the SAPIEN 3 TAVI device derived little to no benefit from CEP compared to other TAVI device types used in the trial, for reasons that are not clear. Study relevance, design, and conduct limitations are summarized in Tables 11 and 12.

The SENTINEL trial formed the basis for de novo regulatory approval in the United States. (10) The FDA Circulatory System Devices Panel of the Medical Devices Advisory Committee concluded that the device demonstrated reasonable assurance of safety, but only possible benefit for reducing peri-procedural ischemic injury to the brain. The panel agreed that while MRI evaluations of new lesion volume had limitations as a surrogate endpoint for clinical stroke, consistent capture of embolic debris is a meaningful outcome to clinicians and patients.

PROTECTED TAVR

The Stroke PROTECTion with Sentinel During Transcatheter Aortic Valve Replacement study (PROTECTED TAVR) was an open label, randomized trial of TAVI with (n=1501) and without CEP (n=1499) with the Sentinel device conducted across 51 sites in the United States, Australia, and Europe. (121) The primary end point was incidence of stroke within 72 hours after TAVI or before discharge. Study characteristics and results are summarized in Tables 9 and 10. CEP device deployment was considered successful in 94.4% of patients. The incidence of the primary outcome was not significantly different between CEP and control groups (p=.30). Disabling stroke occurred in 0.5% of the patients in the CEP group and 1.3% of those in the control group, with a number needed to treat of 125. No significant differences between CEP and control groups were observed for total deaths (0.5% vs. 0.3%), stroke, transient ischemic attack, or delirium (3.1% vs. 3.7%), or acute kidney injury (0.5% vs. 0.5%). One patient (0.1%) had a vascular complication at the CEP access site. Study relevance, design, and conduct limitations are summarized in Tables 11 and 12.

BHF PROTECT-TAVI

Kharbanda et al. (2025) reported results of the BHF PROTECT-TAVI trial, a prospective, multicenter, open-label, RCT evaluating routine CEP during TAVI using the Sentinel device. (122) A total of 7,635 patients undergoing TAVI across 33 UK centers were randomized 1:1 to receive CEP (n=3815) or no CEP (n=3820). The trial used an adaptive design with planned interim analyses and was stopped early for futility after 134 stroke events, as the prespecified boundary excluded a 40% relative risk reduction, indicating the primary efficacy objective was unlikely to be met. The primary endpoint was stroke within 72 hours or before hospital discharge, which occurred in 2.1% of the CEP group and 2.2% of the control group (risk difference, −0.02 percentage points; 95% CI, −0.68 to 0.63; p=.94), with no significant between-group differences observed. Disabling stroke at 6–8 weeks occurred in 1.2% vs. 1.4% and severe stroke within 72 hours in 0.5% vs. 0.5%, respectively, with no observed benefit in the CEP arm. Secondary outcomes were similar between groups, including death within 72 hours (0.8% vs. 0.7%), and the composite of death or stroke (2.8% vs. 2.7%). The trial also reported no difference in transient ischemic attack (0.5% vs. 0.3%) or combined death/stroke/TIA (3.3% vs. 3.1%). Serious adverse events occurred more frequently in the CEP group (0.6% vs. 0.3%), and access-site complications were slightly higher at both hospital discharge (8.1% vs. 7.7%) and 6 to 8 week follow-up (0.8% vs. 0.4%). The results were consistent across all prespecified subgroups and complier-adjusted analyses.

Table 9. Characteristics of Randomized Controlled Trials (RCTs) Comparing Transcatheter Aortic Valve Implantation (TAVI) With and Without Transcatheter Cerebral Embolic Protection

					Interventions	
Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**TAVI + CEP**	**TAVI**
Haussig et al. (2016) (118); CLEAN-TAVI	Germany	1	2013-2014	• Mean age, 79-80 y (female, 28%-29%) • Severe, symptomatic aortic stenosis • Elevated surgical risk (mean STS PROM score, 5.2-5.6) • <4% STS PROM risk level (38%-40%) • 4%-10% STS PROM risk level (48%-52%)	• Transfemoral TAVI using the Medtronic Core Valve plus cerebral embolic protection with the Claret Montage Dual Filter System (n=50)	• Transfemoral TAVI without CEP (n=50) • The control group had significantly more patients with insulin-dependent diabetes (30% vs. 10%), less pre-existing stage 3 kidney disease (22% vs. 46%), and less prior coronary artery bypass surgery (4% vs. 16%)

Van Mieghem et al. (2016); (119) MISTRAL-C	Nether-lands	4	2013-2015	• Median age, 81 years (female, 48%)
				• Elevated surgical risk (median STS PROM, 4.8%)
				• TAVI device (%)
				  ○ SAPIEN 3 (54)
				  ○ CoreValve (25)
				  ○ SAPIEN XT (15)
					• Transfemoral TAVI plus CEP with the Sentinel system (n=32)
					• Median STS PROM risk level, 4.6 (IQR, 3.4 to 6.3)
						• Transfemoral TAVI without CEP (n=32)
						• Median STS PROM risk level, 5.8 (IQR, 3.5 to 9.8) (p=.029 compared to CEP)

Kapadia et al. (2017); (120) SENTINEL	U.S. and Germany	19	2014-2016	• Mean age, 83.4 y (female, 52.1%)	• CEP device, Sentinel system	• Efficacy population, n=119 • TAVI device (%)

				• Severe, symptomatic aortic stenosis
				• Elevated surgical risk (median STS PROM score, 6.0 [IQR, 4.2 to 8.1])
				• No contra-indications for right radial or brachial artery access or MRI
				• Transfemoral transapical TAVI permitted depending on device
					• Efficacy population, n=121
					• TAVI device (%)
					  ○ SAPIEN 3 (55.8)
					  ○ CoreValve Evolut R (24.2)
					  ○ SAPIEN XT (17.5)
					  ○ CoreValve (2.5)
					• Safety population, n=123
					• TAVI device (%)
					  ○ SAPIEN 3 (47.9)
					  ○ CoreValve Evolut R (29.8)
					  ○ SAPIEN XT (19.0)
					  ○ CoreValve (3.3)
						○ SAPIEN 3 (53.4)
						○ CoreValve Evolut R (23.7)
						○ SAPIEN XT (16.9)
						○ CoreValve (5.9)

Kapadia et al. (2022); (121) PROTECTED TAVR	U.S., Australia, Denmark, France, Germany, and Italy	51	2020-2022	• Mean age, 78.9 y (female, 38%-42%) • Symptomatic aortic stenosis • High or extreme surgical risk, 30.4% • Intermediate surgical risk, 33%-34% • Low surgical risk, 35%-36% • TAVI device (%) ○ SAPIEN 3 or iteration (64%)	• Transfemoral TAVI plus Sentinel CEP system (n=1501)	• Transfemoral TAVI without cerebral embolic protection (n=1499)

				○ Evolut R/ Evolut PRO or iteration (24%)		

CEP: cerebral embolic protection; IQR: interquartile range; MRI: magnetic resonance imaging; STS PROM: Society of Thoracic Surgeons predicted risk of operative mortality; TAVR: transcatheter aortic valve replacement.

Table 10a. Results of RCTs Comparing TAVI With and Without Transcatheter Cerebral Embolic Protection

Study	Safety Outcome	Results of Safety Outcome, %			
Haussig et al. (2016); (118), CLEAN-TAVI	Neurological symptoms indicative of stroke at 2, 7, and 30 days	TAVI + CEP	TAVI	TE (95% CI)	p-value
		2 days: 5 (10%); 7 days: 5 (10%); 30 days: 4 (8%)	2 days: 5 (10%); 7 days: 5 (10%); 30 days: 4 (8%)	NR	NR (NSD)
Van Mieghem et al. (2016); (119), MISTRAL-C	Deaths at 30 days or stroke	TAVI + CEP	TAVI	TE (95% CI)	p-value
	Deaths	1 (3%)	3 (10%)	RR, 0.36 (0.04-3.43)	.371
	Strokes (disabling, non-disabling, or delirium)	1 (3%)	7 (21%)	NR	NR
Kapadia et al. (2017); (120), SENTINEL	MACCE rate at 30 days (all death, all stroke, or stage 3 acute kidney injury)	TAVI + CEP	TAVI	TE (95% CI)	p-value
	Safety population	7.3	18.3[a]	NR	<.001[b]
	Efficacy population	7.3	9.9	NR	.405

Kapadia et al. (2022); (121), PROTECTED TAVR	Death from any cause or stroke within 72 hours	TAVI + CEP	TAVI	TE (95% CI)	p-value
		2.7	3.0	MD, 0.3 (-1.5 to 0.9)	NR (NSD)

CEP: cerebral embolic protection; CI: confidence interval; IQR: interquartile range; MACCE: major adverse cardiac and cerebrovascular events; MD: mean deviation; MRI: magnetic resonance imaging; NA: not applicable; NR: not reported; NSD: no significant difference; RR: relative risk; TAVR: transcatheter aortic valve replacement; TE: treatment effect.

[a] Historical performance criterion for noninferiority.

[b] Noninferiority margin met.

[c] Although the CEP group exceeded the prespecified 30% reduction goal compared to the control arm, the difference between groups was not significantly different.

[d] Study was considered underpowered due to higher-than-expected number of patients with missing follow-up MRI imaging.

Table 10b. Results of RCTs Comparing TAVI With and Without Transcatheter Cerebral Embolic Protection

Study	**Safety Outcome**	**Primary Efficacy Outcome**	**Results of Primary Efficacy Outcome, median (IQR)**			
Haussig et al. (2016); (118), CLEAN-TAVI	Neurological symptoms indicative of stroke at 2, 7, and 30 days	Median new lesion number on MRI in potentially protected regions at 2 days	TAVI + CEP	TAVI	TE (95% CI)	p-value
			4.00 (3.00-7.25)	10.00 (6.75-17.00)	MD, 5.0 (2.0-8.0)	<.001
Van Mieghem et al. (2016); (119), MISTRAL-C	Deaths at 30 days or stroke	New cerebral lesions and lesion volume on MRI at 5-7 days after TAVI	TAVI + CEP	TAVI	TE (95% CI)	p-value
	Deaths		95 (10-257)	197 (95-525)	NR	NR[d]
	Strokes (disabling, non-		--	--	--	--

	disabling, or delirium)					
Kapadia et al. (2017); (120), SENTINEL	MACCE rate at 30 days (all death, all stroke, or stage 3 acute kidney injury)	Median total new lesion volume (mm^3) on MRI in protected territories on days 2-7	TAVI + CEP	TAVI	TE (95% CI)	p-value
	Safety population		NA	NA	NA	NA
	Efficacy population		02.83 (NR)	177.98 (NR)	NR	.33[c]
Kapadia et al. (2022); (121), PROTECTED TAVR	Death from any cause or stroke within 72 hours	Stroke within 72 hours after TAVI or before discharge	TAVI + CEP	TAVI	TE (95% CI)	p-value
			2.3	2.9	MD, -0.6 (-1.7 to 0.5)	.30

CEP: cerebral embolic protection; CI: confidence interval; IQR: interquartile range; MACCE: major adverse cardiac and cerebrovascular events; MD: mean deviation; MRI: magnetic resonance imaging; NA: not applicable; NR: not reported; NSD: no significant difference; RR: relative risk; TAVR: transcatheter aortic valve replacement; TE: treatment effect.

[a] Historical performance criterion for noninferiority.

[b] Noninferiority margin met.

[c] Although the CEP group exceeded the prespecified 30% reduction goal compared to the control arm, the difference between groups was not significantly different.

[d] Study was considered underpowered due to higher-than-expected number of patients with missing follow-up MRI imaging.

Table 11. Study Relevance Limitations

Study, Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Haussig et al. (2016); (118), CLEAN-TAVI	3: Included patients with varying surgical risk; median STS risk score was 5.2-5.6; 4: Study population racial and	4: CEP device used in this trial is a precursor to the currently marketed Sentinel device.		2: Unclear how neuroimaging outcomes correlate with neurofunctional health outcomes; 6: No rationale for clinically significant	1, 2: Outcome reporting limited to 2, 7, and 30 days.

	ethnic demographics not reported.			difference provided.	
Van Mieghem et al. (2016); (119), MISTRAL-C	3: Included patients with varying surgical risks; surgical risks were significantly different between CEP and control arms; 4. Study population racial and ethnic demographics not reported.	5: Various TAVI devices used with CEP which may limit generalizability of results.		2: Unclear how neuroimaging outcomes correlate with neurofunctional health outcomes; only pooled neuroimaging outcomes reported.	1, 2: Major outcome reporting limited to 5-7 and 30 days.
Kapadia et al. (2017); (120), SENTINEL	3: Included patients with varying surgical risk; median STS risk score was <8; 4: Study population racial and ethnic demographics not reported.	5: Various TAVI devices used with CEP which may limit generalizability of results; unclear what proportion of patients were treated with transfemoral versus transapical TAVI.		2: Unclear how neuroimaging outcomes correlate with neurofunctional health outcomes.	1, 2: Primary outcome endpoints limited to 2-7 or 30 days for efficacy and safety, respectively.
Kapadia et al. (2022); (121), PROTECTED TAVR	3: Included patients with varying surgical risk; 4: Study population racial and ethnic demographics not reported.	5: Various TAVI devices used with CEP which may limit generalizability of results;		2: Unclear how neuroimaging outcomes correlate with neurofunctional health outcomes.	1, 2: Outcomes limited to 72 hours post-procedure.

CEP: cerebral embolic protection; STS: Society of Thoracic Surgeons; TAVR: transcatheter aortic valve replacement.

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled study populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest; 5. Other.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not established and validated measurements; 5. Clinically significant difference not prespecified; 6. Clinically significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 12. Study Design and Conduct Limitations

Study; Trial	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Haussig et al. (2016); (118), CLEAN-TAVI					3: Rationale for power calculations not specified.	
Van Mieghem et al. (2016); (119), MISTRAL-C				1: Study considered underpowered due to higher than expected number of patients with missing follow-up MRI (43%).	3: Rationale for power calculations not specified.	
Kapadia et al. (2017); (120), SENTINEL						3: Confidence intervals not reported.
Kapadia et al. (2022); (121), PROTECTED TAVR					3: Rationale for power calculations unclear.	

MRI: magnetic resonance imaging.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

[b] Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.
[c] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[d] Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
[e] Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
[f] Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4.Comparative treatment effects not calculated.

Section Summary: Cerebral Embolic Protection During Transcatheter Aortic Valve Implantation

The evidence related to the use of CEP devices during TAVI consists of 1 meta-analysis and 5 RCTs with follow-up ranging from 72 hours to 8 weeks. One meta-analysis found that patients with CEP had a lower rate of major adverse cardiac events, mortality, and stroke than patients with no CEP at 30 days post-TAVI; no differences were noted in the rate of vascular complications, AKI, or major life-threatening bleeding. The other meta-analysis, which didn't include observational evidence, found no significant differences in the rate of stroke, disabling stroke, or all-cause mortality when comparing outcomes between CEP and non-CEP TAVI. Three RCTs largely focused on the number and/or volume of new brain lesions detected on MRI. Only the CLEAN-TAVI trial found a statistically significant reduction in the number of new brain lesions with CEP; however, the relevance of this trial is limited as it used a precursor to the currently marketed Sentinel device. The PROTECTED TAVR trial, enrolled 3000 patients and found the incidence of stroke within 72 hours post-TAVI or before hospital discharge, was not significantly different between CEP and control groups. The largest RCT to date evaluating CEP during TAVI enrolled 7635 participants and found that routine use of the Sentinel device did not reduce the incidence of stroke within 72 hours or before hospital discharge compared to TAVI without CEP; secondary outcomes, including disabling stroke and all-cause mortality, were similar between groups, with no differences in overall complication rates. Prior trials have also generally failed to show a significant reduction in major cardiac and cerebrovascular events or neurocognitive protection. While trials enrolled patients across all surgical risk levels, outcome reporting was not stratified by risk level. The pivotal SENTINEL trial also noted that TAVI procedures performed with the SAPIEN 3 valve derived little to no benefit from CEP compared to other TAVI valves used in the trial for reasons that are not clear.

Summary of Evidence

For individuals who have severe symptomatic aortic stenosis who are at prohibitive risk for open surgery who receive transcatheter aortic valve implantation (TAVI), the evidence includes a randomized controlled trial (RCT) comparing TAVI with medical management in individuals at prohibitive risk of surgery, a single-arm prospective trial, multiple case series, and multiple systematic reviews. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related mortality and morbidity. For patients who are not surgical candidates due to excessive surgical risk, the Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN

Transcatheter HeartValve (PARTNER B) trial reported on results for patients treated with TAVI by the transfemoral approach compared with continued medical care with or without balloon valvuloplasty. There was a large decrease in mortality for the TAVI patients at 1 year compared with medical care. This trial also reported improvements in other relevant clinical outcomes for the TAVI group. There was an increased risk of stroke and vascular complications in the TAVI group. Despite these concerns, the overall balance of benefits and risks from this trial indicate that health outcomes are improved. For patients who are not surgical candidates, no randomized trials have compared the self-expandable valve with best medical therapy. However, results from the single-arm CoreValve Extreme Risk Pivotal Trial met trialists' prespecified objective performance goal. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have severe symptomatic aortic stenosis who are at high risk for open surgery who receive TAVI, the evidence includes 2 RCTs comparing TAVI with surgical repair in individuals at high risk for surgery and 1 RCT comparing 2 types of valves, multiple nonrandomized comparative studies, and systematic reviews of these studies. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related mortality and morbidity. For patients who are high risk for open surgery and are surgical candidates, the PARTNER A trial reported noninferiority for survival at 1 year for the balloon-expandable valve compared with open surgery. In this trial, TAVI patients also had higher risks for stroke and vascular complications. Nonrandomized comparative studies of TAVI vs open surgery in high-risk patients have reported no major differences in rates of mortality or stroke between the 2 procedures. Since the publication of the PARTNER A trial, the CoreValve High Risk Trial demonstrated noninferiority for survival at 1 and 2 years for the self-expanding prosthesis. This trial reported no significant differences in stroke rates between groups. An RCT directly comparing the Portico valve with other FDA-approved valves found an increase in safety outcomes with Portico at 30 days but no major differences at 2 years. Gender-specific meta-analyses have found improved mortality with TAVI compared with surgical aortic valve replacement (SAVR) in women. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have severe symptomatic aortic stenosis who are at intermediate risk for open surgery who receive TAVI, the evidence includes 4 RCTs comparing TAVI with surgical repair including individuals at intermediate surgical risk, 2 RCTs only in patients with intermediate risk, and multiple systematic reviews and nonrandomized cohort studies. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related mortality and morbidity. Five RCTs have evaluated TAVI in patients with intermediate risk for open surgery. Four of them, which included over 4000 patients combined, reported noninferiority of TAVI vs SAVR for their composite outcome measures (generally including death and stroke). A subset analysis of patients (n=383) with low and intermediate surgical risk from a fourth trial reported higher rates of death at 2 years for TAVI vs SAVR. The final study (N=70) had an unclear hypothesis and reported 30-day mortality rates favoring SAVR (15% vs 2%, p=0.07) but used a transthoracic approach. The rates of adverse events differed between groups, with bleeding, cardiogenic shock, and acute kidney injury higher in patients randomized to open surgery and

permanent pacemaker requirement higher in patients randomized to TAVI. Subgroup analyses of meta-analyses and the transthoracic arm of the Leon et al. (2010) RCT has suggested that the benefit of TAVI may be limited to patients who are candidates for transfemoral access. Although several RCTs have 2 years of follow-up postprocedure, it is uncertain how many individuals require reoperation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have severe symptomatic aortic stenosis who are at low risk for open surgery who receive TAVI, the evidence includes RCTs comparing TAVI with surgical repair in individuals selected without specific surgical risk criteria but including patients at low surgical risk and RCTs enrolling only low surgical risk patients, systematic reviews, and nonrandomized cohort studies. Relevant outcomes are OS, symptoms, morbid events, and treatment-related mortality and morbidity. Four RCTs (Evolut Low Risk Trial, NOTION-2, EARLY TAVR, and the Study to Establish the Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients Who Have Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement [PARTNER 3]) have been conducted exclusively in patients at low surgical risk and 1 RCT, Nordic Aortic Intervention Trial included predominantly patients at low surgical risk. In the Evolut Low Risk Trial, transcatheter aortic valve replacement was noninferior to SAVR with respect to the composite outcome of death or disabling stroke at 24 months. In the PARTNER 3 trial, the rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVI than SAVR. In the Nordic Aortic Intervention Trial, the risk of the composite outcome of death from any cause, stroke, or myocardial infarction at 5 years was similar for TAVI and SAVR and transcatheter aortic valve replacement showed less structural valve deterioration than SAVR at 10 years. In the publicly sponsored UK TAVI trial, which was conducted in patients aged 70 years or older with predominantly low surgical risk, TAVI was noninferior to SAVR with respect to all-cause mortality at 1 year. The NOTION-2 trial found no significant difference between TAVI and SAVR groups in the composite primary outcome of death, stroke, or valve-related rehospitalization at 1 year. TAVI was associated with lower risks of bleeding and atrial fibrillation but higher rates of pacemaker implantation, non-disabling stroke, and paravalvular regurgitation. The EARLY TAVR trial compared early TAVI versus clinical surveillance in asymptomatic patients with severe aortic stenosis and preserved LVEF and found that early TAVI significantly reduced the composite primary outcome of death, stroke, or unplanned cardiovascular hospitalization, primarily due to fewer hospitalizations. Secondary outcomes favored early TAVR in terms of quality of life and preservation of cardiac structure and function. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have valve dysfunction and aortic stenosis or regurgitation after open surgical aortic valve repair who receive transcatheter aortic “valve-in-valve” (ViV) implantation, the evidence includes observational studies including registry data with follow-up ranging from 1 month to 5 years and a systematic review. Relevant outcomes are OS, symptoms, morbid events, and treatment-related mortality and morbidity. Recent meta-analyses of observational studies have compared ViV TAVI to redo-SAVR and have reported a reduced risk of short-term mortality (<30 days) with ViV TAVI. Beyond 30 days, meta-analyses have reported conflicting

mortality outcomes, with some favoring ViV TAVI, others favoring rSAVR, and others showing no significant difference between the two treatments. The PARTNER 2 registry reported a 50.6% rate of all-cause mortality after 5 years among patients with high surgical risk; patients who received a 23-mm SAPIEN XT valve had a significantly higher risk of mortality compared to those who received a 26-mm valve (hazard ratio, 1.55; 95% confidence interval, 1.09 to 2.20; p=.01). The CorHealth Ontario Cardiac Registry found that at 5 years after treatment, patients who underwent ViV TAVI had greater OS than rSAVR in a matched cohort of patients (absolute risk difference, -7.5; 95% confidence interval, -12.6% to -2.3%). An analysis using the Danish National Patient Registry data reported that ViV TAVI had similar mortality and rehospitalization rates compared to native valve TAVI at 1 and 5 years follow-up. Given that no RCTs are available, selection bias cannot be ruled out. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have symptomatic aortic stenosis who receive a cerebral embolic protection (CEP) device while undergoing TAVI, the evidence includes 2 meta-analysis and 5 RCTs of patients with low- to high-risk for open surgery. Relevant outcomes are OS, symptoms, morbid events, and treatment-related mortality and morbidity. One meta-analysis found that patients with CEP had a lower rate of major adverse cardiac events, mortality, and stroke than patients with no CEP at 30 days post-TAVI; no differences were noted in the rate of vascular complications, acute kidney injury, or major life-threatening bleeding. The other meta-analysis, which didn't include observational evidence, found no significant differences in the rate of stroke, disabling stroke, or all-cause mortality when comparing outcomes between CEP and non-CEP TAVI. Three RCTs have primarily focused on the number and/or volume of new brain lesions detected on magnetic resonance imaging with unclear correlations to neurocognitive outcomes. Only 1 of these trials (CLEAN-TAVI) found a significant reduction in brain lesion number; however, the relevance of this trial is limited as it used a precursor to the currently marketed Sentinel device. The PROTECTED TAVR trial, enrolled 3000 patients and found the incidence of stroke within 72 hours post-TAVI or before hospital discharge, was not significantly different between CEP and control groups. The largest RCT to date evaluating CEP during TAVI enrolled 7635 participants and found that routine use of the Sentinel device did not reduce the incidence of stroke within 72 hours or before hospital discharge compared to TAVI without CEP; secondary outcomes, including disabling stroke and all-cause mortality, were similar between groups, with no differences in overall complication rates. Prior trials have generally failed to demonstrate neurocognitive protection or significant reductions in major cardiac and cerebrovascular events. Studies have not stratified results by operative risk levels and have suggested differential benefits based on valve type. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

2024 Clinical Input

For individuals with valve dysfunction and aortic stenosis or regurgitation after open surgical aortic valve repair, clinical input provides consistent support that the use of transcatheter ViV implantation provides a clinically meaningful improvement in the net health outcome and is consistent with generally accepted medical practice.

For individuals with valve dysfunction and aortic stenosis or regurgitation after open surgical aortic valve repair, clinical input provides consistent support that the use of transcatheter ViV implantation provides a clinically meaningful improvement in the net health outcome and is consistent with generally accepted medical practice.

The following patient selection criteria for transcatheter aortic valve replacement (TAVR) with a transcatheter heart valve system approved for use for repair of a degenerated bioprosthetic valve (ViV) were informed by clinical input and the published evidence:

- Failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve; AND
- New York Heath Association heart failure class II, III, or IV symptoms; AND
- Individual is not an operable candidate for open surgery, as documented by at least 2 cardiovascular specialists (including a cardiac surgeon); OR
- Individual is an operable candidate but is considered at increased surgical risk for open surgery, as documented by at least 2 cardiovascular specialists (including a cardiac surgeon; see Policy Guidelines section); OR
- Individual is considered at increased surgical risk for open surgery (e.g., repeat sternotomy) due to a history of congenital vascular anomalies AND/OR has a complex intrathoracic surgical history, as documented by at least 2 cardiovascular specialists (including a cardiac surgeon).

Clinical input noted that there are certain technical impediments that may increase the risk of redo surgical aortic valve replacement (rSAVR) that are not captured by Society of Thoracic Surgeons risk score, including porcelain aorta, prior mediastinal surgeries, patent bypass grafts, or a particularly adherent left internal mammary artery. Additionally, elderly individuals that do not meet high-risk criteria can benefit from the early recovery offered by TAVR. Clinical input also emphasized that there is unlikely to be equipoise for randomization of patients with structural bioprosthetic valve degeneration to aortic valve replacement via any modality versus conservative therapy.

Practice Guidelines and Position Statements

American College of Cardiology and American Heart Association

In 2014, the American College of Cardiology and the American Heart Association published joint guidelines on the management of valvular heart disease. (123) Both groups issued a joint focused update in 2017. (124) In 2020, a new full guideline was published that replaces the 2014 revision and 2017 focused update. (125) The 2020 guidelines made the following recommendations on timing of intervention and choice of surgical or transcatheter intervention for treatment of aortic stenosis (Table 13). Additionally, the guidelines state the following:

- "Treatment of severe aortic stenosis with either a transcatheter or surgical valve prosthesis should be based primarily on symptoms or reduced ventricular systolic function. Earlier intervention may be considered if indicated by results of exercise testing, biomarkers, rapid progression, or the presence of very severe stenosis."
- "Indications for TAVI are expanding as a result of multiple randomized trials of TAVI versus surgical aortic valve replacement. The choice of type of intervention for a patient with

severe aortic stenosis should be a shared decision-making process that considers the lifetime risks and benefits associated with type of valve (mechanical versus bioprosthetic) and type of approach (transcatheter versus surgical)."

Table 13. Recommendations on Surgical or Transcatheter Intervention for Aortic Stenosis

Recommendation	COR	LOE
Timing of Intervention of AS		
"In adults with severe high-gradient AS (Stage D1) and symptoms of exertional dyspnea, heart failure, angina, syncope, or presyncope by history or on exercise testing, AVR is indicated."	I	A
"In asymptomatic patients with severe AS and a left ventricular ejection fraction <50% (Stage C2), AVR is indicated."	I	B
"In asymptomatic patients with severe AS (Stage C1) who are undergoing cardiac surgery for other indications, AVR is indicated."	I	B
"In symptomatic patients with low-flow, low-gradient severe AS with reduced left ventricular ejection fraction (Stage D2), AVR is recommended."	I	B
"In symptomatic patients with low-flow, low-gradient severe AS with reduced left ventricular ejection fraction (Stage D3), AVR is recommended if AS is the most likely cause of symptoms."	I	B
"In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when an exercise test demonstrates decreased exercise tolerance (normalized for age and sex) or a fall in systolic blood pressure of ≥10 mmHg from baseline to peak exercise."	IIa	B
"In asymptomatic patients with very severe AS (defined as an aortic velocity of ≥5 m/s) and low surgical risk, AVR is reasonable."	IIa	B
"In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when the serum B-type natriuretic peptide level is >3 times normal."	IIa	B
"In asymptomatic patients with high-gradient severe AS (Stage C1) and low surgical risk, AVR is reasonable when serial testing shows an increase in aortic velocity ≥0.3 m/s per year."	IIa	B
"In asymptomatic patients with severe high-gradient AS (Stage C1) and a progressive decrease in left ventricular ejection fraction on at least 3 serial imaging studies to <60%, AVR may be considered."	IIb	B
"In patients with moderate AS (Stage B) who are undergoing cardiac surgery for other indications, AVR may be considered."	IIb	C
Choice of SAVR Versus TAVI for Patients for Whom a Bioprosthetic AVR is Appropriate		
"For symptomatic and asymptomatic patients with severe AS and any indication for AVR who are <65 years of age or have a life expectancy >20 years, SAVR is recommended."	I	A
"For symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either	I	A

SAVR or transfemoral TAVI is recommended after shared decision-making about the balance between expected patient longevity and valve durability."		
"For symptomatic patients with severe AS who are >80 years of age or for younger patients with a life expectancy of <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to SAVR."	I	A
"In asymptomatic patients with severe AS and a left ventricular ejection fraction <50% who are ≤80 years of age and have no anatomic contraindication to transfemoral TAVI, the decision between TAVI and SAVR should follow the same recommendations as for symptomatic patients in the 3 recommendations above."	I	B
"For asymptomatic patients with severe AS and an abnormal exercise test, very severe AS, rapid progression, or an elevated B-type natriuretic peptide, SAVR is recommended in preference to TAVI."	I	B
"For patients with an indication for AVR for whom a bioprosthetic valve is preferred but valve or vascular anatomy or other factors are not suitable for transfemoral TAVI, SAVR is recommended."	I	A
"For symptomatic patients of any age with severe AS and a high or prohibitive surgical risk, TAVI is recommended if predicted post-TAVI survival is >12 months with an acceptable quality of life."	I	A
"For symptomatic patients with severe AS for whom predicted post-TAVI or post-SAVR survival is <12 months or for whom minimal improvement in quality of life is expected, palliative care is recommended after shared decision-making, including discussion of patient preferences and values."	I	C
"In critically ill patients with severe AS, percutaneous aortic balloon dilation may be considered as a bridge to SAVR or TAVI."	IIb	C
Intervention for Prosthetic Valve Stenosis		
"In patients with symptomatic severe stenosis of a bioprosthetic or mechanical prosthetic valve, repeat surgical intervention is indicated unless surgical risk is prohibitive."	I	B
"For severely symptomatic patients with bioprosthetic aortic valve stenosis and high or prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a Comprehensive Valve Center."	IIa	B
"For patients with significant bioprosthetic valve stenosis attributable to suspected or documented valve thrombosis, oral anticoagulation with a VKA is reasonable."	IIa	B
Prosthetic Valve Regurgitation		
"In patients with intractable hemolysis or HF attributable to prosthetic transvalvular or paravalvular leak, surgery is recommended unless surgical risk is high or prohibitive."	I	B

"In asymptomatic patients with severe prosthetic regurgitation and low operative risk, surgery is reasonable."	IIa	B
"In patients with prosthetic paravalvular regurgitation with the following: 1) either intractable hemolysis or NYHA class III or IV symptoms and 2) who are at high or prohibitive surgical risk and 3) have anatomic features suitable for catheter-based therapy, percutaneous repair of paravalvular leak is reasonable when performed at a Comprehensive Valve Center."	IIa	B
"For patients with severe HF symptoms caused by bioprosthetic valve regurgitation who are at high to prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a Comprehensive Valve Center."	IIa	B

AS: aortic stenosis; AVR: aortic valve replacement; COR: class of recommendation; HF: heart failure; LOE: level of evidence; NYHA: New York Heart Association; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve; ViV: valve-in-valve; VKA: vitamin K antagonist.

National Institute for Health and Care Excellence (NICE)

In June 2019, the NICE published interventional procedures guidance [IPG653] regarding ViV TAVI for aortic bioprosthetic valve dysfunction. (126) The guidance was informed by an interventional procedure overview described previously. (127) The guidance recommendation is that "Current evidence on the safety and efficacy of valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) for aortic bioprosthetic dysfunction is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit."

In November 2021, the NICE updated their guidance on heart valve disease. They recommend patients be offered TAVI if SAVR is contraindicated or the patient is at high surgical risk. (127)

Radiological Society of North America (RSNA) (129)

In 2018, the RSNA 3D printing Special Interest Group (SIG) published practice recommendations for medical 3D printing and appropriateness for clinical scenarios. “The practice parameters and recommendations are not intended as comprehensive standards.” The SIG acknowledges that, “In its current state, medical 3D printing has been performed for a variety of patients, but without evidence-based appropriateness guidelines.” While this group provided recommendations for specific clinical scenarios, they went on to state that, ”Adoption of common clinical standards regarding appropriate use, information and material management, and quality control are needed to ensure the greatest possible clinical benefit from3D printing.”

Medicare National Coverage

The Centers for Medicare & Medicaid Services published a decision memo on the use of TAVR in 2012 and 2019. (128) The 2019 memo indicated that the Centers for Medicare & Medicaid Services covers TAVI when used according to FDA indications when the following conditions are met:

- Device has FDA approval.

- The patient (preoperatively and postoperatively) is under the care of a heart team including an experienced cardiac surgeon and interventional cardiologist, who have independently examined the patient, as well as providers from other physician groups, advanced patient practitioners, nurses, research personnel, and administrators.
- The interventional cardiologist(s) and cardiac surgeon(s) jointly participate in the intra-operative technical aspects of TAVR.
- The hospital meets qualifications for performing TAVR.
- The heart team and hospital are participating in a prospective, national, audited registry that follows patients for at least 1 year and collects specific patient, practitioner, and facility level outcomes.
- The registry collects necessary data and has an analysis plan to address specific questions and results are reported publicly.

The memo also stated that TAVR could be covered for non-FDA-approved indications under the Coverage with Evidence Development program. The following is a summary of the main conditions required for Coverage with Evidence Development:

- The interventional cardiologist(s) and cardiac surgeon(s) jointly participate in the intra-operative technical aspects of TAVR.

TAVR is performed within a clinical study that has the following characteristics:

- "The clinical study must adhere to the … standards of scientific integrity and relevance to the Medicare population."
- The study must address quality of life and adverse events at follow-up periods of 1 year or longer.

The decision memo does not address concurrent use of a cerebral embolic protection device.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 14.

Table 14. Summary of Key Trials

NCT Number	Trial Name	Planned Enrollment	Completion Date
NCT06597188	Comparison of Transcatheter Aortic Valve Replacement with Surgical Aortic Valve Replacecment: a Prospective, Multicenter, International, Randomized Controlled, Non-inferiority Study for Bicuspid Aortic Valve Stenosis (PROMIS-BAV)	420	Aug 2031
NCT06818084	Transcatheter Treatment of Pure Aortic Regurgitation with VitaFlow Liberty System: a Prospective, Multicenter Study	120	Nov 2027

NCT06861361	Surgical Bioprosthesis Aortic Valve Replacement Vs. Myval Balloon-Expandable THV Series in Patients Aged 65 to 75 with Symptomatic Severe Aortic Stenosis Judged Eligible by Heart Team	1180	Nov 2031
NCT02701283	Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement	1016	Feb 2036
NCT06777368	REdo tranScatheter Aortic Valve Replacement for Transcatheter aOrtic Valve failuRE	225	Jul 2033
NCT06557798	REdo Transcatheter Aortic VALVE Implantation for the Management of Transcatheter Aortic Valve Failure (REVALVE)	550	Mar 2033
NCT06817148	Bicuspid Aortic Valve Replacement: EvaLuatIon of transcathetEr Versus surgEry-PILOT Trial	250	Feb 2037
NCT06257043	RECORD TAVR REGISTRY: Prospective, Multi-Center Registry of "Real World" Chinese Patients Undergoing Transcatheter Aortic Valve Replacement	3000	Jan 2034
NCT02701283	Transcatheter Aortic Valve Replacement With the Medtronic Transcatheter Aortic Valve Replacement System In Patients at Low Risk for Surgical Aortic Valve Replacement	2223	Mar 2026
NCT05261204	Transcatheter Aortic Valve Implantation Versus Standard Surgical Aortic Valve Operation for Aortic-Valve Stenosis in Patients at Risk to Severe Valve Obstruction.	1950	Mar 2024
NCT05002088[a]	Retrospective Assessment of the Portico Transcatheter Aortic Valve for Valve-in-Valve Use	100	Jun 2027
NCT03042104[a]	Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis	901	Mar 2032
NCT03112980	Randomized, Multi-Center, Event-Driven Trial of TAVI versus SAVR in Patients with	1417	Mar 2027

	Symptomatic Severe Aortic Valve Stenosis and Intermediate Risk of Mortality-DEDICATE		
NCT01586910[a]	Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI)	1746 (actual enrollment)	Nov 2026
NCT01057173	Transcatheter Versus Surgical Aortic Valve Implantation in Patients With Severe Aortic Valve Stenosis (NOTION)	280	Apr 2033
NCT01314313[a]	The PARTNER II Trial "Placement of AoRTic TraNscathetER Valves Trial" (US)	2032	Nov 2024
NCT01737528	Society of Thoracic Surgeons and American College of Cardiology Transcatheter Valve Therapy Registry (STS/ACC TVT Registry)	16,000	Jun 2035
NCT02000115[a]	Portico Re-sheathable Transcatheter Aortic Valve System US IDE Trial (PORTICO-IDE)	1150	Jul 2025
NCT02825134[a]	Nordic Aortic Valve Intervention Trial 2 - A Randomized Multicenter Comparison of Transcatheter Versus Surgical Aortic Valve Replacement in Younger Low Surgical Risk Patients With Severe Aortic Stenosis (NOTION-2)	372	Jun 2029
NCT02675114[a]	A Prospective, Randomized, Controlled, Multi-Center Study to Establish the Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients Who Have Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement (PARTNER 3)	1000	Dec 2029
NCT02163850[a]	SALUS Trial: TranScatheter Aortic Valve RepLacement System Pivotal Trial The Safety and Effectiveness of the Direct Flow Medical Transcatheter Aortic Valve System	878	Dec 2021 (unknown)

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	33361, 33362, 33363, 33364, 33365, 33366, 33367, 33368, 33369, 33370
HCPCS Codes	C9793

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
01/01/2026	Document updated. Coverage unchanged. Added references 96, 97, 99, 102, 122 and 128-129; others removed.
02/01/2025	Document updated with literature review. Coverage unchanged. References 107 and 108 added.
08/01/2024	Document updated with literature review, The following changes were made to coverage: 1) Removed the criterion of left ventricular ejection fraction greater than 20% for TAVI and ViV TAVI; 2) Modified criteria for TAVI ViV regarding risk/candidacy for open surgery; 3) Added: "Use of a cerebral embolic protection device (e.g., Sentinel) during transcatheter aortic valve replacement procedures is considered experimental, investigational and/or unproven"; and 4) Added: "3D predictive model generation for preplanning of a cardiac procedure, using data from cardiac computed tomographic angiography is considered experimental, investigational and/or unproven for all indications." References 1, 2, 10-12, 22, 69-73, 87, 89-90, 93, 98-100, 105-116 and 122-125 added; others updated and some deleted.
10/01/2022	Document updated with literature review. Coverage unchanged. References 7, 8, 24, 32, 47, 80, 83-85, and 94 added; others removed.
02/01/2022	Document updated with literature review. Policy updated to reflect U.S. Food and Drug Administration approval of the Portico™ Transcatheter Aortic Valve device. References 88-89 added.
07/01/2021	Document updated with literature review. Coverage unchanged. References 7, 40, 58-62, 77-78, and 85 added.
07/15/2020	Document updated with literature review. The following changes were made to Coverage: Medically necessary policy statement related to patients with native valve aortic stenosis changed to add an exclusion for patients with unicuspid or bicuspid aortic valve and to add an inclusion for patients at low risk for open surgery. The following references were added: 7, 15, 41-43, 56, 65-66, 69-74, and 77; other references removed.
07/01/2019	Reviewed. No changes.
11/01/2018	Document updated with literature review. Coverage revised in final bullet point of each statement to include the word "or" in these statements: "Patient is not an operable candidate for open surgery, as judged by at least two cardiovascular specialists (cardiologist and/or cardiac surgeon)…" Previously stated "(cardiologist and cardiac surgeon)." Added "Intermediate

	risk: Society of Thoracic Surgeons predicted operative risk score of 3% to 7%" to Note 2. References and rationale completely revised.
07/15/2017	Document updated with literature review. Coverage changed for transcatheter aortic valve replacement with a transcatheter heart valve system approved for use for repair of a degenerated bioprosthetic valve may be considered medically necessary when criteria are met. Previously this indication was considered experimental, investigational and/or unproven.
07/01/2016	Reviewed. No changes.
11/01/2015	Document updated with literature review. 1. The following was added to the conditional medically necessary statement: Transcatheter aortic valve replacement, with an FDA-approved transcatheter heart valve system performed via an approach consistent with the device's FDA-approved labeling may be considered medically necessary when criteria are met. 2. The following additional criteria to define severe aortic stenosis were added to the *NOTE: specific to the SAPIEN or CoreValve device to include an aortic valve area index of less than or equal to 0.6cm^2/m^2. The words peak aortic were added to the peak aortic-jet velocity greater than 4.0m/sec criteria and the aortic valve area of less than 0.8 cm^2 was changed to 1 cm^2. An additional ** NOTE was added to the coverage section to provide FDA guidance related to high risk, extreme risk or inoperable patients for open surgery. The following lists of procedural approaches were removed from the experimental, investigational and/or unproven Coverage statement: Procedures performed via the transaxillary, transiliac, transaortic or other approaches.
03/01/2014	Document updated with literature review. The following was added to the coverage section: 1) "Left ventricular ejection fraction >20%;" and "patients who are operable candidates but are at high risk for open surgery" were added to existing criteria for Transcatheter aortic valve replacement, performed via the transfemoral approach, for patients with aortic stenosis. 2) Transcatheter aortic valve replacement, performed via the transapical approach, may be considered medically necessary for patients with aortic stenosis when additional criteria are met. 3) Transcatheter aortic valve replacement is considered experimental, investigational, and/or unproven for all other indications, including but not limited to: Patients with a degenerated bio-prosthetic valve ("Valve-in-Valve" implantation) or Procedures performed via the transaxillary, transiliac, transaortic, or other approaches. 4) FDA definition of high risk for open surgery was added to the coverage section. CPT/HCPCS code(s) updated.
01/01/2013	Document updated. The following was added under coverage: Transcatheter aortic valve replacement performed via approaches other than transfemoral, including but not limited to the transapical approach for any indication is considered experimental, investigational and unproven. CPT/HCPCS code(s) updated.

10/15/2012	Document updated with literature review. Title changed from "Transcatheter Heart Valve Replacement". The following was added: Transcatheter aortic valve replacement, performed via the transfemoral approach, may be considered medically necessary for patients with aortic stenosis when stated criteria are present. Transcatheter aortic valve replacement is considered experimental, investigational, and unproven for all other indications, including but not limited to, patients at high risk for open surgery but who are operable candidates. Transcatheter aortic valve replacement performed via the transapical approach for any indication is considered experimental, investigational, and unproven. Transcatheter Pulmonary Valve Implantation was moved from this document to SUR707.029.
06/15/2011	Document updated with literature review. Coverage unchanged. The following was added: Medtronic Melody® Transcatheter Pulmonary Valve (TPV) and Ensemble® Transcatheter Valve Delivery System was added. The number of the policy was changed from SUR717.015 to SUR707.028.
03/01/2011	New Medical Document converted from position statement. Percutaneous heart valve replacement is considered experimental, investigational, and unproven by any method.
01/01/2011	Position Statement. Percutaneous heart valve replacement is considered experimental, investigational, and unproven by any method.