Medical Policy

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Title: Transcatheter Aortic Valve Implantation for Aortic Stenosis

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Populations	Interventions	Comparators	Outcomes
Individuals: • With severe symptomatic aortic stenosis who are at prohibitive risk for open surgery	Interventions of interest are: • Transcatheter aortic valve implantation	Comparators of interest are: • Medical management	Relevant outcomes include: • Overall survival • Symptoms • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With severe symptomatic aortic stenosis who are at high risk for open surgery	Interventions of interest are: • Transcatheter aortic valve implantation	Comparators of interest are: • Surgical aortic valve repair	Relevant outcomes include: • Overall survival • Symptoms • Morbid events

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Populations	Interventions	Comparators	Outcomes
			• Treatment-related mortality • Treatment-related morbidity
Individuals: • With severe symptomatic aortic stenosis who are at intermediate risk for open surgery	Interventions of interest are: • Transcatheter aortic valve implantation	Comparators of interest are: • Surgical aortic valve repair	Relevant outcomes include: • Overall survival • Symptoms • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With severe symptomatic aortic stenosis who are at low risk for open surgery	Interventions of interest are: • Transcatheter aortic valve implantation	Comparators of interest are: • Surgical aortic valve repair	Relevant outcomes include: • Overall survival • Symptoms • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With severe asymptomatic aortic stenosis who are at low risk for open surgery	Interventions of interest are: • Transcatheter aortic valve implantation	Comparators of interest are: • Clinical surveillance	Relevant outcomes include: • Overall survival • Symptoms • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With valve dysfunction and aortic stenosis or regurgitation after aortic valve repair	Interventions of interest are: • Transcatheter aortic • Valve-in-valve • implantation	Comparators of interest are: • Surgical aortic valve repair • Medical management	Relevant outcomes include: • Overall survival • Symptoms • Morbid events • Treatment-related mortality • Treatment-related morbidity
Individuals: • With severe symptomatic aortic stenosis who undergo transcatheter aortic valve implantation	Interventions of interest are: • Transcatheter aortic valve implantation with cerebral embolic protection	Comparators of interest are: • Transcatheter aortic valve implantation without cerebral embolic protection	Relevant outcomes include: • Overall survival • Symptoms • Morbid events • Treatment-related mortality • Treatment-related morbidity

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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.

OBJECTIVE

The objective of this evidence review is to evaluate whether the use of transcatheter aortic valve replacement, with or without the use of a cerebral embolic protection device, improves the net health outcome in individuals with severe aortic stenosis, depending on an individual's risk for open-heart surgery.

BACKGROUND

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 (ie, 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.

Disease Burden

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 aged 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

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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.

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. U.S. Food and Drug Administration 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		10/12	P110021

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Device and Indication	Manufacturer	Date Cleared	PMA
• Expanded to include high-risk aortic stenosis (transapical approach)			
• 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 a bioprosthetic valve with 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, 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
• Expanded to include failure of a bioprosthetic valve with intermediate or greater risk for open surgical therapy		10/24	P140031/S162

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Device and Indication	Manufacturer	Date Cleared	PMA
• Expanded to include asymptomatic severe native calcific aortic stenosis		05/25	P140031/S182
Medtronic CoreValve System™ • Severe native aortic stenosis at extreme risk or inoperable for open surgical therapy	Medtronic	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)		08/21	P130021/S091
• Expanded to include redo-transcatheter aortic valve replacement for patients at high risk for open-heart surgery		08/25	P130021/S174
LOTUS Edge™ Valve System • Severe native aortic stenosis at high or greater risk for open surgical therapy • See Note	Boston Scientific Corporation	04/19	P180029

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Device and Indication	Manufacturer	Date Cleared	PMA
Portico™ with FlexNav™ • Severe native aortic stenosis at high or greater risk for open surgical therapy	Abbott Medical	09/21	P190023
Navitor™ Transcatheter Aortic Valve Implantation System with FlexNav™ • Severe native aortic stenosis at high or greater risk for open surgical therapy	Abbott Medical	10/23	P190023/S016
Trilogy™ Transcatheter Heart Valve (THV) System • Symptomatic, severe native aortic regurgitation (AR) in patients at high or greater risk for surgical aortic valve replacement (SAVR)	JenaValve Technology, Inc.	03/26	P250024

FDA: U.S. Food and Drug Administration: PMA: premarket approval.

Note: 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 patients 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 :

- 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 device 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).[9,] With the Sentinel system serving as the predicate device, the panel expressed that the proposed indications for use of the

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TriGUARD 3 device were not supported by the safety and effectiveness data from the REFLECT II trial. Previously, the TriGUARD 3 device was granted CE mark approval in Europe in March 2020.[11,9,]

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POLICY

A. Transcatheter aortic valve replacement with an 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:

   1. Severe aortic stenosis (see Policy Guidelines) with a calcified aortic valve; **AND**

   2. New York Heart Association heart failure class II, III, or IV symptoms, or syncope or progressive angina due to aortic valve stenosis; **AND**

   3. Individual does not have unicuspid aortic valves.

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

   1. Failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve; **AND**

   2. New York Heart Association heart failure class II, III or IV symptoms, or syncope or progressive angina due to aortic valve stenosis; **AND**

   3. 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, (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).

C. Transcatheter aortic valve replacement (TAVR), is considered **experimental / investigational** for all other indications, including, but not limited to, asymptomatic severe aortic stenosis.

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

POLICY GUIDELINES

A. The U.S. Food and Drug Administration (FDA) definition of extreme risk or inoperable for open surgery:
   1. Predicted risk of operative mortality and/or serious irreversible morbidity 50% or higher for open surgery.

B. The FDA definition of high risk for open surgery:
   1. Society of Thoracic Surgeons (STS) predicted operative risk score of 8% or higher; or

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2. 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.

C. The FDA definition of intermediate risk:
   1. Society of Thoracic Surgeons predicted operative risk score of 3% to 7%.

D. Individuals with Society of Thoracic Surgeons predicted operative risk score of less than 3% or 4% are considered at low risk for open surgery.

E. 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,]

F. For the use of the SAPIEN or CoreValve devices, severe aortic stenosis is defined by the presence of one or more of the following criteria:
   1. An aortic valve area of less than or equal to 1 cm^2
   2. An aortic valve area index of less than or equal to 0.6 cm2/m2
   3. A mean aortic valve gradient greater than or equal to 40 mm Hg.
   4. A peak aortic-jet velocity greater than or equal to 4.0 m/s.

Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

RATIONALE

This evidence review was created using searches of the PubMed database. The most recent literature update was performed through March 30, 2026.

Evidence reviews assess the clinical evidence to determine whether the use of a 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 1 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 controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large

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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.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

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 evidence review 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 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 review.

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. Food and Drug Administration (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.

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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.[12,]

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.

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.

REVIEW OF EVIDENCE

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).[13,] 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

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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.[14,] 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 postsurgery. 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 (eg, 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=.04), and the STS score was numerically higher but was not statistically significant (12.1 vs. 11.2, respectively; p=.14). Significantly more patients in the standard therapy group had chronic obstructive pulmonary disease (52.5% vs. 41.3% ; p=.04) and atrial fibrillation (48.8% vs. 32.9%,; p=.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% vs. 49.7%,; p<.001). This represents a 19% absolute risk reduction, a 38.2% relative risk (RR) reduction, and a number needed to treat (NNT) 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<.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%

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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<.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=.04). Major bleeding and vascular complications occurred in a substantial percentage of patients undergoing TAVI (22.3% vs. 11.2%,; p=.007) and were significantly higher than in the standard therapy group (32.4% vs. 7.3%,; p<.001).

Quality of life outcomes from this trial were reported by Reynolds et al (2011).[15,] 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<.001). This mean difference increased at later time points to 20.8 points (95% CI, 14.7 to 27.0; p<.001) at 6 months and to 26.0 points (95% CI, 18.7 to 33.3; p<.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).[16,] 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=.02). Cardiovascular mortality was also lower with TAVI (31.0%) than with medical therapy (62.4%; p<.001). The rate of hospitalization over the 2-year period was lower with TAVI (35.0%) than with medical therapy (72.5%; p<.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).[17,] 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.[18,] 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<.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=.012). However, at

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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<.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<.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.[19,] The trial used a noninferiority design; for its primary endpoint, 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<.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 TAVI from a propensity-matched study of 1204 pairs of patients in the PARTNER trials.[20,] 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=.018). In both groups, risk of stroke peaked in the first postprocedure 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).[21,]

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 devices' approvals (ie, Popma et al [2014][22,] and Reardon et al [2014][23,]) or on postapproval registries (ie, Mack et al [2013][24,]).

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.[22,] 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 postprocedure. This goal was based on 2 sources: (1) a weighted meta-analysis of 7 balloon

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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% ($p<.001$). The rate of all-cause mortality at 1 year 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).[25,] 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 TAVI 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%.[26,] 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.[27,]

Osnabrugge et al (2015) reported on health status outcomes for the 471 patients who underwent TAVI via the transfemoral approach.[28,] 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.[23,] 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 postprocedure, 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 postprocedure, 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.[24,] From November 2011 to May 2013, the

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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.[29,] 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[30,] and 339 patients treated with the SAPIEN valve.[31,] 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 years or older, or (3) age of 65 years 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/m2 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.[32,] Procedural success was 98.4%, and 30-day mortality was 12.4%. Another large case series

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(2011) from Italy included 663 patients treated with the CoreValve device.[33,] Procedural success was 98%, and mortality at 1 year was 15%.

Section Summary: Transcatheter Aortic Valve Implantation 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 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 review.

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 a 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 a STS predicted operative risk score of 3% to 7%. In the PARTNER 3 trial, low-risk was defined as a STS predicted operative risk score of less than 4%.

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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 patient 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.[12,]

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.

REVIEW OF EVIDENCE

Systematic Reviews
Puri et al (2025) reported a patient-level meta-analysis pooling 3 prospective studies, the PORTICO IDE RCT, the PORTICO I postmarket study, and the PORTICO continued access protocol, to characterize 5-year clinical outcomes and valve durability in patients undergoing TAVI with Portico transcatheter heart valves.[34,] All 3 studies prospectively enrolled patients with severe symptomatic aortic stenosis at high or extreme surgical risk under harmonized inclusion/exclusion criteria, with follow-up at discharge, 30 days, and annually through 5 years. Random-effects pooling included 1,464 patients (median age 83 years, 61.7% female, median STS score 4.9%). At 5 years, all-cause mortality was 49.4% and stroke incidence was 12.3%. Paravalvular leak of moderate or greater severity was observed in 1.9% of patients. The 5-year

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bioprosthetic valve failure rate was 2.7%, comprising a 0.7% valve-related death rate and a 2.0% valve reintervention rate. No patients exhibited severe hemodynamic structural valve deterioration, and moderate hemodynamic structural valve deterioration occurred in 0.9%.

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.[35,] The 4 RCTs comprised 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 [OR], 0.68; 95% CI, 0.50 to 0.94). There was no statistical difference in mortality in men undergoing TAVI 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.[36,]

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.[37,] Trial methods were described in the meta-analysis protocol, which was registered with PROSPERO.[37,] 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[38,] and the CoreValve High Risk Trial[39,]). Results from the subgroup analyses focused on high-risk patients are shown in Table 2.

Table 2. Transcatheter Aortic Valve Implantation 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 postprocedure mortality	508/8552 (5.9%)	804/29323 (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

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Outcomes	TAVI[a]	Surgical Repair[a]	RR for TAVI vs. Surgical Repair (95% CI)	I^2, %
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
AKI incidence	294/3446 (8.5%)	396/3528 (11.2%)	0.73 (0.53 to 1.01)	68.4

Adapted from Villablanca et al (2016).[37,]
AF: atrial fibrillation; AKI: acute kidney injury; 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.[40,] 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<.001). In a similar meta-analysis (Takagi et al 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).[41,]

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.[42,] 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

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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 1 sided noninferiority boundary of 7.5% absolute difference in mortality at 1 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 1-year follow-up. A second powered endpoint was noninferiority at 1 year for patients undergoing TAVI by the transfemoral approach. Secondary endpoints 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 demographic 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=.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=.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=.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=.002 for noninferiority). The secondary outcomes of cardiovascular mortality (14.3% vs. 13.0% ; p=.63) and rehospitalizations (18.2% vs. 15.5% ; p=.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=.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=.04). Vascular complications occurred in 18.0% of patients undergoing TAVI compared with 4.8% in the open AVR group (p=.01), and major vascular complications were also higher in the TAVI group (11.3% vs. 3.5% ; p=.01). On the other hand, major bleeding was more common in the open group (25.7%) compared with the TAVI group (14.7%; p=.01).

Five-year results from the PARTNER trial were reported by Mack et al (2015).[38,] 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

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(62.4%; HR, 1.04; 95% CI, 0.86 to 1.24; p=.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=.003).

Reynolds et al (2012) published QOL results from the PARTNER A trial.[43,] 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<.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.[44,]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<.001).

U.S. CoreValve High-Risk Study

Adams et al (2014) published results of the U.S. CoreValve High Risk Study.[45,] 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<.001; superiority, p=.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=.003), while permanent pacemaker implantation was required in 19.8% of the TAVI group compared with 7.1% of the surgical group (p<.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=.10).

Two-year follow-up results from the U.S. CoreValve High Risk Study were published by Reardon et al (2015).[39,] 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.[46,] 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

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patients for the same outcome (p=.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=.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<.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 (TAVI, 7.62 mmHg vs. SAVR, 11.40 mmHg; p<.001).

Additional analyses of the U.S. CoreValve High RiskStudy have focused on the impact of patient and prosthesis mismatch[47,] and health status.[48,]

Conte et al (2017) analyzed both periprocedural and early complications (0 to 3 days and 4 to 30 days postoperative, respectively) in patients from the U.S. CoreValve High Risk Study.[49,] There were no statistically significant differences in all-cause mortality, stroke, MI, or major infection in either the periprocedural period (0 to 3 days) or between 4 and 30 days postprocedure. The major vascular complication rate within 3 days was significantly higher with TAVI (6.4% vs. 1.4% ; p=.003). Life-threatening or disabling bleeding (12.0% vs. 34.0% ; p<.001), encephalopathy (7.2% vs. 12.3% ; p=.02), atrial fibrillation (8.4% vs. 18.7%; p<.001), and AKI (6.1% vs. 15.0% ; p<.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 TAVI vs. 55.4% for SAVR) and stroke rates (12.3% for TAVI vs. 13.2% for SAVR) in high-risk patients. Valve reinterventions were uncommon; freedom from valve reintervention was 97.0% for TAVI and 98.9% for SAVR.[50,]

PORTICO IDE

The Portico Re-sheathable Transcatheter Aortic Valve System US Investigational Device Exemption (PORTICO IDE) trial enrolled patients with severe aortic stenosis at high or extreme surgical risk.[51,] 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 repair with TAVI.[52,53,54,] Given the availability of RCT evidence, these studies provide limited additional information on the efficacy of TAVI.

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Section Summary: Transcatheter Aortic Valve Implantation 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 a 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. Quality of life 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 and stable hemodynamic performance with low bioprosthetic valve failure at 5 years.

TRANSCATHETER AORTIC VALVE IMPLANTATION 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 or guideline-recommended clinical surveillance, 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 review.

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 a 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 a STS predicted operative risk score of 3% to 7%. In the Study to Establish the Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart

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Valve in Low Risk Patients Who Have Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement (PARTNER 3) trial, low-risk was defined as a 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 patient age and overall health. For asymptomatic severe aortic stenosis at low surgical risk, the comparator of interest is guideline-recommended clinical surveillance until symptom onset, decline in left ventricular ejection fraction, or other guideline-based triggers recommend aortic valve replacement.

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.[12,]

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.

Review of Evidence
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.

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Systematic Reviews

Several systematic reviews and meta-analyses were published in 2017 through 2026,[55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,] including many overlapping RCTs and observational studies.

Ludwig et al (2025) reported a pooled analysis of TAVI versus SAVR in severe symptomatic low- to intermediate-risk patients to date, combining a 2-stage individual participant data meta-analysis of the 4 investigator-initiated RCTs (DEDICATE-DZHK6, NOTION, NOTION-2, UK TAVI; n=2,873 patients; mean age, 76.7 years) with an aggregate-data meta-analysis incorporating 4 additional industry-sponsored RCTs (PARTNER 2A, PARTNER 3, SURTAVI, Evolut Low Risk).[74,] In the individual-level analysis at 1 year, TAVI was associated with a lower risk of the composite primary endpoint of all-cause death or any stroke compared with SAVR (HR, 0.73; 95% CI, 0.56 to 0.95) and a numerically lower but nonsignificant risk in the 2-stage analysis (HR, 0.79; 95% CI, 0.49 to 1.27). The overall 2-stage meta-analysis incorporating aggregate data from all 8 RCTs yielded an HR of 0.76 (95% CI, 0.60 to 0.97) favoring TAVI.

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), MI (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.[57,] 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 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)	.84	0
Stroke incidence	7.3	8.1	0.91 (0.74 to 1.11)	.35	0
AKI incidence	1.8	4.7	0.38 (0.26 to 0.54)	<.001	0

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Outcomes	TAVI	Surgical Repair	RR for TAVI vs. Surgical Repair (95% CI)	p	I^2
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)	.002	66
Requirement for permanent pacemaker incidence	20.0	7.9	3.10 (1.44 to 6.66)	.004	92

Adapted from Garg (2017).[57,]
Values are percent unless other noted.
AKI: acute kidney injury; 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 (Nordic Aortic Intervention Trial [NOTION; 2015],[77,] Transapical Transcatheter Aortic Valve Implantation vs. Surgical Aortic Valve Replacement in Operable Elderly Patients with Aortic Stenosis [STACCATO; 2012],[78,] Leon et al [2016][79,]), and 4 observational studies (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 Versus Surgical Repair in Low- or Intermediate-Risk Patients

Outcomes	TAVI	Surgical Repair	OR for TAVI vs. Surgical Repair (95% CI)	p	I2
Short-term postprocedure mortality	2.59	3.94	0.63 (0.37 to 1.08)	.09	56
Short-term cardiovascular mortality	1.96	3.15	0.51 (0.23 to 1.15)	.11	68
AKI incidence	1.92	4.8	0.34 (0.17 to 0.67)	.002	61
Stroke incidence	3.57	4.90	0.72 (0.56 to 0.92)	.01	42
Myocardial infarction incidence	0.7	1.7	0.51 (0.23 to 0.69)	<.001	10
Major vascular complication incidence	7.2	3.6	3.54 (1.42 to 8.81)	.006	86
Requirement for permanent pacemaker incidence	11.9	6.1	2.79 (1.49 to 5.23)	.001	88
All-cause mortality (1 year)	10.1	12.2	0.82 (0.58 to 1.16)	.26	67

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

Earlier systematic reviews came to similar conclusions.[80,81,] Siemieniuk et al (2016) 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 5 and 6 and the following paragraphs.

Table 5. Characteristics of Randomized Controlled Trials Comparing Transcatheter Aortic Valve Implantation With Surgical Aortic Valve Replacement in Patients at Low and Intermediate Surgical Risk

					Interventions		
Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**TAVI**	**SAVR**	**Sponsor**
Nielsen et al (2012)[78,] STACATTO	Denmark	2	Nov 2008 to May 2011	• Mean age, 81 y • No significant coronary artery disease • Any surgical risk (mean STS PROM, 3.3)	• n=34 • Edwards Sapien THV	• n=36 • Conventional open-heart surgery with CPB	Participating hospitals and 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)	Denmark, Sweden	3	Dec 2009 to Apr 2013	• Mean age, 79 y • No significant coronary artery disease • Any surgical risk (mean STS PROM,	• n=145 • Core-Valve	• n=135 • Conventional open-heart surgery with CPB	Danish Heart Foundation

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					Interventions		
Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**TAVI**	**SAVR**	**Sponsor**
				3.0; 82% low-risk)			
Reardon et al (2016)[86], CoreValve U.S. Pivotal (NCT01240902)	U.S.	45	Feb 2011 to Sep 2012	• Mean age, 81 y • STS score <7a (median, 5.3) • Symptomatic (NYHA class ≥II)	• n=202 • Core-Valve	• n=181 • Conventional open-heart surgery with CPB	Manufacturer
Leon et al (2016)[79], PARTNER 2A (NCT01314313)	U.S., Canada	57	Dec 2011 to 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)	• n=1011 • SAPIEN XT	• n=1021 • Conventional surgery	Manufacturer
Reardon et al (2017)[87]; van Mieghem et al (2022)[88], SURTAVI (NCT01586910)	U.S., Spain, Netherlands, Germany, UK, Canada, Switzerland, Sweden	87	NR	• Mean age, 80 y • STS PROM ≥4 and <15 (mean, 4.5) • Symptomatic (NYHA class ≥II)	• n=879 • Core-Valve	• n=867 • Conventional surgery with coronary revascularization if needed	Manufacturer
Popma et al (2019);[89]; Forrest et al (2022);[90]; Forrest et al (2023)[91], Evolut Low Risk Trial (NCT02701283)	Australia, Canada, France, Japan, Netherlands, New Zealand, U.S.	86	Mar 2016 to Nov 2018	• Mean age, 74 y • STS PROM ≤3 (mean, 1.9) • 90% NYHA class ≥II (symptomatic); 10%	• n=734 • CoreValve, Evolut R, or Evolut PRO	• n=734 • Conventional surgery	Manufacturer

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					Interventions		
Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**TAVI**	**SAVR**	**Sponsor**
				NYHA class I (asymptomatic)			
Mack et al (2019);[92,] Leon et al (2021)[93,] PARTNER 3 (NCT02675114)	U.S., Canada, Australia, New Zealand, Japan	71	Mar 2016 to Oct 2017	• Mean age, 73 y • STS PROM <4 (mean, 1.9) • 28% NYHA III or IV	• n=503 • SAPIEN 3	• n=497 • Conventional surgery	Manufacturer
Toff et al (2022);[94,] UK TAVI (ISRCTN57819173)	UK	34	Apr 2014 to Apr 2018	• Mean age, 81 y • Median STS PROM, 2.7b • 43% NYHA III or IV	• n=458 • SAPIEN 3 (45.1%)	• n=455 • Conventional surgery	NIHR HTA Programme; University of Leicester
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	• n=187 • Any CE mark approved aortic bioprosthesis	• n=183 • Conventional surgery	Manufacturer
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	• 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.
a Includes analysis of a subset of originally randomized patients. b No specified risk threshold for trial inclusion.

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Table 6. Randomized Controlled Trials Comparing Transcatheter Aortic Valve Implantation 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
Nielsen et al (2012)[78], STACATTO	Death from any cause, stroke, or renal failure at 30 d										
All patients		14.7	2.8	RD (NR)	.07	NR	NR		NR	NR	
Thyregod et al (2015)[77],; Søndergaard et al (2016)[83],, Thyregod et al (2019)[84],; Søndergaard et al (2019)[85],; Thyregod et al (2024) [97], NOTION (NCT01057173)	Death from any cause, stroke, or MI at 1 y										
All patients		13.1	16.3	RD=-3.2	.43a	4.9	7.5	.38	34.1	1.6	<.001
Reardon et al (2016)[86], CoreValve U.S. Pivotal (NCT01240902)	Death from any cause at 2 y										

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Study	Primary Outcome	Results of Primary Outcomes, %				All-Cause Mortality (2 y), %			New Permanent Pacemaker (2 y), %		
STS score ≤7		26.3	15.0	HR (NR)	.01	See previous columns			27.7	10.5	<.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	.29
Transfemoral access		16.8	20.4	HR=0.79 (0.62 to 1.00)		14.2	17.2	.11	11.4	10.8	.71
Transthoracic access		27.7	23.4	HR=1.21 (0.84 to 1.74)		25.2	20.7	.26	13.1	8.6	.13
Reardon et al (2017)[87],; van Mieghem et al (2022)[88], SURTAVI (NCT01586910)	Death from any cause or disabling stroke										
All patients at 2 y		12.6	14.0	RD=-1.4		11.4	11.6	-3.	25.9	6.6	15.9 to

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Study	Primary Outcome	Results of Primary Outcomes, %				All-Cause Mortality (2 y), %			New Permanent Pacemaker (2 y), %		
				(-5.2 to 2.3)b				8 to 3.3b			22.7b
All patients at 5 y		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										
All patients at 2 y		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 y		7.4	10.4	HR=0.7 (0.49 to 1); p=.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		11.5	17.4		NR		

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Study	Primary Outcome	Results of Primary Outcomes, %				All-Cause Mortality (2 y), %			New Permanent Pacemaker (2 y), %		
				(-10.8 to -2.5)b							
Toff et al (2022);[94,] UK TAVI (ISRCTN57819173)	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					At 1 year			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		

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Study	Primary Outcome	Results of Primary Outcomes, %				All-Cause Mortality (2 y), %			New Permanent Pacemaker (2 y), %		
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; ISRCTN: International Standard Randomised Controlled Trial Number; MI: myocardial infarction; NR: not reported; RD: risk difference; STS: Society of Thoracic Surgeons; Surg: surgical repair; TAVI: transcatheter aortic valve implantation; TE: treatment effect.
[a] Superiority. [b] Bayesian credible interval. [c] Noninferiority with 97.5% confidence interval. [d] Noninferiority with 95% 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 a 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 TAVI; 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 TAVI versus SAVR in the subgroup with a STS score less than 7.0 was 15% (95% CI, 9% to 20%) versus 26% (95% CI, 20% to 33%; p=.01). The rates of stroke at 2 years for TAVI versus SAVR were 11% versus 15% (p=.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 the 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=.03), cardiogenic shock (4.2% vs. 10.4% ; p=.05), stage 2 or 3 AKI (0.7% vs. 6.7% ; p=.01), and new-onset or worsening atrial fibrillation (16.9% vs. 57.8% ; p<.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=.01).

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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=.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=.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<.001); for the latter, only 4.2% of surgical patients received implantation versus 41.3% of the TAVI group (p<.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<.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 TAVI and SAVR in the incidence of the composite primary outcome (38.0% vs. 36.3% ; p=.86) or any of the components of the composite. The incidence of moderate/severe total aortic regurgitation (8.2% vs. 0.0% ; p<.001) and a new pacemaker (43.7% vs. 8.7% ; p<.001) were both higher in the TAVI group. Four patients had prosthetic re-intervention. Søndergaard et al (2019) compared the durability of TAVI versus SAVR after 6 years of follow-up from NOTION. At 6 years, the rates of all-cause mortality were similar for TAVI (42.5%) and SAVR (37.7%) patients. The rate of moderate to severe structural valve deterioration was higher for SAVR than TAVI (24.0% vs. 4.8%; p<.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.

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

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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. A predefined subgroup analysis (n=1,394; 43.3% women) found 1-year death or stroke rates of 5.2% with TAVR versus 11.5% with SAVR among women (HR, 0.46; 95% CI, 0.25 to 0.82) and 5.4% versus 9.0% among men (HR, 0.61; 95% CI, 0.35 to 1.03), with all-cause mortality favoring TAVR in both sexes.[98,]

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 TAVI or SAVR.[87,] For the primary outcome (composite death at 2 years), an improvement was observed in the TAVI-treated group, compared with surgery (12.6% of TAVI patients vs. 14.0% of SAVR patients; 95% credible interval, -5.2% to 2.3% ; posterior probability, >.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 TAVI 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 had a 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 endpoint 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 (ie, 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

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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 of 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<.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=.21).[99,] 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 TAVI (n=734) to SAVR (n=734) in patients who had severe aortic stenosis and were at low surgical risk (STS-PROM ≤3%).[89], Patients with bicuspid aortic valves were excluded. Patients assigned to TAVI 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 TAVI group and 6.7% in the SAVR group (RD, −1.4%; 95% Bayesian credible interval, −4.9 to 2.1; posterior probability of noninferiority, >.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%), AKI (0.9% vs. 2.8%), and atrial fibrillation (7.7% vs. 35.4%) were lower with TAVI 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 with TAVI 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 TAVI group vs. 78.6±18.9 in the SAVR group). In 2022, Forrest et al published 2-year outcomes.[90], 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 3-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).[100],Forrest et al (2026) reported 6-year and 7-year data and found the composite outcome of all-cause mortality or disabling stroke remained similar between groups at 6 years

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(TAVR 23.3% vs. surgery 20.4%; difference, 2.8%; 95% CI, -1.9% to 7.6%; p=.43).[101], At 7 years, the cumulative reintervention rate was higher with TAVR (9.8% vs. 6.0%; sHR, 1.68; 95% CI, 1.10 to 2.58; p=.02), driven by reintervention for regurgitation (5.6% vs. 1.6%; HR, 3.39; 95% CI, 1.62 to 7.07; p<.001) rather than stenosis.

Mack et al (2019) reported results of the multinational PARTNER 3 trial, randomizing patients with severe aortic stenosis and low surgical risk to either TAVI with the SAPIEN (n=503) or SAVR (n=497) in 2016 to 2017.[92], Patients with 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 TAVI; 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 commonly reported reason was refusal to undergo surgery or choosing to undergo surgery at a nonatrial site. The estimated incidence of the primary outcome at 1 year was significantly lower with TAVI versus SAVR (8.5% vs. 15.1%; RD, -6.6%; 95% CI, -10.8% to -2.5%; p<.001 for noninferiority). All components of the composite (death, stroke, and hospitalization) individually favored TAVI 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=.02) and new-onset atrial fibrillation (5.0% vs. 39.5%; HR, 0.10; 95% CI, 0.06 to 0.16; p<.001) was lower with TAVI than SAVR and index hospitalization time was shorter (3 days vs. 7 days ; p<.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 TAVI (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 TAVI and SAVR groups at 30 days (0.8% vs. 0.2%; p=.38); mild aortic regurgitation occurred more frequently after TAVI than SAVR (28.8% vs. 4.2%; p<.001).[102], Mean transvalvular gradient (13.7±5.6 vs. 11.6±5.0 mmHg; p=.12) and aortic valve area (1.72±0.37 vs. 1.76±0.42 cm2; p=.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).[103], 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],Hahn et al (2025) reported 5-year core lab-adjudicated ECG outcomes from PARTNER 3 and found ≥ mild aortic regurgitation more common after TAVR (24.5% vs. 6.3%; p<.001).[104],At 7 years, no significant differences were observed between TAVR and surgery for the composite of death, stroke, or rehospitalization (34.6% vs. 37.2%; difference -2.6 percentage points, 95% CI, -9.0 to 3.7), with valve failure of 6.9% vs. 7.5%, respectively.[105],

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-

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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. Jørgensen et al (2025) reported 3-year outcomes in which the composite primary endpoint occurred in 16.1% of TAVR versus 12.6% of SAVR patients (HR, 1.3; 95% CI, 0.8 to 2.2), with comparable rates among patients with tricuspid aortic stenosis (14.5% vs. 14.4%) but a numerically higher rate with TAVR among patients with bicuspid aortic stenosis (20.4% vs. 7.8%; HR, 2.9; 95% CI, 0.9 to 9.0).[106], Moderate or greater structural valve deterioration (4.5% vs. 5.2%; HR, 1.2; 95% CI, 0.4 to 3.1) and bioprosthetic valve failure (1.6% vs. 2.9%) were similar between groups.

Asymptomatic Low-Risk Only

Généreux et al (2025) reported results of EARLY TAVR, a multicenter superiority RCT, comparing early TAVR using SAPIEN 3 or SAPIEN 3 Ultra valve versus guideline-recommended clinical surveillance in 901 patients with asymptomatic severe aortic stenosis and preserved left ventricular ejection fraction.[107], The trial enrolled patients ≥ 65 years of age at 75 sites in the U.S. and Canada (mean age, 75.8 years; mean STS-PROM, 1.8%; 83.6% at low surgical risk; 8.4% with bicuspid aortic valves; 1:1 randomization to TAVR n=455 vs. clinical surveillance n=446). Asymptomatic status was confirmed by a negative treadmill stress test in 90.6% of patients. The primary composite of death from any cause, stroke, or unplanned cardiovascular hospitalization (with conversion to AVR within 6 months counted as an unplanned cardiovascular hospitalization) occurred in 26.8% of patients assigned to early TAVR versus 45.3% assigned to clinical surveillance (HR, 0.50; 95% CI, 0.40 to 0.63; p<.001 for superiority) over a median follow-up of 3.8 years. The composite benefit was driven primarily by a reduction in unplanned cardiovascular hospitalization (20.9% vs. 41.7%; HR, 0.43; 95% CI, 0.33 to 0.55), with smaller numerical reductions in stroke (4.2% vs. 6.7%; HR, 0.62; 95% CI, 0.35 to 1.10) and in all-cause mortality (8.4% vs. 9.2%; HR, 0.93; 95% CI, 0.60 to 1.44) which did not reach statistical significance. Overall, 116 of the 186 unplanned cardiovascular hospitalizations in the surveillance group were conversions to AVR within 6 months of randomization, which were counted as endpoint events per protocol definition. The dominant component of the composite outcome substantially reflects the timing of protocol-driven conversion rather than prevention of clinical decompensation. A favorable health status outcome at 2 years (defined as alive with KCCQ score ≥ 75 and a decrease of ≤ 10 points from baseline) was achieved in 86.6% of TAVR patients versus 68.0% of surveillance patients (18.5%; 95% CI, 12.6 to 24.3; p<.001); however, no differences in KCCQ scores overall were observed between groups at 2 years follow-up. The prespecified composite of integrated left ventricular and left atrial health at 2 years (LV global longitudinal strain ≥15%, LV mass index <115 g/m2 for men or <95 g/m2 for women, and left atrial volume index ≤34 mL/m2) was achieved in 48.1% versus 35.9%, respectively (absolute difference, 12.2 percentage points; 95% CI, 4.4 to 19.4; p=.001). During follow-up, 87.0% of clinical surveillance patients ultimately underwent AVR (median time to conversion, 11.1 months), with 39.2% of converters presenting with advanced or acute signs and symptoms of aortic valve

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disease at the time of conversion. In a prespecified secondary endpoint analysis of LV health, the benefit of early TAVR over clinical surveillance was consistent across patients with normal and abnormal baseline integrated LV health (interaction p=.48 for the primary endpoint; interaction p=.96 and p=.40 for two prespecified secondary composites), and clinical surveillance was associated with progressive decline in LV health relative to early intervention, with 48.1% of early TAVR patients versus 35.9% of surveillance patients having normal integrated LV health at 2 years (p=.001).[108], Limitations include an unblinded clinical events committee and a primary endpoint driven by unplanned cardiovascular hospitalization without a corresponding difference in stroke or all-cause mortality.

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 alternative access	4: Transapical TAVI, multidetecto r computed tomography was not performed before procedure			1,2: Terminate d early
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/intermediat e risk by STS-PROM but deemed at high surgical risk based on screening committee assessment despite their STS scores				

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Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Leon et al (2016)[79], PARTNER 2A	4: 12% of the study 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				

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Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Généreux et al (2025); [107],EARLY TAVR	1. Includes asymptomatic patients only			4: Composite primary endpoint includes unplanned cardiovascular hospitalization, which may be subject to ascertainment bias in an unblinded design	

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 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				

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Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
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: Outcome adjudication not blinded		1: High frequency of withdrawals in patients assigned to undergo surgery		

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Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Toff et al (2022);[94], UK TAVI		1: Patients and study 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				
Généreux et al (2025); [107],EARLY TAVR		1: Patients and study staff not blinded; 3: Outcome adjudication not blinded		3: High rate of surveillance to AVR (87.0%) during study period		

RCT: randomized controlled trial.
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: TRANSCATHETER AORTIC VALVE IMPLANTATION OUTCOMES IN PATIENTS AT INTERMEDIATE- OR LOW-RISK FOR OPEN SURGERY

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Intermediate-Risk

Most participants in 6 RCTs were intermediate risk, and 2 RCTs 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 occurring more frequently in patients randomized to open surgery and permanent pacemaker requirement occurring more frequently 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 are 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 TAVI versus SAVR at the 30-day mark. Mortality rates were found to be comparable between the 2 procedures. An individual participant data meta-analysis of 4 investigator-initiated RCTs and an aggregate-data overall meta-analysis of 8 RCTs in low- to intermediate-risk patients both demonstrated lower risk of the 1-year composite of death or stroke with TAVI compared with SAVR.

Low-Risk

The NOTION and UK TAVI trials were predominantly low surgical risk patients; the Evolut Low Risk Trial, NOTION-2, EARLY TAVR, 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=.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. At 6 years, the composite outcome remained similar between groups (23.3% vs. 20.4%; p=.43), and at 7 years the cumulative reintervention rate was higher with TAVR (9.8% vs. 6.0%; sHR, 1.68; 95% CI, 1.10 to 2.58), driven by reintervention for regurgitation rather than stenosis. 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. At 5 years, ≥ mild aortic regurgitation was more common after TAVR than SAVR (24.5% vs. 6.3%; p<.001), and at 7 years there were no significant differences between groups in the composite outcome (34.6% vs. 37.2%) 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. At 3 years, the composite primary endpoint occurred in 16.1% of TAVR versus 12.6% of SAVR patients (HR, 1.3; 95% CI, 0.8 to 2.2), with comparable rates in patients with tricuspid aortic stenosis (14.5% vs.

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14.4%) but a numerically higher rate with TAVR among patients with bicuspid aortic stenosis (20.4% vs. 7.8%; HR, 2.9; 95% CI, 0.9 to 9.0).

Asymptomatic Low-Risk

EARLY TAVR was the only RCT to evaluate intervention in asymptomatic patients with severe aortic stenosis. In this RCT of 901 low-surgical-risk patients ≥ 65 years of age with preserved left ventricular ejection fraction, early TAVI was superior to guideline-recommended clinical surveillance with respect to the composite of death from any cause, stroke, or unplanned cardiovascular hospitalization (26.8% vs. 45.3%; HR, 0.50; 95% CI, 0.40 to 0.63; p<.001) at a median follow-up of 3.8 years. The composite benefit was driven primarily by a reduction in unplanned cardiovascular hospitalization, with no difference in stroke or all-cause mortality. Notably, 116 of the 186 unplanned cardiovascular hospitalizations in the surveillance group were conversions to AVR within 6 months of randomization, counted as endpoint events by protocol definition; the dominant component of the composite, therefore, substantially reflects the timing of protocol-driven conversion rather than prevention of clinical decompensation. Patient-reported quality of life prior to the surveillance group receiving TAVR showed a significant difference but after 2 years follow-up no difference in KCCQ scores were observed between groups. Echocardiographic measures of left ventricular and left atrial structure and function at 2 years favored early TAVR. In a secondary analysis, the benefit of early TAVR was consistent across patients with normal and abnormal baseline integrated LV health (interaction p=.48), and clinical surveillance was associated with progressive decline in LV health relative to early intervention. During follow-up, the majority of clinical surveillance patients underwent TAVI (87.0%; median time to conversion, 11.1 months), and 39.2% of converters presented with advanced or acute signs and symptoms at the time of conversion. Limitations include an unblinded clinical events committee and a primary endpoint driven by unplanned cardiovascular hospitalization without a corresponding difference in stroke or mortality. Generalizability is limited by enrollment restricted to patients ≥ 65 years with preserved LVEF; asymptomatic status was confirmed by a negative treadmill stress test in 90.6%, underrepresenting patients unable to exercise; only balloon-expandable SAPIEN 3 or SAPIEN 3 Ultra valves were used, with no data on self-expanding platforms; and the cohort was predominantly White. Because nearly all surveillance patients ultimately required AVR, the comparison focuses on the optimal timing of intervention rather than on whether to intervene.

TRANSCATHETER AORTIC VALVE IMPLANTATION 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 review.

Populations

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

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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 review.

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 ViV 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.

REVIEW OF EVIDENCE

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).[109], 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; I2=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; I2=61.5%), major bleeding (RR, 0.44; 95% CI, 0.31 to 0.62; p<.001; I2=93.8%), stroke or TIA (RR, 0.70; 95% CI, 0.51 to 0.96; p<.05; I2=0%), and new pacemaker implantation (RR, 0.69; 95% CI, 0.48 to 0.99; p<.05; I2=83.4%). However, redo-SAVR was associated with

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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 ViV TAVI compared to redo-surgical aortic valve replacement (rSAVR).[110], 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 rSAVR.[111], 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 rSAVR. Short-term mortality (<30 days) was 2.8% in patients undergoing ViV TAVI compared with 5.0% in patients undergoing rSAVR (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 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 rSAVR 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).[112], A HR reversal was observed after 197 days favoring rSAVR (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 prepared an interventional procedure overview on safety and efficacy of ViV TAVI for aortic bioprosthetic valve dysfunction based on a rapid review of medical literature including publications through August 2018 and specialist opinion. [113],The review included 3 systematic reviews and meta-analyses[114,115,116], and 8 case series (registries) totaling 4256 patients, although the authors note that there may be some overlap of patients in the global ViV register and other registries. There are no RCTs comparing

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ViV TAVI with rSAVR. 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-analyses compared ViV TAVI with rSAVR and 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 ViV TAVI and rSAVR 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 ViV 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 ViV 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 ViV registry were published by Webb et al (2019).[117], The registry included 365 patients who had ViV TAVI[115,116], procedures with a mean age of 79 (±10) years 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<.0001). Quality of life as measured by the KCCQ overall score also increased from baseline to 3 years (43.1 to 73.1; p<.0001).

Hahn et al (2022) published 5-year follow-up outcomes from the PARTNER 2 registry.[118], 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.[119], 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,

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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.[120], 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.[121], 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 rSAVR via a propensity score-matched analysis of data from the Netherlands Heart Registry collected between 2014 and 2018 from 16 cardiac centers.[122], 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 rSAVR; following propensity score-matching, 165 pairs were included for analysis. EuroSCORE I surgical risk was significantly higher for ViV TAVI patients compared to rSAVR (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

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TAVI and rSAVR (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 postoperative 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.[123], 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.

Tran et al (2024) reported a retrospective cohort study comparing ViV TAVI with rSAVR using statewide administrative databases (California, New York, and New Jersey) for procedures performed between 2015 and 2020. A total of 1,771 patients with a history of SAVR were identified, with patients undergoing intervention within 5 years of initial SAVR. Propensity matching yielded 375 patient pairs.[124], The median (IQR) follow-up was 2.3 (1.1 to 4.0) years, and the mean (SD) age was 74.4 (11.3) years. The proportion of patients undergoing ViV TAVI rather than rSAVR increased from 35.3% in 2015 to 62.5% in 2020. In the propensity-matched analysis, periprocedural mortality and stroke rates were similar between groups, but the ViV TAVI group had lower periprocedural rates of major bleeding (2.4% vs. 5.1%; p=.05), acute kidney failure (1.3% vs. 7.2%; p<.001), and new pacemaker implantation (3.5% vs. 10.9%; p<.001). The 5-year all-cause mortality rate was 23.4% (95% CI, 15.7% to 34.1%) in the ViV TAVI group and 13.3% (95% CI, 9.2% to 18.9%) in the rSAVR group. Because the proportional hazards assumption was violated, a landmark analysis was performed: through 2 years there was no difference in mortality (HR, 1.03; 95% CI, 0.59 to 1.78), but after 2 years ViV TAVI was associated with higher mortality (HR, 2.97; 95% CI, 1.18 to 7.47) and a higher incidence of heart failure hospitalization (HR, 3.81; 95% CI, 1.57 to 9.22). There were no differences in 5-year incidence of stroke, reoperation, major bleeding, or infective endocarditis.

Awtry et al (2025) reported a US Medicare propensity-matched comparison of rSAVR and ViV TAVI for degenerated bioprosthetic aortic valves to date, using CMS data from between 2011 and 2020.[125], Patients with endocarditis, concomitant cardiac surgery, or aortic valve reintervention during the same admission were excluded. The primary outcome was 5-year survival; composite secondary outcomes included major adverse cardiovascular events (30-day operative mortality, stroke, or acute myocardial infarction) and major valve event-free survival (congestive heart failure readmission, endocarditis, or aortic valve reintervention). A total of 4,699 patients were identified (1,775 rSAVR and 2,924 ViV TAVI), with 1:1 propensity score matching yielding 1,256 patients per group. The median follow-up was 35.7 months (46.9 months for redo-SAVR, 32.1 months for ViV TAVI) for a total of 15,929 patient-years. Annual ViV TAVI volume increased from 76 cases in 2012 to 700 cases in 2020, while rSAVR volume increased from 130 to 225 cases over the same period. In the propensity-matched cohorts, redo-SAVR had higher major adverse cardiovascular events (17.4% vs. 13.1%; p=.003) but better major valve event-free survival

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(median 71 [IQR, 62 to 79] months vs. 43 [IQR, 38 to 47] months; p<.001) and 5-year survival (62.3% vs. 46.7%; p<.001). After stratification by Charlson comorbidity index, the long-term survival benefit for rSAVR persisted in both lower-risk patients (67.6% vs. 54.9%; p=.001) and medium- or higher-risk patients (55.1% vs. 36.7%; p<.001).

Section Summary: Transcatheter Aortic Valve Implantation 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 conflicting mortality outcomes, with some favoring ViV TAVI, others favoring rSAVR, and others showing no significant difference between the two treatments. Two propensity-matched cohort analyses reported a late-mortality signal favoring rSAVR, with equivalent mortality through 2 years but higher mortality with ViV TAVI thereafter, and significantly better 5-year survival with rSAVR, which persisted across Charlson comorbidity strata. 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 (CEP) is to provide an adjunct treatment option to improve outcomes in individuals who undergo TAVI compared to standard TAVI without CEP.

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

Populations

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

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

Interventions

The therapy being considered is use of a CEP device (eg, Sentinel Cerebral Protection System) during TAVI. The device is a single-use percutaneous catheter system with blood filters designed

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to prevent embolic material from the TAVI 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 CEP.

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 CEP 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.[12],

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. (eg, TriGUARD 3 [Keystone Heart]) were excluded. See the Regulatory Section for additional details.

REVIEW OF EVIDENCE

Systematic Reviews
Zahid et al (2023) conducted a meta-analysis evaluating the safety and efficacy of TAVI with CEP devices versus TAVI alone.[126], 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

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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.

Warraich et al (2025) conducted a meta-analysis with trial sequential analysis to evaluate the safety and efficacy of CEP devices during TAVI, using data from 7 RCTs with a total of 4,031 patients (n=2,171 CEPD; n=1,860 no CEPD).[127], The authors found no statistically significant difference between CEPD and no CEPD for all stroke (relative risk [RR], 0.85; 95% CI, 0.61 to 1.18; p=.339), disabling stroke (RR, 0.59; 95% CI, 0.30 to 1.13; p=.113), or all-cause mortality (RR, 1.03; 95% CI, 0.49 to 2.17; p=.928). Secondary outcomes, including life-threatening or disabling bleeding, major vascular complications, acute kidney injury, and several neurological endpoints (Montreal Cognitive Assessment score worsening, National Institutes of Health Stroke Scale score worsening, and the presence of cerebral ischemic lesions), also showed no statistically significant differences between groups. Trial sequential analysis found that for most secondary outcomes and the primary outcome of stroke, these assessments were likely underpowered, and additional trial data would be required to adequately assess if CEP provided a protective effect during TAVI.

RANDOMIZED CONTROLLED TRIALS

CLEAN-TAVI

The Claret Embolic Protection and TAVI (CLEAN-TAVI) trial was a single-center, blinded, RCT performed at the Heart Center at the University of Leipzig, Germany.[128], 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 primary endpoint was the numerical reduction in positive postprocedure diffusion-weighted magnetic resonance imaging (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.

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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.[129], The primary endpoint 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 mm3 vs. 197 mm3, 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.[130], 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 AKI (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 AKI (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 T2/FLAIR lesion volume, and their interaction

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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 at 51 sites in the United States, Australia, and Europe.[131], The primary endpoint 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, TIA, delirium (3.1% vs. 3.7%), or AKI (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.[132], 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. Kennedy et al (2025) reported a secondary analysis in 3,535 participants (1,763 CEP vs. 1,772 control), with a primary outcome of mean change in telephone

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Montreal Cognitive Assessment (t-MoCA) score from baseline to 6 to 8 weeks post-TAVI.[133], The adjusted mean change did not differ between groups (0.83 [95% CI, 0.70 to 0.96] CEP vs. 0.91 [95% CI, 0.79 to 1.04] control; mean difference, -0.07; 95% CI, -0.22 to 0.09; p=.42), nor did the proportion with a ≥3-point t-MoCA drop (8.7% vs 8.0%; risk difference, 0.72%; 95% CI, -1.10 to 2.55; p=.44), with the authors concluding that CEP did not impact cognition after TAVI.

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

					Interventions	
Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**TAVI + CEP**	**TAVI**
Haussig et al (2016);[128], CLEAN-TAVI	Germany	1	2013 - 2014	• Mean age, 79 to 80 y (female, 28% to 29%) • Severe, symptomatic aortic stenosis • Elevated surgical risk (mean STS PROM score, 5.2 to 5.6) • <4% STS PROM risk level (38% to 40%) • 4%-10% STS PROM risk level (48% to 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);[129], MISTRAL-C	Netherlands	4	2013 - 2015	• Median age, 81 y (female, 48%) • Elevated surgical risk (median STS PROM, 4.8%) • TAVI device (%)	• 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)

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					Interventions	
Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**TAVI + CEP**	**TAVI**
				• SAPIEN 3 (54) • CoreValve (25) • SAPIEN XT (15)		
Kapadia et al (2017);[130], SENTINEL	U.S. and Germany	19	2014 - 2016	• Mean age, 83.4 y (female, 52.1%) • Severe, symptomatic aortic stenosis • Elevated surgical risk (median STS PROM score, 6.0 [IQR, 4.2 to 8.1]) • No contraindications for right radial or brachial artery access or MRI • Transfemoral or transapical TAVI permitted depending on device	• CEP device, Sentinel system • 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)	• Efficacy population, n=119 • TAVI device (%) ○ SAPIEN 3 (53.4) ○ CoreValve Evolut R (23.7) ○ SAPIEN XT (16.9) ○ CoreValve (5.9)
Kapadia et al (2022);[131],	U.S., Australia, Denmark, France,	51	2020 - 2022	• Mean age, 78.9 y (female, 38% to 42%)	• Transfemoral TAVI plus Sentinel CEP system (n=1501)	• Transfemoral TAVI without CEP (n=1499)

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					Interventions	
Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**TAVI + CEP**	**TAVI**
PROTECTED TAVR	Germany, and Italy			• Symptomatic aortic stenosis • High or extreme surgical risk, 30.4% • Intermediate surgical risk, 33% to 34% • Low surgical risk, 35% to 36% • TAVI device (%) ○ SAPIEN 3 or iteration (64%) ○ Evolut R/Evolut PRO or iteration (24%)		
Kharbanda et al (2025);[132],BHF PROTECT-TAVI	U.K.	33	2020-2024	• Mean age, 81.2y • Symptomatic aortic stenosis and anatomically suitable for Sentinel CEP device • EuroSCORE II, median 2.4% • TAVI device (%) ○ Self-expanding valve (e.g. CoreValv	• Transfemoral TAVI plus Sentinel CEP system (n=3795)	• Transfemoral TAVI without CEP (n=3799)

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					Interventions	
Study; Trial	**Countries**	**Sites**	**Dates**	**Participants**	**TAVI + CEP**	**TAVI**
				e/Evolut) (42%) ○ Balloon-expandable valve (Sapien) (58%)		

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

Table 10. Results of Randomized Controlled Trials Comparing Transcatheter Aortic Valve Implantation With and Without Transcatheter Cerebral Embolic Protection

Study	**Safety Outcome**	**Results of Safety Outcome, %**				**Primary Efficacy Outcome**	**Results of Primary Efficacy Outcome, median (IQR)**			
Haussig et al (2016);[128], CLEAN-TAVI	Neurological symptoms indicative of stroke at 2, 7, and 30 days	TAVI + CEP	TAVI	TE (95% CI)	p-value	Median new lesion number on MRI in potentially protected regions at 2 days	TAVI + CEP	TAVI	TE (95% CI)	p-value
		2 days: 5 (10%); 7 days: 5 (10%);	2 days: 5 (10%); 7 days: 5 (10%);	NR	NR (NSD)		4.00 (3.00 to 7.25)	10.00 (6.75 to 17.00)	MD, 5.0 (2.0 to 8.0)	<.001

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Study	Safety Outcome	Results of Safety Outcome, %				Primary Efficacy Outcome	Results of Primary Efficacy Outcome, median (IQR)			
		30 days : 4 (8%)	30 days : 4 (8%)							
Van Mieghem et al (2016);[129], MISTRAL-C	Deaths at 30 days or stroke	TAVI + CEP	TAVI	TE (95% CI)	p-value	New cerebral lesions and lesion volume on MRI at 5 to 7 days after TAVI	TAVI + CEP	TAVI	TE (95% CI)	p-value
	Deaths	1 (3%)	3 (10%)	RR, 0.36 (0.04 to 3.43)	.371		95 (10 to 257)	197 (95 to 525)	NR	NR[d]
	Strokes (disabling, non-disabling, or delirium)	1 (3%)	7 (21%)	NR	NR		-	-	-	-
Kapadia et al (2017);[130], SENTINEL	MACCE rate at 30 days (all death, all stroke, or stage 3 acute	TAVI + CEP	TAVI	TE (95% CI)	p-value	Median total new lesion volume (mm3) on MRI in protect	TAVI + CEP	TAVI	TE (95% CI)	p-value

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Study	Safety Outcome	Results of Safety Outcome, %				Primary Efficacy Outcome	Results of Primary Efficacy Outcome, median (IQR)			
	kidney injury)					ed territories on days 2 to 7				
	Safety population	7.3	18.3[a]	NR	<.001[b]	Safety population	NA	NA	NA	NA
	Efficacy population	7.3	9.9	NR	.405	Efficacy population	102.83 (NR)	177.98 (NR)	NR	.33[c]
Kapadia et al (2022);[131], PROTECTED TAVR	Death from any cause or stroke within 72 hours	TAVI + CEP	TAVI	TE (95% CI)	p-value	Stroke within 72 hours after TAVI or before discharge	TAVI + CEP	TAVI	TE (95% CI)	p-value
		2.7	3.0	MD, 0.3 (-1.5 to 0.9)	NR (NSD)		2.3	2.9	MD, -0.6 (-1.7 to 0.5)	.30
Kharbanda et al (2025); [132],BHF PROTECT-TAVI	Deaths	.8	.7		NR (NSD)	Stroke within 72 hours after TAVI or before discharge	2.1	2.2	RD, -.02 (-.68 to.63)	NS

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Study	Safety Outcome	Results of Safety Outcome, %				Primary Efficacy Outcome	Results of Primary Efficacy Outcome, median (IQR)			
	Disabling stroke within 6 to 8 wks of TAVI	1.2	1.4	RD, -.2 (-.7 to.4)	NS					

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; RD: risk difference; RR: relative risk; TAVI: transcatheter aortic valve implantation; 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.

STUDY LIMITATIONS

Table 11. Study Relevance Limitations

Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Haussig et al (2016);[128,] CLEAN-TAVI	3: Included patients with varying surgical risk; median STS risk score was 5.2 to 5.6; 4: Study population racial and ethnic demographics not reported.	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 difference provided.	1, 2: Outcome reporting limited to 2, 7, and 30 days.
Van Mieghem et al (2016);[129,] MISTRAL-C	3: Included patients with varying surgical risks; surgical risks were significantly	5: Various TAVI devices used with CEP which may limit generalizability of results.		2: Unclear how neuroimaging outcomes correlate with neurofunctional health outcomes; only	1, 2: Major outcome reporting limited to 5 to 7 and 30 days.

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Study; Trial	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
	different between CEP and control arms; 4. Study population racial and ethnic demographics not reported.			pooled neuroimaging outcomes reported.	
Kapadia et al (2017);[130,] 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 to 7 or 30 days for efficacy and safety, respectively.
Kapadia et al (2022);[131,] 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.
Kharbanda et al (2025); [132,]BHF PROTECT-TAVI	3: Included patients with varying surgical risk; median STS risk score was <2.	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: Major outcome reporting limited to 3 day to 8 weeks.

CEP: cerebral embolic protection; STS: Society of Thoracic Surgeons; TAVI: transcatheter aortic valve implantation. The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

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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. 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 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);[128], CLEAN-TAVI					3: Rationale for power calculations not specified.	
Van Mieghem et al (2016);[129], 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);[130], SENTINEL						3: Confidence intervals not reported.
Kapadia et al (2022);[131], PROTECTED TAVR					3: Rationale for power calculations unclear.	
Kharbanda et al (2025); [132],BHF PROTECT-TAVI		1. Open-label trial patients not blinded to allocation with CEP.			4. Power calculations based on higher than observed rate of stroke requiring more participants to be enrolled; adaptive trial design stopped early for futility.	

CEP: cerebral embolic protection; MRI: magnetic resonance imaging.
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps

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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 2 meta-analyses 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.

SUPPLEMENTAL INFORMATION

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

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2024 Input

Clinical input was sought to help determine whether the use of transcatheter aortic valve-in-valve (ViV) implantation for individuals who have valve dysfunction and aortic stenosis or regurgitation after open surgical aortic valve repair provides a clinically meaningful improvement in net health outcome and whether the use is consistent with generally accepted medical practice. In response to requests, clinical input was received from 4 respondents, including: 3 physician-level responses with academic affiliations identified by specialty medical societies and 1 physician-level response identified by an academic health system.

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 Heart 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 (eg, 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).

Respondents noted that there are certain technical impediments that may increase the risk of redo surgical aortic valve replacement (rSAVR) that are not captured by STS 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.

Further details from clinical input are included in the Appendix.

2016 Input

In response to requests, input was received from 2 specialty societies (1 of which provided 2 responses) and 2 academic medical centers (1 of which provided 3 responses) while this policy was under review in 2016. Although there was no support for the use of ViV transcatheter aortic valve implantation (TAVI) to replace a failed bioprosthetic valve in general use, there was general support for the use of ViV TAVI for patients at high and prohibitive risk for surgery.

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2014 Input

In response to requests, input was received from 2 specialty societies (1 of which provided 2 responses) and 6 academic medical centers while this policy was under review in 2014. All reviewers who responded considered TAVI medically necessary for patients with severe aortic stenosis with a calcified aortic annulus and New York Heart Association functional class II, III, or IV symptoms, and who are not candidates for open surgery or who are operable candidates but are at high-risk for open surgery. Most reviewers would require a patient to have a left ventricular ejection fraction greater than 20% for the procedure to be medically necessary. All reviewers indicated support for limiting the use of TAVI to patients who are not candidates for open surgery or who are operable candidates but are at high-risk for open surgery, and most supported using the U.S. Food and Drug Administration (FDA) definition of high-risk and extreme risk for surgery. Most reviewers noted that self-expanding valves have been associated with higher rates of postprocedural pacemaker requirements but that neither type of valve was clearly superior to the other.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.134, Both groups issued a joint focused update in 2017.135, In 2020, a new full guideline was published that replaces the 2014 revision and 2017 focused update.136, 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)."

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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, HF, 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

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Recommendation	COR	LOE
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 SAVR or transfemoral TAVI is recommended after shared decision-making about the balance between expected patient longevity and valve durability."	I	A
"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		

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Recommendation	COR	LOE
"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; HR: heart failure; LOE: level of evidence; SAVR: surgical aortic valve replacement; TAVI: transcatheter aortic valve implantation; ViV: valve-in-valve; VKA: vitamin K antagonist; NYHA: New York Heart Association.

European Society of Cardiology and European Association for Cardio-Thoracic Surgery
In August 2025, the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery published joint updated guidelines on the management of valvular heart disease, replacing the 2021 ESC/EACTS guideline.137, The 2025 guidelines made the following recommendations on intervention and mode of intervention in severe AS (Table 14). Among the new recommendations introduced in this update, the guidelines state:

"Intervention should be considered in asymptomatic patients (confirmed by a normal exercise test, if feasible) with severe, high-gradient AS and LVEF ≥50%, as an alternative to close active surveillance, if the procedural risk is low." (COR IIa, LOE A)

"TAVI may be considered for the treatment of severe BAV stenosis in patients at increased surgical risk, if the anatomy is suitable." (COR IIb, LOE B)

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Table 14. ESC/EACTS Recommendations on Indications for Intervention and Mode of Intervention in Severe Aortic Stenosis

Recommendation	COR	LOE
Symptomatic patients with severe aortic stenosis		
Intervention is recommended in symptomatic patients with severe, high-gradient AS [mean gradient ≥40 mmHg, V_{max} ≥4.0 m/s, and AVA ≤1.0 cm² (or ≤0.6 cm²/m² BSA)].	I	B
Intervention is recommended in symptomatic patients with low-flow (SVi ≤35 mL/m²), low-gradient (<40 mmHg) AS with reduced LVEF (<50%) after careful confirmation that AS is severe.	I	B
Intervention should be considered in symptomatic patients with low-flow (SVi ≤35 mL/m²), low-gradient (<40 mmHg) AS with normal LVEF (≥50%) after careful confirmation that AS is severe.	IIa	B
Asymptomatic patients with severe aortic stenosis		
Intervention is recommended in asymptomatic patients with severe AS and LVEF <50% without another cause.	I	B
Intervention should be considered in asymptomatic patients (confirmed by a normal exercise test, if feasible) with severe, high-gradient AS and LVEF ≥50% as an alternative to close active surveillance, if the procedural risk is low.	IIa	A
Intervention should be considered in asymptomatic patients with severe AS and LVEF ≥50% if the procedural risk is low and one of the following parameters is present: Very severe AS (mean gradient ≥60 mmHg or V_{max} >5.0 m/s); Severe valve calcification (ideally assessed by CCT) and V_{max} progression ≥0.3 m/s/year; Markedly elevated BNP/NT-proBNP levels (more than three times age- and sex-corrected normal range, confirmed on repeated measurement without other explanation); LVEF <55% without another cause.	IIa	B
Intervention should be considered in asymptomatic patients with severe AS and a sustained fall in BP (>20 mmHg) during exercise testing.	IIa	C
Mode of intervention		
It is recommended that AV interventions are performed in Heart Valve Centres that report their local expertise and outcome data, have on-site interventional cardiology and cardiac surgical programmes, and a structured collaborative Heart Team.	I	C

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Recommendation	COR	LOE
It is recommended that the mode of intervention is based on Heart Team assessment of individual clinical, anatomical, and procedural characteristics, incorporating lifetime management considerations and estimated life expectancy.	I	C
TAVI is recommended in patients ≥70 years of age with tricuspid AV stenosis, if the anatomy is suitable.	I	A
SAVR is recommended in patients <70 years of age, if the surgical risk is low.	I	B
SAVR or TAVI are recommended for all remaining candidates for an aortic BHV according to Heart Team assessment.	I	B
Non-transfemoral TAVI should be considered in patients who are unsuitable for surgery and transfemoral access.	IIa	B
TAVI may be considered for the treatment of severe BAV stenosis in patients at increased surgical risk, if the anatomy is suitable.	IIb	B
Balloon aortic valvotomy may be considered as a bridge to SAVR or TAVI in haemodynamically unstable patients, and (if feasible) in those with severe AS who require urgent high-risk NCS.	IIb	C

National Institute for Health and Care Excellence
In June 2019, the NICE published interventional procedures guidance [IPG653] regarding ViV TAVI for aortic bioprosthetic valve dysfunction.[113,] The guidance was informed by an Interventional procedure overview described previously.[138],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 surgical aortic valve replacement (SAVR) is contraindicated or the patient is at high surgical risk.[138,]

U.S. Preventive Services Task Force Recommendations
Not applicable.

Ongoing and Unpublished Clinical Trials
Some currently ongoing trials that might influence this review are listed in Table 14.

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Table 15. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT03972644	Danish National Randomized Study on Early Aortic Valve Replacement in Patients With Asymptomatic Severe Aortic Stenosis	1700	Sep 2029
NCT04204915	A Randomised Controlled Trial of Early Valve Replacement in Severe ASYmptomatic Aortic Stenosis	2844	Apr 2031
NCT05172960[a]	ALLIANCE: Safety and Effectiveness of Balloon-Expandable Bioprosthetic SAPIEN X4 Transcatheter Heart Valve	915	Dec 2034
NCT05172973[a]	ALLIANCE AVIV: Safety and Effectiveness of Balloon-Expandable Bioprosthetic SAPIEN X4 Transcatheter Heart Valve in Failing Aortic Bioprosthetic Valves	200	Feb 2036
NCT05932615[a]	ENVISION: Evaluation of the Navitor Transcatheter Heart Valve in Low and Intermediate Risk Patients Who Have Severe, Symptomatic, Aortic Stenosis Requiring Aortic Valve Replacement	1500	Apr 2036
NCT05149755[a]	Evolut EXPAND TAVR II Pivotal Trial	650	Dec 2034
NCT07278310	STAR Trial (Siegel Transcatheter Aortic Valve Replacement in Patients With Symptomatic Severe Aortic Stenosis)	1025	Apr 2028
NCT07343674	PERFECT - Portuguese Evolut Registry Studying the Outcomes of Medtronic Evolut™ FX+ TAVI System by Evaluating an Optimal Care Pathway for TAVI	500	Apr 2028
NCT06924151	The Prospective, Randomized, Controlled, Multi-center Study to Establish the Safety and Effectiveness of Isolated Surgical Aortic Valve Replacement in Low Risk Patients Who Have Symptomatic Severe Aortic Stenosis	800	May 2037

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NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT06597188	Comparison of Transcatheter Aortic Valve Replacement with Surgical Aortic Valve Replacement: a Prospective, Multicenter, International, Randomized Controlled, Non-inferiority Study for Bicuspid Aortic Valve Stenosis (PROMIS-BAV)	452	Sep 2032
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
NCT06608823	A Study to Assess Safety and Effectiveness of the JenaValve Trilogy™ Transcatheter Heart Valve System Versus Surgical Valve Replacement in Patients with Aortic Regurgitation	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	Jun 2029
NCT05261204	Transcatheter Aortic Valve Implantation Versus Standard Surgical Aortic Valve Operation for Aortic-	1950	Dec 2025

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NCT No.	Trial Name	Planned Enrollment	Completion Date
	Valve Stenosis in Patients at Risk to Severe Valve Obstruction.		
NCT03042104a	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 Symptomatic Severe Aortic Valve Stenosis and Intermediate Risk of Mortality - DEDICATE	1417	Mar 2027
NCT01586910a	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
NCT01737528	Society of Thoracic Surgeons and American College of Cardiology Transcatheter Valve Therapy Registry (STS/ACC TVT Registry)	16,000	Jun 2035
NCT02000115a	Portico Re-sheathable Transcatheter Aortic Valve System US IDE Trial (PORTICO-IDE)	1242	Dec 2026
NCT02825134a	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)	376	Jun 2029
NCT02675114a	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
Unpublished			
NCT02163850a	SALUS Trial: TranScatheter Aortic Valve RepLacement System Pivotal Trial The Safety and	878	Dec 2021 (unknown)

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NCT No.	Trial Name	Planned Enrollment	Completion Date
	Effectiveness of the Direct Flow Medical Transcatheter Aortic Valve System		

NCT: national clinical trial.
a Denotes industry-sponsored or cosponsored trial.

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CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

CPT/HCPCS	
33361	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach
33362	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open femoral artery approach
33363	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open axillary artery approach
33364	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open iliac artery approach
33365	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transaortic approach (e.g., median sternotomy, mediastinotomy)
33366	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transapical exposure (e.g., left thoracotomy)
33367	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with percutaneous peripheral arterial and venous cannulation (e.g., femoral vessels) (List separately in addition to code for primary procedure)
33368	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with open peripheral arterial and venous cannulation (e.g., femoral, iliac, axillary vessels) (List separately in addition to code for primary procedure)
33369	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with central arterial and venous cannulation (e.g., aorta, right atrium, pulmonary artery) (List separately in addition to code for primary procedure)
33370	Transcatheter placement and subsequent removal of cerebral embolic protection device(s), including arterial access, catheterization, imaging, and radiological supervision and interpretation, percutaneous (List separately in addition to code for primary procedure)

REVISIONS	
07-10-2015	Policy added to the bcbsks.com web site on 06-10-2015 with 30 day notice.
10-12-2016	Updated Description section.

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REVISIONS	
	In Policy section: ▪ Added new Item B, "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 all of the following conditions are present: 1. Failed (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve; AND 2. NYHA heart failure class II, III or IV symptoms; AND 3. Left ventricular ejection fraction greater than 20%; AND 4. Patient is not an operable candidate for open surgery, as judged by at least 2 cardiovascular specialists (cardiologist and/or cardiac surgeon); or patient is an operable candidate but is at high risk for open surgery (see Policy Guidelines). ▪ In new Item C (previously Item B), removed ", including, but not limited to: 1. Patients with a degenerated bio-prosthetic valve ("Valve-in-Valve" implantation)" to read, "Transcatheter aortic valve replacement is considered experimental / investigational for all other indications."
	Updated Rationale section.
	In Coding section: ▪ Removed coding bullets.
	Updated References section.
03-29-2017	Updated Description section.
	In Policy section: ▪ In Item A, added "native valve" to read, "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 for patients with native valve aortic stenosis when ALL of the following conditions are present".
	Updated Rationale section.
	In Coding section: ▪ Added ICD-10 codes: T89.01XA, T89.01XD, T82.01XS, T82.02XA, T82.02XD, T82.02XS, T82.03XA, T82.03XD, T82.03XS, T82.09XA, T82.09XD, T82.09XS, T82.857A, T82.857D, T82.857S
	Updated References section.
06-06-2018	Updated Description section.
	In Policy section: ▪ In Item A 4, added "or intermediate" to read, "Patient is not an operable candidate for open surgery, as judged by at least 2 cardiovascular specialists (cardiologist and/or cardiac surgeon); or patient is an operable candidate but is at high or intermediate risk for open surgery" ▪ In Policy Guidelines, added new Item 1, "FDA definition of intermediate risk: a) Society of Thoracic Surgeons predicted operative risk score of 3% to 7%."
	Updated Rationale section.
	In Coding section: ▪ Removed ICD-9 codes.
	Updated References section.
03-27-2019	Updated Description section.
	In Policy section: ▪ In Item B 1, removed "Failed" and added "Failure" and "of a" to read, "Failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve;"
	Updated Rationale section.
	Updated References section.
02-27-2021	Updated Description section
	In Policy section:

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REVISIONS	
	• Item A "U.S. Food and Drug Administration (FDA) was added • Item A.4 was added • Item B added "(valve-in-valve)" • Policy Guideline 1: added "The U.S. Food and Drug Administration (FDA)" • Policy Guideline 4 was added
	Updated the Rationale section
	In the Coding Section the following ICD-10 diagnosis codes were added: • I06.8, I06.4, I08.8, I08.9, I35.8, I35.9
	Updated References section
04-08-2022	Updated Description Section
	Updated Rationale Section
	Updated Coding Section ▪ Converted ICD-10 codes to ranges
	Updated References Section
01-10-2023	Updated Policy Section ▪ Section A2 and B2 added "or syncope or progressive angina due to aortic valve stenosis" to the statement ▪ Section A4 removed "or bicuspid" ▪ Section B added "use with bicuspid aortic valve or"
04-27-2023	Updated Description Section
	Updated Policy Section ▪ Added Section D: "Use of a cerebral embolic protection device (e.g., Sentinel) during transcatheter aortic valve replacement procedures is considered experimental / investigational."
	Updated Rationale Section
	Updated Coding Section ▪ Added code 33370 ▪ Removed ICD-10 codes
	Updated References Section
03-26-2024	Updated Description Section
	Updated Policy Section ▪ Section A1: Changed "annulus" to "valve" ▪ Section A3: Removed "Left ventricular ejection fraction greater than 20%; AND" ▪ Section B3: Removed "Left ventricular ejection fraction greater than 20%; AND" ▪ Section B4: Removed "cardiologist and/or" Added "including a" Added ", (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)"
	Updated Policy Guidelines ▪ Added Section E: "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,"
	Updated Rationale Section
	Updated References Section
06-24-2025	Updated Description Section
	Updated Rationale Section
	Updated Reference Section

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REVISIONS	
10-27-2026	Updated Description Section
	Updated Policy Section ▪ Statement E Added "including, but not limited to, asymptomatic severe aortic stenosis."
	Updated Rationale Section
	Updated Reference Section

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