

<b>7.01.132</b>	<b>Transcatheter Aortic-Valve Implantation for Aortic Stenosis</b>		
<b>Original Policy Date:</b>	March 30, 2012	<b>Effective Date:</b>	April 1, 2021
<b>Section:</b>	7.0 Surgery	<b>Page:</b>	Page 1 of 45

## Policy Statement

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 patients with native valve aortic stenosis when **all** of the following conditions are present:

- I. Severe aortic stenosis (see Policy Guidelines section) with a calcified aortic annulus
- II. New York Heart Association (NYHA) heart failure class II, III, or IV symptoms
- III. Left ventricular ejection fraction greater than 20%
- IV. Patient does not have unicuspid or bicuspid aortic valves
- V. 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 (see Policy Guidelines section)

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

- I. Failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve
- II. NYHA heart failure class II, III, or IV symptoms
- III. Left ventricular ejection fraction greater than 20%
- IV. 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 section)

Transcatheter aortic valve replacement is considered **investigational** for all other indications.

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

## Policy Guidelines

The U.S. Food and Drug Administration (FDA) definition of extreme risk or inoperable for open surgery is:

- Predicted risk of operative mortality and/or serious irreversible morbidity 50% or higher for open surgery

The FDA definition of high risk for open surgery is:

- Society of Thoracic Surgeons 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:

- Society of Thoracic Surgeons predicted operative risk score of 3% to 7%

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

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:

- An aortic valve area of less than or equal to 1 cm<sup>2</sup>
- An aortic valve area index of less than or equal to 0.6 cm<sup>2</sup>/m<sup>2</sup>

- A mean aortic valve gradient greater than or equal to 40 mmHg
- A peak aortic-jet velocity greater than or equal to 4.0 m/s

### Coding

The following are category I CPT codes for this procedure:

- **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)

### 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 (also known as transcatheter aortic valve replacement) 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.

### Related Policies

- Transcatheter Pulmonary Valve Implantation

### Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. 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.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

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

**Table 1. FDA Approved Transcatheter Aortic Valve Device Systems**

Device and Indication	Manufacturer	Date Cleared	PMA
Edwards SAPIEN Transcatheter Heart Valve System™	Edwards Lifesciences	11/11	P100041
<ul style="list-style-type: none"> <li>Severe native aortic valve stenosis determined to be inoperable for open aortic valve replacement (transfemoral approach)</li> </ul>		10/12	P110021
<ul style="list-style-type: none"> <li>Edwards SAPIEN™ Transcatheter Heart Valve, Model 9000TFX</li> <li>Expanded to include high-risk aortic stenosis (transapical approach)</li> </ul>		07/14	P130009
<ul style="list-style-type: none"> <li>Edwards SAPIEN XT Transcatheter Heart Valve (model 9300TFX) and accessories</li> <li>Severe native aortic valve stenosis at high or greater risk for open surgical therapy</li> </ul>		10/15	P130009/S034
<ul style="list-style-type: none"> <li>Expanded to include severe aortic stenosis with intermediate surgical risk</li> </ul>		08/16	P130009/S057
<ul style="list-style-type: none"> <li>SAPIEN 3 Ultra THV System, a design iteration</li> </ul>		12/18	P140031
<p>Note: In August 2019, the FDA issued a recall for the Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System (Recall event ID: 83293) due to "reports of burst balloons which have resulted in significant difficulty retrieving the device into the sheath and withdrawing the system from the patient during procedures".</p>		08/19	P140031/S085
<ul style="list-style-type: none"> <li>Expanded to include severe aortic stenosis with low surgical risk</li> </ul>			
Medtronic CoreValve System™	Medtronic CoreValve	01/14	P130021
<ul style="list-style-type: none"> <li>Severe native aortic stenosis at extreme risk or inoperable for open surgical therapy</li> </ul>		06/16	P130021/S002
<ul style="list-style-type: none"> <li>Expanded to include high-risk for open surgical therapy</li> </ul>		07/17	P130021/S033
<ul style="list-style-type: none"> <li>Expanded to include intermediate risk for open surgical therapy</li> </ul>		06/15	P130021/S014
<ul style="list-style-type: none"> <li>Medtronic CoreValve Evolut R System™ (design iteration for valve and accessories)</li> </ul>		07/17	P130021/S033
<ul style="list-style-type: none"> <li>Expanded to include intermediate risk for open surgical therapy</li> </ul>		03/17	P130021/S029
<ul style="list-style-type: none"> <li>Medtronic CoreValve Evolut PRO System™ (design iteration for valve and accessories, includes porcine pericardial tissue wrap)</li> </ul>		07/17	P130021/S033
<ul style="list-style-type: none"> <li>Expanded to include intermediate risk for open surgical therapy</li> </ul>		08/19	P130021/S058
<ul style="list-style-type: none"> <li>Expanded to include severe aortic stenosis with low surgical risk</li> </ul>		08/19	P130021/S059
<ul style="list-style-type: none"> <li>Medtronic CoreValve Evolut PRO+ System™ (design iteration)</li> </ul>			
LOTUS Edge™ Valve System	Boston Scientific Corporation	04/19	P180029
<ul style="list-style-type: none"> <li>Severe native aortic stenosis at high or greater risk for open surgical therapy</li> <li>See Note</li> </ul>			

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.<sup>7</sup> 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. The following repositionable valves are under investigation:

- Portico™ Transcatheter Aortic Valve (Abbott)
- JenaValve™ (JenaValve Technology); designed for transapical placement. The FDA granted breakthrough designation to this device system in January 2020.

## Rationale

### 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.<sup>1</sup> 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.<sup>1</sup> Thus, the pathogenesis of calcific aortic stenosis is thought to be similar to that of atherosclerosis, i.e., deposition of atherogenic lipids and infiltration of inflammatory cells, followed by progressive calcification.

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

#### 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,<sup>1</sup> increasing up to 8% of people by age 85 years.<sup>2</sup> In the Helsinki Aging Study (1993), a population-based study of 501 patients, ages 75 to 86 years, the prevalence of severe aortic stenosis by echocardiography was estimated to be 2.9%.<sup>3</sup> 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.<sup>4</sup> Open surgical repair is an effective treatment for reversing aortic stenosis, and artificial valves have demonstrated good durability for up to 20 years.<sup>4</sup> However, these benefits are accompanied by perioperative mortality of approximately 3% to 4% and substantial morbidity,<sup>4</sup> 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.<sup>5</sup> 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.<sup>6</sup> 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.

### Literature Review

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 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 enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

The literature evaluating transcatheter aortic valve implantation (TAVI), also known as transcatheter aortic valve replacement (TAVR), has reported on 4 main potential populations: (1) patients who are not surgical candidates, (2) patients who are at high-risk for surgery but still considered to be surgical candidate, (3) patients who at intermediate-risk for surgery, and (4) patients who are at low-risk for surgery. This 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 patients with severe symptomatic aortic stenosis who are at prohibitive risk of open surgery.

The question addressed in this evidence review is: Does the use of TAVI improve the net health outcome for individuals with severe symptomatic aortic stenosis who are at prohibitive risk for 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. There are currently 2 FDA approved valves available in the United States: the balloon-expandable SAPIEN 3 valve and self-expanding valves (Evolut and Evolut PRO).

### **Comparators**

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

### **Outcomes**

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

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a tool for measuring health-related quality of life (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.<sup>8</sup>

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=2,375 patients).<sup>2</sup> 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).<sup>9</sup> It included studies that enrolled symptomatic patients with severe aortic stenosis who had a mean age of 75 years or older, reported on 10 or more patients, and had a follow-up duration of 12 months or more. Twelve studies met these criteria and were compared with a group of 11 studies that treated severe aortic stenosis with nonsurgical therapy. The procedural success in these studies ranged from 86% to 100%, and the 30-day mortality ranged from 5.3% to 23%. The combined mean survival rate at 1 year was 75.9% (95% confidence interval [CI], 73.3% to 78.4%). This 1-year survival rate compared favorably with medical therapy, which was estimated to be 62.4% (95% CI, 59.3% to 65.5%).

### Randomized Controlled Trials

#### SAPIEN and SAPIEN XT

The Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve (PARTNER) trial was a pivotal multicenter RCT of TAVI performed in the United States, Canada, and Germany, using the SAPIEN system. Leon et al (2010) reported on trial results for patients with severe aortic stenosis who were not candidates for open surgery, referred to as the PARTNER B trial.<sup>10</sup> 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 (e.g., myocardial infarction [MI], stroke, acute kidney injury [AKI], vascular complications, bleeding).

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

therapy group having a lower ejection fraction (51.1% vs. 53.9%) and frailty, as determined by prespecified criteria (28.0% vs. 18.1%), all respectively.

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

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

QOL outcomes from this trial were reported by Reynolds et al (2011).<sup>11</sup> QOL outcomes were evaluated using the KCCQ summary score, the 12-Item Short-Form Health Survey (SF-12), and the EuroQoL (EQ-5D). The number of participants who completed the QOL measures was not clearly reported; estimates from graphical representation show that between 149 and 170 patients in the TAVI group and 138 and 157 patients in the medical therapy group completed baseline QOL measures. At follow-up time points of 30 days, 6 months, and 12 months, change in the QOL scores was greater for the TAVI group. At 30 days, the mean difference in the KCCQ score was 13.3 points (95% CI, 7.6 to 19.0;  $p<0.001$ ). This mean difference increased at later time points to 20.8 points (95% CI, 14.7 to 27.0;  $p<0.001$ ) at 6 months and to 26.0 points (95% CI, 18.7 to 33.3;  $p<0.001$ ) at 12 months. Changes in the SF-12 and EQ-5D measures showed similar patterns.

Two-year outcomes were reported from the PARTNER trial by Makkar et al (2012).<sup>12</sup> Mortality at 2 years was 43.3% in the TAVI group compared with 68.0% in the medical therapy group (hazard ratio [HR], 0.58; 95% CI, 0.36 to 0.92;  $p=0.02$ ). Cardiovascular mortality was also lower with TAVI (31.0%) than with medical therapy (62.4%;  $p<0.001$ ). The rate of hospitalization over the 2-year period was lower with TAVI (35.0%) than with medical therapy (72.5%;  $p<0.001$ ).

Svensson et al (2014) reported detailed mortality outcomes for both arms of the PARTNER trial: the PARTNER B RCT (previously described), which compared surgical repair with TAVI in prohibitive surgical risk patients, and the PARTNER A RCT, which compared surgical repair with TAVI in high surgical risk patients (described next).<sup>13</sup> 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.<sup>14</sup> Analysis of the pooled randomized patients was anticipated in the study protocol. At the 3-year follow-up for the pivotal trial subjects, all-cause mortality was 54.1% in the TAVI group and 80.9% in the standard therapy group (HR=0.53; 95% CI, 0.41 to 0.68;  $p<0.001$ ). The incidence of stroke was higher in the TAVI group (15.7%) than in the standard therapy group at 3 years (5.5%; HR=3.81; 95% CI, 1.26 to 6.26;  $p=0.012$ ). However, at 3 years, the



incidence of the composite of death or stroke was significantly lower in the TAVI group (57.4% vs. 80.9%; HR=0.60; 95% CI, 0.46 to 0.77;  $p<0.001$ ). Survivors at 3 years who had undergone TAVI were more likely to have NYHA class I or II symptoms than those who had received standard therapy. In the pooled sample, at the 2- and 3-year follow-ups, mortality was lower for patients who had undergone TAVI than in those who had standard therapy (2 years: 44.8% vs. 64.3%; 3 years: 54.9% vs. 78.0%; all  $p<0.001$ ).

Webb et al (2015) reported on a multicenter RCT comparing a newer-generation SAPIEN XT system with the original SAPIEN system in 560 patients with severe, symptomatic aortic stenosis considered at prohibitive risk for open surgery.<sup>15</sup> 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 ( $p<0.002$ ), which met the criteria for noninferiority.

Kapadia et al (2019) reported an analysis of stroke risk and its association with QOL after surgical aortic valve replacement (SAVR) versus TAVR from a propensity-matched study of 1204 pairs of patients in the PARTNER trials.<sup>16</sup> The analysis focused only on as-treated SAVR and transfemoral TAVR. The incidence of stroke by 30 days was 5.1% in SAVR versus 3.7% in TAVR; incidence of 30-day major stroke was 3.9% versus 2.2% ( $p=0.018$ ). In both groups, risk of stroke peaked in the first post-procedure day but then remained low out to 48 months. Major stroke was associated with a decline in QOL as measured by the KCCQ at 1 year.

### 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 (i.e., Popma et al [2014]<sup>17</sup> and Reardon et al [2014]<sup>18</sup>) or on postapproval registries (i.e., Mack et al [2013]<sup>19</sup>).

### 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  $\geq$ II) for SAVR.<sup>17</sup> 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 aortic valvuloplasty studies, which yielded a rate of 12-month all-cause mortality or major stroke of 42.7% (95% CI, 34.0% to 51.4%); and (2) an adjusted estimate based on the lower 95% confidence bound of 43% in the standard therapy arm of inoperable patients in the PARTNER trial.

Four hundred eighty-nine patients were included in the attempted implant analysis population of 506 patients recruited (11 of whom exited the study before treatment, 6 of whom did not complete the procedure with iliofemoral access). The Kaplan-Meier estimate of the primary endpoint (all-cause mortality or major stroke) was 26.0% (upper bound of 95% CI, 29.9%), which was lower than the prespecified performance goal of 43% ( $p<0.001$ ). The rate of all-cause mortality at 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).<sup>20</sup> The Kaplan-Meier estimate of all-cause mortality or major stroke was 38.0% (upper bound of 95% CI, 42.6%). The incremental rates between years 1 and 2 were 12.3% for all-cause mortality, 7.9% for cardiovascular mortality, and 0.8% for stroke. Baron et al (2017) reported on 3-year results of the QOL data. The QOL improvements following TAVR were largely sustained through 3 years with clinically meaningful ( $\geq 10$  points) improvements in the KCCQ overall summary score at 3 years observed in greater than 83.0%.<sup>21</sup>

Osnabrugge et al (2015) reported on health status outcomes for the 471 patients who underwent TAVI via the transfemoral approach.<sup>22</sup> 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.<sup>18</sup> 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.<sup>19</sup> From November 2011 to May 2013, the registry included 7710 patients who underwent TAVI placement, of whom 1559 (20%) patients were considered inoperable and 6151 (80%) were considered high-risk but operable. Of those considered inoperable, 1139 underwent device placement via transfemoral access, while 420 underwent device placement via nontransfemoral access. In-hospital mortality was 5.4% and 7.1% for the inoperable patients who underwent TAVI via transfemoral and nontransfemoral access, respectively. Thirty-day clinical outcomes were reported for 694 inoperable patients; of those, 30-day mortality was 6.7% and 12.6% for patients who underwent TAVI via transfemoral and nontransfemoral access, respectively.

### Additional Case Series

The prospective nonrandomized Treatment of Aortic Stenosis With a Self-Expanding Transcatheter Valve: the International Multi-Centre ADVANCE study had central adjudication of endpoints and adverse events to evaluate the CoreValve implants in individuals with severe symptomatic aortic stenosis who were considered inoperable or at higher risk for SAVR.<sup>23</sup> 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 ( $\leq 10\%$ ,  $>10\%$  but  $\leq 20\%$ , 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<sup>2</sup> (described previously) reported on 646 patients treated with the CoreValve<sup>24</sup> and 339 patients treated with the SAPIEN valve.<sup>25</sup> The CoreValve study by Piazza et al (2008) was notable in that it used more objective patient selection criteria than is common in this literature. Their criteria for eligibility included: (1) logistic EuroSCORE of 15% or higher, (2) age of 75 or older, or (3) age of 65 or older with liver cirrhosis, pulmonary insufficiency, pulmonary hypertension, previous cardiac surgery, porcelain aorta, recurrent pulmonary emboli, right ventricular insufficiency, previous chest burns, or radiation precluding open surgery, or body mass index of 18 kg/m<sup>2</sup> 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.<sup>26</sup> Procedural success was 98.4%, and 30-day mortality was 12.4%. Another large case series (2011) from Italy included 663 patients treated with the CoreValve device.<sup>27</sup> 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 patients with severe symptomatic aortic stenosis who are at high-risk of open surgery.

The question addressed in this evidence review is: Does the use of TAVI improve the net health outcome for individuals with severe symptomatic aortic stenosis who are at high-risk for 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%.

### **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.

There are currently 2 FDA approved valves available in the United States: the balloon-expandable SAPIEN 3 valve and self-expanding valves (Evolut and Evolut PRO).

### **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.<sup>8</sup>

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

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.<sup>28</sup> 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, 0.68; 95% CI, 0.50 to 0.94). There was no statistical difference in mortality in men undergoing TAVR versus men undergoing SAVR.

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.<sup>29</sup> Trial methods were described in the meta-analysis protocol, which was registered with PROSPERO.<sup>29</sup> 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<sup>30</sup> and the CoreValve High Risk Trial<sup>31</sup>). 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 <sup>a</sup>	Surgical Repair <sup>a</sup>	RR for TAVI vs. Surgical Repair (95% CI)	<i>p</i> , %
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
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).<sup>29</sup>

AF: atrial fibrillation; AKI: acute kidney injury; CI: confidence interval; RR: relative risk; TAVI: transcatheter aortic valve implantation.

<sup>a</sup> 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.<sup>32</sup> Patients in the TAVI group were more severely ill, as evidenced by a EuroSCORE for predicted 30-day mortality, which was higher by a mean of 3.7 points compared with patients undergoing open surgery. On combined analysis, there were no differences between groups for 30-day mortality, mortality at longest follow-up, cardiovascular mortality, MI, stroke, or TIA. Patients in the open surgery group had a higher incidence of major bleeding complications (RR=1.42; 95% CI, 1.20 to 1.67; *p*<0.001). In a similar meta-analysis (2013) that included 17 studies reporting on 4873 patients, there were no differences between TAVI and open surgery in early mortality (OR=0.92; 95% CI, 0.70 to 1.2) or mid-term mortality, defined as between 3 months and 3 years (HR=0.99; 95% CI, 0.83 to 1.2).<sup>33</sup>

## 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.<sup>34</sup> The inclusion and exclusion criteria were generally the same as those for the prior cohort, except that these patients were classified as high-risk for surgery rather than unsuitable for surgery. For high-risk, patients had to have a predicted perioperative mortality of 15% or higher, as determined by a cardiac surgeon and cardiologist using clinical judgment. An STS Risk Score of 10 or higher was included as a guide for high-risk, but an STS Risk Score threshold was not a required criterion for enrollment. The executive committee of the PARTNER trial reviewed all patient selection decisions and approved the classification of patients as high-risk for surgery. A total of 3105 patients were screened for aortic valve surgery, and 22.5% of them were included in the cohort of patients deemed high-risk for surgery.

A total of 699 patients were randomized to TAVI or surgical aortic valve repair. The primary hypothesis was that TAVI was noninferior to open AVR, using a 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=0.06).

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

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

Five-year results from the PARTNER trial were reported by Mack et al (2015).<sup>30</sup> At 5-year follow-up, in the intention-to-treat population, the risk of death from any cause did not differ significantly between patients treated with TAVI (67.8%) and those treated with surgical repair (62.4%;

HR=1.04; 95% CI, 0.86 to 1.24; p=0.76). As reported in the original PARTNER trial findings, moderate or severe aortic regurgitation, primarily paravalvular regurgitation, was more common among TAVI-treated patients. Among TAVI-treated patients, the presence of aortic regurgitation was associated with increased 5-year mortality risk (72.4% for moderate or severe aortic regurgitation vs. 56.6% for mild aortic regurgitation or less; p=0.003).

Reynolds et al (2012) published QOL results from the PARTNER A trial.<sup>35</sup> QOL outcomes were evaluated using the KCCQ summary score, the SF-12, and the EQ-5D. Of 699 patients in the trial, 628 completed baseline QOL measures. Patients in both the TAVI group and the SAVR group demonstrated significant improvements in all QOL measures over the 12 months following treatment. The TAVI group had superior improvement at 1 month on the KCCQ (mean difference, 9.9; 95% CI, 4.9 to 14.9; p<0.001), but this difference was no longer present at 6 or 12 months. A similar pattern of results was reported for the SF-12 and EQ-5D measures.

Genereux et al (2014) published a follow-up study from the PARTNER A trial reporting on bleeding complications.<sup>36</sup> Using an as-treated approach, this analysis included 313 patients treated with surgical repair, 240 patients treated with transfemoral TAVI, and 104 patients treated with transapical TAVI. Seventy-one (22.7%) patients treated with surgery had major bleeding complications within 30 days of the procedure, compared with 27 (11.3%) of those treated with transfemoral TAVI and 9 (8.8%) of those treated with transapical TAVI (p<0.001).

### U.S. CoreValve High-Risk Study

Adams et al (2014) published results of the U.S. CoreValve High Risk Study.<sup>37</sup> This RCT compared SAVR with TAVI using the CoreValve device in patients who had severe aortic stenosis and were considered at increased risk of death during surgery. The study randomized 795 patients in a 1:1 ratio to TAVI or open AVR. Patients were considered to be at "increased surgical risk" if 2 cardiac surgeons and 1 interventional cardiologist estimated that the risk of death within 30 days of surgery was 15% or more and that the risk of death or irreversible complications within 30 days after surgery was less than 50%. The primary analysis was based on the as-treated population, which included all patients who underwent attempted implantation. For the study's primary outcome, the rate of death from any cause at 1 year was lower in the TAVI group (14.2%) than in the surgical group (19.1%; absolute risk reduction, 4.9%; upper boundary of 95% CI, -0.4%, which was less than the predefined noninferiority margin of 7.5%-point difference between groups; noninferiority, p<0.001; superiority, p=0.04). Major vascular complications and permanent pacemaker implantations were significantly more frequent in the TAVI group than in the surgical group: at 30 days, major vascular complications occurred in 5.9% of the TAVI group compared with 1.7% of the surgical group (p=0.003), while permanent pacemaker implantation was required in 19.8% of the TAVI group compared with 7.1% of the surgical group (p<0.001). In contrast to the PARTNER trial, the TAVI group did not have a higher rate of any stroke at 1 year postprocedure (8.8%) than the surgical group (12.6%; p=0.10).

Two-year follow-up results from the U.S. CoreValve High Risk Study were published by Reardon et al (2015).<sup>31</sup> 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.<sup>38</sup> At 3 years, 37.3% (n=142) of TAVI-treated patients experienced all-cause mortality or stroke, which was significantly less than the 46.7% (n=160) of surgical patients for the same outcome (p=0.006). In the TAVI group, MACCE was observed in 40.2% (n=153) of patients; in the surgical group, MACCE occurred in 47.9% (n=164) of patients (p=0.025). Other outcomes that were improved in the TAVI group compared with surgery were life-threatening or disabling bleeding, AKI, aortic valve area, and mean aortic valve gradient. More TAVI-treated patients required implantation of a pacemaker (28.0%) than did surgical patients (14.5%; p<0.001); also, more patients in the TAVI group (6.8%) had moderate atrial regurgitation than in the surgery group (0.0%) at 3 years. The authors noted the improvement in mean aortic valve gradient for both cohorts (TAVR, 7.62 mm Hg vs. SAVR, 11.40 mm Hg; p<0.001).

Additional analyses of the U.S. CoreValve High Risk Study have focused on the impact of patient and prosthesis mismatch [39](#) and health status [40](#).

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 [41](#). 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 30 days was significantly higher with TAVR (6.4% vs. 1.4%,  $p=0.003$ ). Life-threatening or disabling bleeding (12.0% vs. 34.0%,  $p<0.001$ ), encephalopathy (7.2% vs. 12.3%,  $p=0.02$ ), atrial fibrillation (8.4% vs. 18.7%  $p<0.001$ ), and AKI (6.1% vs. 15.0%,  $p<0.001$ ) were significantly higher with SAVR.

Gleason et al (2019) reported 5-year follow-up of the CoreValve High Risk Trial and estimated similar 5-year survival (55.3% for TAVR vs. 55.4% for SAVR) and stroke rates (12.3% for TAVR versus 13.2% for SAVR) in high-risk patients. Valve reinterventions were uncommon; freedom from valve reintervention was 97.0% for TAVR and 98.9% for SAVR [42](#).

### REPRISE III

The Repositionable Percutaneous Replacement of Stenotic Aortic Valve Through Implantation of Lotus Valve System—Randomized Clinical Evaluation (REPRISE III) trial was an RCT comparing 2 different TAVR platforms: the mechanically expanded Lotus valve (which was discontinued in January 2021) and self-expanding CoreValve. Thirty-day and 1-year results were reported in the Summary of Safety and Effectiveness compiled by the FDA and 2-year results were published by Reardon et al (2019) [43,44](#). The trial enrolled 912 patients ( $n=607$  in Lotus;  $n=305$  in CoreValve) with high/extreme risk and severe, symptomatic aortic stenosis between September 2014 and December 2015 at 55 centers in North America, Europe, and Australia. An early-generation CoreValve device was used. Follow-up is scheduled to continue for up to 5 years. Patients were required to have an STS-PROM risk score of  $\geq 8\%$  or another indicator of high or extreme risk. The mean age was 83 years ( $SD=7$ ) years and the mean STS-PROM score was 6.8%. The primary safety outcome was a composite of all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 AKI, or major vascular complications at 30 days. The primary effectiveness outcome was a composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation at 1 year. At 30 days, the incidence of the primary safety outcome was 20% versus 17% for Lotus versus CoreValve (risk difference [RD]=3.1%; 95% CI, -2.3 to 8.5) and met the criteria for noninferiority. All of the individual components of the 30-day primary safety outcome were similar between the 2 groups. The incidence of the primary effectiveness outcome was 16% versus 26% in Lotus versus CoreValve (RD=-10.2%; 95% CI, -16.3 to 4.0) and met the criteria for noninferiority. At 2 years, all-cause death was 21% versus 22.5% with Lotus versus CoreValve (HR=0.94; 95% CI, 0.69 to 1.26) and all-cause mortality or disabling stroke was 23% versus 27% with Lotus versus CoreValve (HR=0.81; 95% CI, 0.61 to 1.07). Placement of a new permanent pacemaker was more common in the Lotus group (42% vs. 26%; HR= 1.9; 95% CI, 1.4 to 2.5). Valve thrombosis was also more common in the Lotus group (3% vs. 0%). Repeated procedures were more common in the CoreValve group (0.6% vs. 2.9%; HR=0.19; 95% CI, 0.05 to 0.70), as was valve migration (0.0% vs. 0.7%) and embolization (0.0% vs. 2.0%).

### 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 TAVR [45,46,47](#). Given the availability of RCT evidence, these studies provide limited additional information on the efficacy of TAVI.

### 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. QOL was also similar at 1 year between the TAVI and AVR groups. Stroke and TIA were significantly more common for the TAVI group, occurring at a rate of almost 2 times that reported for open surgery. Other secondary outcomes were similar between groups, except for higher rates of vascular complications in the TAVI group and higher rates of major bleeding in the open surgery group. As in the first PARTNER cohort, there is concern about the generalizability of results because the patient selection process relied largely on the judgment of surgeons and cardiologists participating in the trial. The U.S. CoreValve High Risk Study reported that TAVI was noninferior to open surgical repair. Although unlike the PARTNER A RCT, stroke rates were not higher in patients who underwent TAVI, a requirement for permanent pacemaker was more common in the TAVI group. Follow-up analyses of the U.S. CoreValve High Risk Study showed sustained improvements in the TAVI group for the outcome of all-cause mortality and a number of secondary outcomes. The incidence of pacemaker implantation continued to be higher in TAVI-treated patients.

One trial has compared 2 different FDA approved valves, the mechanically expanded Lotus valve and self-expanding CoreValve in patients at high surgical risk. For follow-up of up to 2 years, all-cause mortality rates and all-cause mortality or disabling stroke composite outcome rates with Lotus or CoreValve were similar.

### **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, in patients with severe symptomatic aortic stenosis who are at intermediate or low-risk of open surgery.

The question addressed in this evidence review is: Does the use of TAVI improve the net health outcome for individuals with severe symptomatic aortic stenosis who are at intermediate or low-risk for 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 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.

There are currently 2 FDA approved valves available in the United States: the balloon-expandable SAPIEN 3 valve and self-expanding valves (Evolut and Evolut PRO).

### 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.<sup>8</sup>

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.

### Systematic Reviews

Several systematic reviews and meta-analyses were published in 2017 through 2020,<sup>48,49,50,51,52,53,54,55,56,57,58,59,60,61</sup> including many overlapping RCTs and observational studies.

In a Cochrane review, Kolkailah et al (2019) evaluated the literature on TAVI versus SAVR for severe aortic stenosis in patients with low surgical risk.<sup>62</sup> The review included 4 studies (N=2818) and 1 ongoing study. Results revealed that there is probably little or no difference between TAVI and SAVR with regard to the following short-term outcomes: all-cause mortality (RR=0.69; 95% CI, 0.33 to 1.44), stroke (RR=0.73; 95% CI, 0.42 to 1.25), myocardial infarction (RR=0.82; 95% CI, 0.42 to 1.58), and cardiac death (RR=0.71; 95% CI, 0.32 to 1.56). TAVI may potentially reduce the risk of short-term hospitalization as well (RR=0.64; 95% CI, 0.39 to 1.06) and result in an increased risk of permanent pacemaker implantation (RR=3.65; 95% CI, 1.50 to 8.87). TAVI reduces the risk of atrial fibrillation (RR=0.21; 95% CI, 0.15 to 0.3), AKI (RR=0.3; 95% CI, 0.16 to 0.58), and bleeding (RR=0.31; 95% CI, 0.16 to 0.62) compared to SAVR.

Garg et al (2017) published a systematic review and meta-analyses that included RCTs and prospective observational studies comparing TAVI with SAVR published between January 2000 and March 2017 including low-to-intermediate surgical risk patients with severe aortic stenosis.<sup>50</sup> Five RCTs (n=4,425 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	P <sup>2</sup>
30-day mortality	3.1	3.0	1.04 (0.73 to 1.47)	0.84	0
Stroke incidence	7.3	8.1	0.91 (0.74 to 1.11)	0.35	0
AKI incidence	1.8	4.7	0.38 (0.26 to 0.54)	<0.001	0
Myocardial infarction incidence	3.1	3.1	1.00 (0.71 to 1.41)	1.00	0
Major vascular complication incidence	7.3	3.2	3.09 (1.51 to 6.35)	0.002	66
Requirement for permanent pacemaker incidence	20.0	7.9	3.10 (1.44 to 6.66)	0.004	92

Adapted from Garg (2017).<sup>50</sup>

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.<sup>63</sup> Seven studies were included, 3 RCTs (Nordic Aortic Intervention Trial [NOTION; 2015],<sup>64</sup> Transapical Transcatheter Aortic Valve Implantation vs. Surgical Aortic Valve Replacement in Operable Elderly Patients with Aortic Stenosis [STACCATO; 2012]<sup>65</sup>, Leon et al [2016]<sup>66</sup>), and 4 observational studies (N=6,214 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	P <sup>2</sup>
Short-term postprocedure mortality	2.59	3.94	0.63 (0.37 to 1.08)	0.09	56
Short-term cardiovascular mortality	1.96	3.15	0.51 (0.23 to 1.15)	0.11	68
AKI incidence	1.92	4.8	0.34 (0.17 to 0.67)	0.002	61
Stroke incidence	3.57	4.90	0.72 (0.56 to 0.92)	0.01	42
Myocardial infarction incidence	0.7	1.7	0.51 (0.23 to 0.69)	<0.001	10
Major vascular complication incidence	7.2	3.6	3.54 (1.42 to 8.81)	0.006	86
Requirement for permanent pacemaker incidence	11.9	6.1	2.79 (1.49 to 5.23)	0.001	88
All-cause mortality (1 year)	10.1	12.2	0.82 (0.58 to 1.16)	0.26	67

Adapted from Zhou et al (2016).<sup>63</sup>

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.<sup>67,68</sup> 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.<sup>69</sup>

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

Seven 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**

Study; Trial	Countries	Sites	Dates	Participants	Interventions		Sponsor
					TAVR	SAVR	
Nielsen et al (2012) <sup>65</sup> ; STA CATTO	Denmark	2	Nov 2008 to May 2011	<ul style="list-style-type: none"> <li>• Mean age, 81 y</li> <li>• No significant coronary artery disease</li> <li>• Any surgical risk (mean STS PROM, 3.3)</li> </ul>	<ul style="list-style-type: none"> <li>• n=34</li> <li>• Edwards Sapien THV</li> </ul>	<ul style="list-style-type: none"> <li>• n=36</li> <li>• Conventional open-heart surgery with CPB</li> </ul>	Participating hospitals and Danish Heart Foundation
Thyregod et al (2015) <sup>64</sup> ; Søndergaard et al (2016) <sup>70</sup> ; Thyregod et al (2019) <sup>71</sup> ; Søndergaard et al (2019) <sup>72</sup> ; NOTION (NCT01057173)	Denmark, Sweden	3	Dec 2009 to Apr 2013	<ul style="list-style-type: none"> <li>• Mean age, 79 y</li> <li>• No significant coronary artery disease</li> <li>• Any surgical risk (mean STS PROM, 3.0; 82% low-risk)</li> </ul>	<ul style="list-style-type: none"> <li>• n=145</li> <li>• Core-Valve</li> </ul>	<ul style="list-style-type: none"> <li>• n=135</li> <li>• Conventional open-heart surgery with CPB</li> </ul>	Danish Heart Foundation
Reardon et al (2016) <sup>73</sup> ; CoreValve U.S. Pivotal (NCT01240902)	U.S.	45	Feb 2011 to Sep 2012	<ul style="list-style-type: none"> <li>• Mean age, 81 y</li> <li>• STS score &lt;7<sup>a</sup> (median, 5.3)</li> <li>• Symptomatic (NYHA class ≥II)</li> </ul>	<ul style="list-style-type: none"> <li>• n=202</li> <li>• Core-Valve</li> </ul>	<ul style="list-style-type: none"> <li>• n=181</li> <li>• Conventional open-heart surgery with CPB</li> </ul>	Manufacturer
Leon et al (2016) <sup>66</sup> ; PARTNER 2A (NCT01314313)	U.S., Canada	57	Dec 2011 to Nov 2013	<ul style="list-style-type: none"> <li>• Mean age, 82 y</li> <li>• Symptomatic (NYHA class ≥II)</li> <li>• STS PROM ≥4 and ≤8 or</li> <li>• STS PROM &lt;4 with coexisting conditions (mean, 5.8)</li> </ul>	<ul style="list-style-type: none"> <li>• n=1011</li> <li>• SAPIEN XT</li> </ul>	<ul style="list-style-type: none"> <li>• n=1021</li> <li>• Conventional surgery</li> </ul>	Manufacturer
Reardon et al (2017) <sup>74</sup> ; SURTAVI (NCT01586910)	U.S., Spain, Netherlands, Germany, UK, Canada, Switzerland, Sweden, Australia	87	NR	<ul style="list-style-type: none"> <li>• Mean age, 80 y</li> <li>• STS PROM ≥4 and &lt;15 (mean, 4.5)</li> <li>• Symptomatic (NYHA class ≥II)</li> </ul>	<ul style="list-style-type: none"> <li>• n=879</li> <li>• Core-Valve</li> </ul>	<ul style="list-style-type: none"> <li>• n=867</li> <li>• Conventional surgery with coronary revascularization if needed</li> </ul>	Manufacturer
Popma et al (2019) <sup>75</sup> ; Evolut Low Risk Trial (NCT02701283)	Canada, France, Japan, Netherlands, New Zealand, U.S.	86	Mar 2016 to Nov 2018	<ul style="list-style-type: none"> <li>• Mean age, 74 y</li> <li>• STS PROM ≤3 (mean, 1.9)</li> <li>• 90% NYHA class ≥II (symptomatic); 10% NYHA class I (asymptomatic)</li> </ul>	<ul style="list-style-type: none"> <li>• n=734</li> <li>• CoreValve, Evolut R, or Evolut PRO</li> </ul>	<ul style="list-style-type: none"> <li>• n=734</li> <li>• Conventional surgery</li> </ul>	Manufacturer

Study; Trial	Countries	Sites	Dates	Participants	Interventions		Sponsor
					TAVR	SAVR	
Mack et al (2019); <sup>76</sup> PARTNER 3, NCT02675114	U.S., Canada, Australia, New Zealand, Japan	71	Mar 2016 to Oct 2017	<ul style="list-style-type: none"> <li>• Mean age, 73 y</li> <li>• STS PROM &lt;4 (mean, 1.9)</li> <li>• 28% NYHA III or IV</li> </ul>	<ul style="list-style-type: none"> <li>• n=503</li> <li>• SAPIEN 3</li> </ul>	<ul style="list-style-type: none"> <li>• n=497</li> <li>• Conventional surgery</li> </ul>	Manufacturer

CPB: cardiopulmonary bypass; NYHA: New York Heart Association; SAVR: surgical aortic valve replacement; STS PROM: Society of Thoracic Surgeons predicted risk of mortality score; TAVR: transcatheter aortic valve replacement; THV: Transcatheter heart valve

<sup>a</sup> Includes analysis of a subset of originally randomized patients.

**Table 6. RCTs 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) <sup>65,65</sup> STACATO <sup>65</sup>	Death from any cause, stroke, or renal failure at 30 d										
All patients		14.7	2.8	RD (NR)	0.07	NR	NR		NR	NR	
Thyregod et al (2015) <sup>64,64</sup> NOTION <sup>64</sup>	Death from any cause, stroke, or MI at 1 y										
All patients		13.1	16.3	RD = -3.2	0.43 <sup>a</sup>	4.9	7.5	0.38	34.1	1.6	<0.001
Reardon et al (2016) <sup>73,73</sup> CoreValve U.S. Pivotal <sup>73</sup>	Death from any cause at 2 y										
STS score ≤7		26.3	15.0	HR (NR)	0.01	See previous columns			27.7	10.5	<0.001
Leon et al (2016) <sup>66,66</sup> PARTNER 2A <sup>66</sup>	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	0.45	11.8	10.9	0.29
Transfemoral access		16.8	20.4	HR=0.79 (0.62 to 1.00)		14.2	17.2	0.11	11.4	10.8	0.71
Transthoracic access		27.7	23.4	HR=1.21 (0.84 to 1.74)		25.2	20.7	0.26	13.1	8.6	0.13
Reardon et al (2017) <sup>74</sup>	Death from any cause										

Study	Primary Outcome	Results of Primary Outcomes, %		All-Cause Mortality (2 y), %		New Permanent Pacemaker (2 y), %			
	or disabling stroke at 2 y								
All patients		12.6	14.0	RD = -1.4 (-5.2 to 2.3) <sup>b</sup>	11.4	11.6	-3.8 to 3.3 <sup>b</sup>	25.9	6.6 to 22.7 <sup>b</sup>
Popma et al (2019) <sup>75</sup> . Evolut Low Risk Trial	Death or disabling stroke at 2 y								
All patients		5.3	6.7	RD = -1.4 (-4.9 to 2.1) <sup>b</sup>	4.5	4.5	NR	NR	
Mack et al (2019) <sup>76</sup> . PARTNER 3	Death, stroke, or rehospitalization at 1 year								
All patients		8.5	15.1	RD = -6.6 (-10.8 to -2.5) <sup>b</sup>	NR			NR	

CI: confidence interval; HR: hazard ratio; RD: risk difference; MI: myocardial infarction; NR: not reported; STS: Society of Thoracic Surgeons; Surg: surgical repair; TAVI: transcatheter aortic valve implantation; TE: treatment effect.

<sup>a</sup> Superiority. <sup>b</sup> Bayesian credible 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).<sup>65</sup> 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.<sup>73</sup> The trial was described in a previous section on high surgical risk. Of the 750 total patients in the trial, 383 (202 TAVR; 181 SAVR) had an STS PROM score of 7% or less, with a median STS PROM score of 5.3%. All-cause mortality at 2 years for TAVR 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%;  $p=0.01$ ). The rates of stroke at 2 years for TAVR versus SAVR were 11% versus 15% ( $p=0.50$ ).

Thyregod et al (2015) reported on the results of the NOTION RCT, which compared TAVI with surgical repair in 280 patients with severe aortic stenosis who were 70 years or older, regardless of the predicted risk of death after surgery.<sup>64</sup> 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%,  $p=0.03$ ), cardiogenic shock (4.2% vs. 10.4%,  $p=0.05$ ), stage 2 or 3 AKI (0.7% vs. 6.7%,  $p=0.01$ ), and new-onset or worsening atrial fibrillation (16.9% vs. 57.8%,  $p<0.001$ ) than surgical

repair patients, all respectively. Both groups showed improvements in NYHA functional class. However, more TAVI-treated patients were in NYHA functional class II at 1-year follow-up (29.5% vs. 15.0%,  $p=0.01$ ).

In a 2-year follow-up of the NOTION trial, Søndergaard et al (2016) reported slight improvements in the TAVI-treated group ( $n=142$ ) compared with the surgical repair group ( $n=134$ ), although between-group differences were almost exclusively not statistically significant.<sup>70</sup> For the composite rate of death at 2 years, the between-group difference was also statistically insignificant (18.8% of surgical repair patients vs. 15.8% of TAVI-treated patients;  $p=0.43$ ). A similar difference was observed for all-cause mortality (8.0% of patients treated with TAVI experienced all-cause mortality vs. 9.8% of the surgical repair patients;  $p=0.54$ ). Cardiovascular mortality rates, stroke rates, and MI were likewise marginally improved in the TAVI-treated patients, although the only significant difference was found for atrial fibrillation and permanent pacemaker implantation. For the former outcome, there were 60.0% of surgical patients, compared with 22.7% of TAVI patients ( $p<0.001$ ); for the latter, only 4.2% of surgical patients received implantation versus 41.3% of the TAVI group ( $p<0.001$ ). As a secondary outcome, moderate aortic regurgitation was improved at 2 years for the TAVI group (15.4%) compared with the surgical group (0.9%;  $p<0.001$ ). The authors noted that the variety of risk levels observed in the patients limited their results, as did the exclusion of patients with coronary artery disease. Further, the trial was limited by its lack of power for subgroup analyses, and its inability to reveal any significant differences between groups with certainty. Overall, the results showed that TAVI-treated patients had comparable, if not improved, outcomes when treated alongside patients who received SAVR.

Results after 5 years of follow-up were reported by Thyregod et al (2019).<sup>71</sup> There were no significant differences between TAVR and SAVR in the incidence of the composite primary outcome (38.0% vs. 36.3%,  $p=0.86$ ) or any of the components of the composite. The incidence of moderate/severe total aortic regurgitation (8.2% vs. 0.0%,  $p<0.001$ ) and a new pacemaker (43.7% vs. 8.7%,  $p<0.001$ ) were both higher in the TAVR group. Four patients had prosthetic re-intervention. Søndergaard et al (2019) compared the durability of TAVR versus SAVR after 6 years of follow-up from NOTION. At 6 years, the rates of all-cause mortality were similar for TAVR (42.5%) and SAVR (37.7%) patients. The rate of moderate to severe structural valve deterioration was higher for SAVR than TAVR (24.0% vs. 4.8%;  $p < 0.001$ ) and there were no differences in non-structural valve deterioration (57.8% vs. 54.0%), bioprosthetic valve failure (6.7% vs. 7.5%), or endocarditis (5.9% vs. 5.8%).<sup>72</sup>

### 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 TAVR or SAVR.<sup>74</sup> For the primary outcome (composite death at 2 years), an improvement was observed in the TAVR-treated group, compared with surgery (12.6% of TAVR patients vs. 14.0% of SAVR patients [95% credible interval, -5.2% to 2.3%]; posterior probability,  $>0.999$ ). Rates of death, MI, and disabling stroke were comparable between groups, as were secondary outcomes that included echocardiographic measurement of aortic valve gradient and paravalvular regurgitation (data reported in the supplemental material). More patients were assigned to the CoreValve bio-prosthesis ( $n=724$ ) than received Evolut R bioprosthesis ( $n=137$ ), which might have affected the results; also, a considerable number of patients withdrew consent before surgery, resulting in an as-treated population of 1660. Finally, the authors acknowledged a gap in knowledge of how baseline characteristics of patients who received surgery differed from those who did not. The authors noted the low 30-day surgical mortality ratio (0.38; observed-to-expected) and the similarity of this rate between groups (2.2% of the TAVR patients vs. 1.7% of surgical patients).

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).<sup>66</sup> 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  $\geq 2$  on the modified Rankin Scale) at 2 years and a noninferiority margin of 1.2 (i.e., noninferiority was considered met if upper bound of 2-sided CI for the RR for the primary outcome was  $< 1.2$ ). A total of 2032 patients were randomized to TAVI (n=1011) or surgical repair (n=1021), with 1550 considered suitable for transfemoral placement (76.3%) and 482 (23.7%) requiring transthoracic access. At baseline, the mean STS Risk Score was 5.8%; 81.3% had a score between 4% and 8%. The primary outcome results and select additional results of the trial are summarized in Table 6. Also, similar to other TAVI trials, the frequency and severity of paravalvular regurgitation was higher after TAVI than in surgical repair. The presence 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;  $p < 0.001$ ). The 5 year outcomes from the PARTNER 2A study revealed no significant difference in the incidence of death from any cause or disabling stroke between the TAVI and surgical repair groups (47.9% vs. 43.4%; HR, 1.09; 95% CI, 0.95 to 1.25;  $p = 0.21$ ).<sup>74</sup> 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 re-interventions (3.2% vs. 0.8%). Improvement in health status at 5 years was similar between the groups.

### Including Low-Risk Only

Popma et al (2019) reported results of prespecified, interim analyses of the multinational Evolut Low Risk Trial, a noninferiority trial conducted from 2016 to 2018 comparing TAVR (n=734) to SAVR (n=734) in patients who had severe aortic stenosis and were at low surgical risk (STS-PROM  $\leq 3$ ).<sup>75</sup> Patients with bicuspid aortic valves were excluded. Patients assigned to TAVR were treated with 1 of 3 Medtronic self-expanding, supra-annular bioprostheses (CoreValve, Evolut R, or Evolut PRO). Preliminary analyses were performed when 850 patients had reached 12-month follow-up. Long-term follow-up is scheduled to continue for 10 years. The primary outcome was a composite of death or disabling stroke at 24 months performed using Bayesian methods. At the time of the preliminary analysis, 149 patients had reached the 24 months visit. The 24-month estimated incidence of the primary outcome was 5.3% in the TAVR group and 6.7% in the SAVR group (RD = -1.4%; 95% Bayesian credible interval, -4.9 to 2.1; posterior probability of non-inferiority  $> 0.999$ ). Several 30-day outcomes were also reported. The incidence at 30 days of disabling stroke (0.5% vs. 1.7%), bleeding complications (2.4% vs. 7.5%), AKI (0.9% vs. 2.8%), and atrial fibrillation (7.7% vs. 35.4%) were lower in TAVR compared to SAVR. The incidence at 30 days of moderate or severe aortic regurgitation (3.5% vs. 0.5%) and pacemaker implantation (17.4% vs. 6.1%) was higher in TAVR compared to SAVR. There was not a statistically significant difference in the KCCQ overall summary score at 30 days (88.7 $\pm$ 14.2 in the TAVR group vs. 78.6 $\pm$ 18.9 in the SAVR group)

Mack et al (2019) reported results of the multinational PARTNER 3 trial, randomizing patients with severe aortic stenosis and low surgical risk to either TAVR with the SAPIEN (n=503) or SAVR (n=497) in 2016 to 2017.<sup>76</sup> 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 the TAVR; n=454 in SAVR) but sensitivity analyses of the primary outcome performed in the intention-to-treat population with multiple imputations for missing data were reportedly consistent with the primary analysis. The number of participants that did not receive the assigned treatment was higher in the SAVR group (7 vs. 43). The most common reported reason was refusal to undergo surgery or choosing to undergo surgery at a nontrial site. The estimated incidence of the primary outcome at 1 year was significantly lower in TAVR versus SAVR (8.5% vs. 15.1%; RD = -6.6%; 95% CI, -10.8 to -2.5;  $p < 0.001$  for noninferiority). All components of the composite (death, stroke, and hospitalization) individually favored TAVR at 30 days and 1 year. At 30 days, the rate of stroke (0.6% vs. 2.4%; HR=0.25; 95% CI, 0.07 to 0.88;  $p = 0.02$ ) and new-onset atrial fibrillation (5.0% vs. 39.5%; HR=0.10; 95% CI, 0.06 to 0.16;  $p < 0.001$ ) was lower in TAVR



than SAVR and index hospitalization time was shorter (3 days vs. 7 days,  $p < 0.001$ ). There were no significant differences at 30 days in major vascular complications, new permanent pacemaker insertions, or moderate or severe paravalvular regurgitation. The incidence of mild paravalvular regurgitation at 1 year was higher with TAVR (29.4% vs. 2.1%). In an analysis specific to the echocardiographic findings of the PARTNER 3 trial, Pibarot et al (2020) reported that the percentage of moderate or severe aortic regurgitation was low and not statistically different between the TAVR and SAVR groups at 30 days (0.8% vs. 0.2%;  $p = 0.38$ ); mild aortic regurgitation occurred more frequently after TAVR than SAVR (28.8% vs. 4.2%;  $p < 0.001$ ).<sup>78</sup> Mean transvalvular gradient ( $13.7 \pm 5.6$  vs.  $11.6 \pm 5.0$  mmHg;  $p = 0.12$ ) and aortic valve area ( $1.72 \pm 0.37$  vs.  $1.76 \pm 0.42$  cm<sup>2</sup>;  $p = 0.12$ ) were similar between groups at 1 year.

### Study limitations

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 <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Nielsen et al (2012) STACATO	4: Included patients with any surgical risk, not limited to patients requiring alternative access	4: Transapical TAVI, multidetector computed tomography was not performed before procedure			1, 2: Terminated early
Thyregod et al (2015) NOTION	4: Included patients with any surgical risk				
Reardon et al (2016) CoreValve U.S. Pivotal	4: Subgroup analysis included patients at low/intermediate risk by STS-PROM but deemed at high surgical risk based on screening committee assessment despite their STS scores				
Leon et al (2016) PARTNER 2A	4: 12% of the study population had an STS risk score > 8				
Reardon et al (2017) SURTAVI					
Popma et al (2019) Evolut Low Risk Trial					1: Results are from a planned interim analysis; data collection is not complete

Study	Population <sup>a</sup>	Intervention <sup>b</sup>	Comparator <sup>c</sup>	Outcomes <sup>d</sup>	Follow-Up <sup>e</sup>
Mack et al (2019) PARTNER 3				4: Rehospitalization was included in the composite primary outcome	1,2: Only 1-year outcomes currently available

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.

<sup>a</sup> 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.

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

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

<sup>d</sup> 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.

<sup>e</sup> Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

**Table 8. Study Design and Conduct Limitations**

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
Nielsen et al (2012) STACATTO		1: Patients and study staff not blinded		1: Study terminated early with only 70 participants		
Thyregod et al (2015) NOTION		1: Patients and study staff not blinded 2,3: Unclear if outcome adjudication was blinded				
Reardon et al (2016) 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) PARTNER 2A		1: Patients and study staff not blinded		1: High frequency of withdrawals in patients assigned to undergo surgery		
Reardon et al (2017) SURTA VI		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) Evolut Low Risk Trial		1: Patients and study staff not blinded		1: High frequency of withdrawals in patients		

Study	Allocation <sup>a</sup>	Blinding <sup>b</sup>	Selective Reporting <sup>c</sup>	Data Completeness <sup>d</sup>	Power <sup>e</sup>	Statistical <sup>f</sup>
				assigned to undergo surgery Results are from a planned interim analysis; data collection is not complete		
Mack et al (2019) 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		

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.

<sup>a</sup> Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

<sup>b</sup> Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

<sup>c</sup> Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

<sup>d</sup> 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).

<sup>e</sup> Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

<sup>f</sup> 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

### Intermediate-Risk

Most participants in 5 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 3 of the 5 RCTs including the 2 RCTs exclusively enrolling intermediate risk patients. The rates of adverse events differed between groups, with bleeding, cardiogenic shock, and AKI higher in patients randomized to open surgery and permanent pacemaker requirement higher in patients randomized to TAVI. Subgroup analyses of meta-analyses and the transthoracic arm of the Leon RCT suggested that the benefit of TAVI may be limited to patients who are candidates for transfemoral access. Two-year follow-up results were published for NOTION, PARTNER 2A, CoreValve U.S. Pivotal, and SURTAVI trials, but reported outcomes did not include rates of reoperation. A number of recently completed meta-analyses evaluated mortality for TAVR versus SAVR at the 30-day mark. Mortality rates were found to be comparable between the 2 procedures.

### Low-Risk

The NOTION trial was predominantly low surgical risk patients; the Evolut Low Risk Trial and PARTNER 3 were only low-risk patients. The STACCATO trial also included some patients at low surgical risk. In the NOTION trial, the risk of the composite outcome of death from any cause, stroke, or MI at 1 year was numerically but not statistically significantly lower in the TAVR group compared to SAVR and, after 5 years of follow-up, there were still no significant differences

between TAVR and SAVR in the incidence of the composite outcome (38.0% vs. 36.3%,  $p=0.86$ ) or any of the components of the composite. Six-year follow-up from NOTION showed less structural valve deterioration in TAVR than SAVR. In the Evolut Low Risk Trial, TAVR was noninferior to SAVR with respect to the composite outcome of death or disabling stroke at 24 months. At 30 days, TAVR was associated with a lower incidence of disabling stroke, AKI, bleeding events, and atrial fibrillation but with a higher incidence of aortic regurgitation and permanent pacemaker use. In the PARTNER 3 trial, the rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVR than SAVR. At 30 days, TAVR was associated with a lower rate of stroke, death or stroke composite, new-onset atrial fibrillation, and shorter index hospitalization. There were no significant between-group differences in major vascular complications or new permanent pacemaker insertions at 30 days. The age of participants in the low-risk RCTs was markedly lower than that in previous TAVR trials and therefore life expectancy is longer. Extended follow-up will be needed to address the long-term advantages and disadvantages of TAVR versus SAVR and valve durability. Both of the low-risk RCTs have planned follow-up of 10 years and both excluded patients with bicuspid aortic valves.

The ongoing NOTION 2 Trial (NCT02825134) includes only patients  $\leq 75$ -years-old and does not exclude patients with bicuspid aortic valves. Data collection of the primary outcome is scheduled for completion in 2020.

### **Transcatheter Aortic Valve Implantation Outcomes for “Valve-in-Valve” Approach**

#### **Clinical Context and Therapy Purpose**

The purpose of transcatheter aortic “valve-in-valve” 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 patients with valve dysfunction and aortic stenosis or regurgitation after aortic valve repair.

The question addressed in this evidence review is: Does the use of transcatheter aortic “valve-in-valve” implantation improve the net health outcome for 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 populations of interest is individuals with valve dysfunction and aortic stenosis or regurgitation after aortic valve repair.

#### **Interventions**

The therapy being considered is transcatheter aortic “valve-in-valve” 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 “valve-in-valve” implantation as a treatment for valve dysfunction and aortic stenosis or regurgitation after aortic valve repair has varying lengths of follow-up, with many following patients for at least 1 year after the “valve-in-valve” 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

In 2019, the National Institute for Health and Care Excellence prepared an interventional procedure overview on safety and efficacy of valve-in-valve TAVI for aortic bioprosthetic valve dysfunction based on a rapid review of medical literature including publications through August 2018 and specialist opinion.<sup>79</sup> The review included 3 systematic reviews and meta-analysis [80,81,82](#) and 8 case series (registries) totaling 4,256 patients, although the authors note that there may be some overlap of patients in the global valve-in-valve register and other registries. There are no RCTs comparing valve-in-valve TAVI with redo SAVR. The available evidence is from observational studies and registry data with follow-up ranging from 1 month to 1 year. Two systematic reviews and meta-analyses compare valve-in-valve TAVI with redo SAVR 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 valve-in-valve TAVI and redo SAVR in perioperative mortality (5% vs. 6%; risk ratio=0.78; 95% CI, 0.33 to 1.84), late mortality (median 1-year follow-up, incident rate ratio=0.93; 95% CI, 0.74 to 1.16), or perioperative stroke (2% vs. 3%; RR=0.73; 95% CI, 0.18 to 3.02), whereas, the rate of permanent pacemaker insertion was statistically significantly lower in the valve-in-valve TAVI group (8% vs. 15%; RR=0.57; 95% CI, 0.32 to 1.0) and the rate of mild or greater paravalvular regurgitation was statistically significantly higher in the valve-in-valve TAVI group (21% vs. 6%; RR=3.83; 95% CI, 1.2 to 12.22). In 2 registries (including 365 and 227 patients), the rate of conversion to surgery or surgical reintervention within 30 days was less than 1%.

#### Registries

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

Following the National Institute for Health and Care Excellence review, 3-year results from the PARTNER 2 valve-in-valve registry were published by Webb et al (2019).<sup>79</sup> The registry included 365 patients who had valve-in-valve [81,82](#) procedures with a mean age of 79 years (± 10) and mean STS-PROM score of 9.1% (±4.7). The estimated incidence of all-cause mortality at 3 years was 32.7%. Aortic valve re-replacement was performed in 1.9% by 3 years. From baseline to year 3, NYHA functional class improved; 90.4% of patients were in class III or IV at baseline and 14.1% were in class III or IV at 3 years (p < 0.0001). QOL as measured by the KCCQ overall score also increased from baseline to 3 years (43.1 to 73.1; p < 0.0001).

**Section Summary: Transcatheter Aortic Valve Implantation Outcomes for “Valve-in-Valve” Approach**

The evidence related to the use of TAVI for valve-in-valve replacement after failed TAVI or degenerated bioprosthetic valve consists of comparative and single-arm observational studies including registry data with follow-up ranging from 1 month to 3 years and systematic reviews. Two systematic reviews of observational studies have compared valve-in-valve TAVI to redo SAVR and have reported similar favorable outcomes. However, selection bias cannot be ruled out given that no RCTs are available.

**Summary of Evidence**

For individuals who have severe symptomatic aortic stenosis who are at prohibitive risk for open surgery who receive transcatheter aortic valve implantation (TAVI), the evidence includes a RCT comparing TAVI with medical management in individuals at prohibitive risk of surgery, a single-arm prospective trial, multiple case series, and multiple systematic reviews. Relevant outcomes are overall survival (OS), symptoms, morbid events, and treatment-related mortality and morbidity. For patients who are not surgical candidates due to excessive surgical risk, the Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve (PARTNER B) trial reported on results for patients treated with TAVI by the transfemoral approach compared with continued medical care with or without balloon valvuloplasty. There was a large decrease in mortality for the TAVI patients at 1 year compared with medical care. This trial also reported improvements in other relevant clinical outcomes for the TAVI group. There was an increased risk of stroke and vascular complications in the TAVI group. Despite these concerns, the overall balance of benefits and risks from this trial indicate that health outcomes are improved. For patients who are not surgical candidates, no randomized trials have compared the self-expandable valve with best medical therapy. However, results from the single-arm CoreValve Extreme Risk Pivotal Trial met trialists' prespecified objective performance goal. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have severe symptomatic aortic stenosis who are at high-risk for open surgery who receive TAVI, the evidence includes 2 RCTs comparing TAVI with surgical repair in individuals at high-risk for surgery and 1 RCT comparing 2 types of valves, multiple non-randomized comparative studies, and systematic reviews of these studies. Relevant outcomes are OS, symptoms, morbid events, and treatment-related mortality and morbidity. For patients who are high-risk for open surgery and are surgical candidates, the PARTNER A trial reported noninferiority for survival at 1 year for the balloon-expandable valve compared with open surgery. In this trial, TAVI patients also had higher risks for stroke and vascular complications. Nonrandomized comparative studies of TAVI versus open surgery in high-risk patients have reported no major differences in rates of mortality or stroke between the 2 procedures. Since the publication of the PARTNER A trial, the CoreValve High Risk Trial demonstrated noninferiority for survival at 1 and 2 years for the self-expanding prosthesis. This trial reported no significant differences in stroke rates between groups. In an RCT directly comparing the self-expandable with the balloon-expandable valve among surgically high-risk patients, the devices had similar 30-day mortality outcomes, although the self-expandable valve was associated with higher rates of residual aortic regurgitation and need for a new permanent pacemaker. Evidence from RCT and nonrandomized studies has suggested that TAVI with a self-expanding device is associated with higher rates for permanent pacemakers postprocedure. However, survival rates appear to be similar between device types, and the evidence does not support the superiority of 1 device over another in all patients. Two sex-specific studies were also identified in a literature search with the objective of observing mortality rates in women undergoing TAVI or surgical aortic valve replacement (SAVR). Results were varied, and further study is needed. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have severe symptomatic aortic stenosis who are at intermediate-risk for open surgery who receive TAVI, the evidence includes 3 RCTs comparing TAVI with surgical

repair including individuals at intermediate surgical risk, 2 RCTs only in patients with intermediate-risk, and multiple systematic reviews and nonrandomized cohort studies. Relevant outcomes are OS, symptoms, morbid events, and treatment-related mortality and morbidity. Five RCTs have evaluated TAVI in patients with intermediate-risk for open surgery. Three of them, which included over 4000 patients combined, reported noninferiority of TAVI versus SAVR for their composite outcome measures (generally including death and stroke). A subset analysis of patients (n=383) with low and intermediate surgical risk from a fourth trial reported higher rates of death at 2 years for TAVI versus SAVR. The final study (N=70) had an unclear hypothesis and reported 30-day mortality rates favoring SAVR (15% vs. 2%, p=0.07) but used a transthoracic approach. The rates of adverse events differed between groups, with bleeding, cardiogenic shock, and acute kidney injury higher in patients randomized to open surgery and permanent pacemaker requirement higher in patients randomized to TAVI. Subgroup analyses of meta-analyses and the transthoracic arm of the Leon et al(2010) RCT have suggested that the benefit of TAVI may be limited to patients who are candidates for transfemoral access. Although several RCTs have 2 years of follow-up postprocedure, it is uncertain how many individuals require reoperation. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have severe symptomatic aortic stenosis who are at low-risk for open surgery who receive TAVI, the evidence includes RCTs comparing TAVI with surgical repair in individuals selected without specific surgical risk criteria but including patients at low surgical risk and RCTs enrolling only low surgical risk patients, systematic reviews, and nonrandomized cohort studies. Relevant outcomes are OS, symptoms, morbid events, and treatment-related mortality and morbidity. Two RCTs (Evolut Low Risk Trial and the Study to Establish the Safety and Effectiveness of the SAPIEN 3 Transcatheter Heart Valve in Low Risk Patients Who Have Severe, Calcific, Aortic Stenosis Requiring Aortic Valve Replacement [PARTNER 3]) have been conducted exclusively in patients at low surgical risk and 1 RCT, Nordic Aortic Intervention Trial included predominantly patients at low surgical risk. In the Evolut Low Risk Trial, transcatheter aortic valve replacement was noninferior to SAVR with respect to the composite outcome of death or disabling stroke at 24 months. In the PARTNER 3 trial, the rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVI than SAVR. In the Nordic Aortic Intervention Trial, the risk of the composite outcome of death from any cause, stroke, or myocardial infarction at 5 years was similar for TAVI and SAVR and transcatheter aortic valve replacement showed less structural valve deterioration than SAVR at 6 years. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have valve dysfunction and aortic stenosis or regurgitation after open surgical aortic valve repair who receive transcatheter aortic “valve-in-valve” implantation, the evidence includes observational studies including registry data with follow-up ranging from 1 month to 3 years and a systematic reviews. Relevant outcomes are OS, symptoms, morbid events, and treatment-related mortality and morbidity. Systematic reviews of observational studies have compared valve-in-valve TAVI to redo SAVR and have reported similar mortality, stroke, and survival rates for the 2 procedures. However, selection bias cannot be ruled out given that no RCTs are available. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### **Supplemental Information**

The purpose of the Supplemental Information is to provide reference material regarding clinical input, existing practice guidelines and position statements, U.S. Preventive Services Task Force Recommendations and Medicare National Coverage Decisions and registered, ongoing clinical trials. Inclusion in the Supplemental Information does not imply endorsement or that the information is used in the evidence review.

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

### 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.

#### 2016 Input

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

#### 2014 Input

In response to requests from Blue Cross Blue Shield Association, input was received from 2 specialty societies (1 of which provided 2 responses) and 6 academic medical centers 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

#### 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.<sup>83</sup> Both groups issued a joint focused update in 2017<sup>84</sup>. In 2020, a new full guideline was published that replaces the 2014 revision and 2017 focused update.<sup>85</sup> The 2020 guidelines made the following recommendations on timing of intervention and choice of surgical or transcatheter intervention for treatment of aortic stenosis (Table 9). Additionally, the guidelines state the following:

- "Treatment of severe aortic stenosis with either a transcatheter or surgical valve prosthesis should be based primarily on symptoms or reduced ventricular systolic function. Earlier intervention may be considered if indicated by results of exercise testing, biomarkers, rapid progression, or the presence of very severe stenosis."
- "Indications for TAVI are expanding as a result of multiple randomized trials of TAVI versus surgical aortic valve replacement. The choice of type of intervention for a patient with severe aortic stenosis should be a shared decision-making process that considers the lifetime risks and benefits associated with type of valve (mechanical versus bioprosthetic) and type of approach (transcatheter versus surgical)."

**Table 9. Recommendations on Surgical or Transcatheter Intervention for Aortic Stenosis**

Recommendation	COR	LOE
<i>Timing of Intervention of AS</i>		
"In adults with severe high-gradient AS (Stage D1) and symptoms of exertional dyspnea, heart failure, angina, syncope, or presyncope by history or on exercise testing, AVR is indicated."	I	A



Recommendation	COR	LOE
"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 $\geq 10$ mmHg from baseline to peak exercise."	IIa	B
"In asymptomatic patients with very severe AS (defined as an aortic velocity of $\geq 5$ 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 $\geq 0.3$ 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
<i>Choice of SAVR Versus TAVI for Patients for Whom a Bioprosthetic AVR is Appropriate</i>		
"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 $\leq 80$ 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

AS: aortic stenosis; AVR: aortic valve replacement; COR: class of recommendation; LOE: level of evidence; SAVR: surgical aortic valve replacement; TAVR: transcatheter aortic valve replacement.

### National Institute for Health and Care Excellence

In June 2019, the National Institute For Health And Care Excellence published interventional procedures guidance [IPG653] regarding valve-in-valve TAVI for aortic bioprosthetic valve dysfunction.<sup>86</sup> The guidance was informed by an Interventional procedure overview described

previously.<sup>79</sup> The guidance recommendation is that "Current evidence on the safety and efficacy of valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) for aortic bio-prosthetic dysfunction is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit."

### U.S. Preventive Services Task Force Recommendations

Not applicable.

### Medicare National Coverage

The Centers for Medicare & Medicaid Services published a decision memo on the use of TAVR in 2012 and 2019.<sup>87</sup> The 2019 memo indicated that the Centers for Medicare & Medicaid Services covers TAVI when used according to FDA indications when the following conditions are met:

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

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

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

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

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

### Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 10.

**Table 10. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT03042104	Evaluation of Transcatheter Aortic Valve Replacement Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis	1109	Dec 2031
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	1760	Dec 2026
NCT01586910 <sup>a</sup>	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 2023

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT02661451 <sup>a</sup>	Transcatheter Aortic Valve Replacement to UNload the Left Ventricle in Patients With ADvanced Heart Failure: A Randomized Trial (TAVR UNLOAD)	300	Mar 2022
NCT02436655	Aortic Valve Replacement Versus Conservative Treatment in Asymptomatic Severe Aortic Stenosis: (AVATAR Trial): A Multicentre Randomized Controlled Trial	312	Jun 2021
NCT01314313 <sup>a</sup>	The PARTNER II Trial "Placement of AoRTic TraNscathetER Valves Trial" (US)	2032	Nov 2024
NCT02163850 <sup>a</sup>	SALUS Trial: TranScatheter Aortic Valve ReplAcement System Pivotal Trial The Safety and Effectiveness of the Direct Flow Medical Transcatheter Aortic Valve System	878	Dec 2021
NCT01737528	Society of Thoracic Surgeons and American College of Cardiology Transcatheter Valve Therapy Registry (STS/ACC TVT Registry)	16,000	Jun 2022
NCT02249000	Safety and Clinical Performance of the Self-expanding Transcatheter BIOVALVE Prosthesis in Subjects With Severe Symptomatic Aortic Stenosis Suitable for Transfemoral Transcatheter Aortic Valve Implantation	86	Dec 2022
NCT02628899	Feasibility of Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic, Severe Aortic Stenosis	300	Jan 2023
NCT02000115	Portico Re-sheathable Transcatheter Aortic Valve System US IDE Trial	1268	Jul 2025
NCT02825134	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)	992	Jun 2029

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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## Documentation for Clinical Review

### Please provide the following documentation:

- History and physical including:
  - NYHA heart failure classification
  - Reason for procedure
  - Severity of aortic stenosis including any calcifications OR evidence of failure of a surgical bioprosthetic valve
  - Left Ventricular Ejection Fraction (LVEF)
  - Lack of unicuspid or bicuspid aortic valve



- Consultation report(s)\* from at least 2 cardiovascular specialists (cardiologist and/or cardiac surgeon) including:
  - Risk factors for open surgery
  - Society of Thoracic Surgeons (STS) predicted operative risk score or expected mortality risk for open surgery (if applicable)
  - Surgical approach planned (e.g., transfemoral, transapical)
- \*Two cardiac surgeon consultation reports are required for patients who are not operable candidates for open surgery. For patients who are operable candidates but are at high risk for open surgery, both cardiac surgeon and cardiologist consultation reports are required
- Echocardiogram results (within the last six months)
- Other cardiovascular studies if applicable

**Post Service (in addition to the above, please include the following):**

- Operative report(s)

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.*

Type	Code	Description
CPT®	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)
HCPCS	None	

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
03/30/2012	BCBSA Medical Policy adoption
02/22/2013	Coding Update
03/29/2013	Policy revision with position change
03/07/2014	Coding and Administrative Update
06/30/2015	Coding update
10/01/2016	Policy title change from Transcatheter Aortic Valve Replacement for Aortic Stenosis Policy revision with position change
04/01/2017	Policy revision without position change
07/01/2018	Policy revision without position change
05/01/2019	Policy revision without position change
05/01/2020	Annual review. Policy statement, guidelines and literature updated.
04/01/2021	Annual review. Policy statement, guidelines and literature updated. Policy title changed from Transcatheter Aortic Valve Implantation for Aortic Stenosis to current one.

### Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well*

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*as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

**Appendix A**

POLICY STATEMENT	
BEFORE <span style="color: red;">Red font: Verbiage removed</span>	AFTER <span style="color: blue;">Blue font: Verbiage Changes/Additions</span>
<p><b>Policy Title 7.01.132</b></p> <p><b>Policy Statement:</b>                      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 <b>medically necessary</b> for patients with native valve aortic stenosis when <b>all</b> of the following conditions are present:</p> <ul style="list-style-type: none"> <li>• Severe aortic stenosis (see Policy Guidelines section) with a calcified aortic annulus</li> <li>• New York Heart Association (NYHA) heart failure class II, III, or IV symptoms</li> <li>• Left ventricular ejection fraction greater than 20%</li> <li>• Patient does not have unicuspid or bicuspid aortic valves</li> </ul> <p>Transcatheter aortic valve replacement with a transcatheter heart valve system approved for use for repair of a degenerated bioprosthetic valve (valve-in-valve) may be considered <b>medically necessary</b> when <b>all</b> of the following conditions are present:</p> <ul style="list-style-type: none"> <li>• Failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve</li> <li>• NYHA heart failure class II, III, or IV symptoms</li> <li>• Left ventricular ejection fraction greater than 20%</li> <li>• 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 section)</li> </ul>	<p><b>Transcatheter Aortic-Valve Implantation for Aortic Stenosis 7.01.132</b></p> <p><b>Policy Statement:</b>                      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 <b>medically necessary</b> for patients with native valve aortic stenosis when <b>all</b> of the following conditions are present:</p> <ol style="list-style-type: none"> <li>I. Severe aortic stenosis (see Policy Guidelines section) with a calcified aortic annulus</li> <li>II. New York Heart Association (NYHA) heart failure class II, III, or IV symptoms</li> <li>III. Left ventricular ejection fraction greater than 20%</li> <li>IV. Patient does not have unicuspid or bicuspid aortic valves</li> <li>V. 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 (see Policy Guidelines section)</li> </ol> <p>Transcatheter aortic valve replacement with a transcatheter heart valve system approved for use for repair of a degenerated bioprosthetic valve (valve-in-valve) may be considered <b>medically necessary</b> when <b>all</b> of the following conditions are present:</p> <ol style="list-style-type: none"> <li>I. Failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve</li> <li>II. NYHA heart failure class II, III, or IV symptoms</li> <li>III. Left ventricular ejection fraction greater than 20%</li> <li>IV. 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 section)</li> </ol>

POLICY STATEMENT	
BEFORE	AFTER
<b>Red font: Verbiage removed</b>	<b>Blue font: Verbiage Changes/Additions</b>
Transcatheter aortic valve replacement is considered <b>investigational</b> for all other indications.	Transcatheter aortic valve replacement is considered <b>investigational</b> for all other indications.