Regence

Medical Policy Manual Surgery, Policy No. 201

Transcatheter Aortic Valve Implantation for Aortic Stenosis

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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Transcatheter aortic valve implantation (also known as transcatheter aortic valve replacement) is an alternative to open valve replacement surgery for patients with aortic stenosis and to nonsurgical therapy for patients with a prohibitive risk for surgery.

MEDICAL POLICY CRITERIA

I. For patients with native valve aortic stenosis, transcatheter aortic valve implantation with an U.S. Food and Drug Administration (FDA)-approved transcatheter heart valve system may be considered **medically necessary** when all of the following criteria (A. – C.) are met:

   A. New York Heart Association heart failure class II, III, or IV symptoms; and

   B. Aortic valve is not unicuspid or bicuspid; and

   C. Severe aortic stenosis, defined as any one or more of the following:

      1. An aortic valve area of less than or equal to 1 cm^2, or
      2. An aortic valve area index of less than or equal to 0.6 cm^2/m^2, or
      3. A mean aortic valve gradient greater than or equal to 40 mmHg, or

4. A peak aortic-jet velocity greater than or equal to 4.0 m/s.

II. For patients with a bioprosthetic aortic valve, transcatheter aortic valve replacement (i.e., valve-in-valve) with an FDA-approved transcatheter heart valve system (e.g., Edwards SAPIEN™ or Medtronic CoreValve System™) may be considered **medically necessary** when all of the following criteria (A. –C.) are met:

A. Failure of a surgical bioprosthetic aortic valve (stenosed or insufficient); and

B. New York Heart Association heart failure class II, III, or IV symptoms; and

C. There is clinical documentation that the patient is either of the following:

1. Not a candidate for open surgery, or

2. At high risk for open surgery, defined as either of the following, as documented by the ordering provider:

a. Society of Thoracic Surgeons predicted operative risk score of 8% or higher (see Policy Guidelines), or

b. An expected mortality risk of 15% or higher for open surgery

III. Transcatheter aortic valve implantation or replacement is considered **investigational** when Criteria I. or II. is not met, including for all other indications and for non-FDA-approved devices.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

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^2
- An aortic valve area index of less than or equal to 0.6 cm^2/m^2
- 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.

The Society of Thoracic Surgeons risk calculator can be found at: https://acsdriskcalc.research.sts.org/.

LIST OF INFORMATION NEEDED FOR REVIEW

It is critical that the list of information below is submitted for review to determine if the policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- History and Physical/Chart Notes
- Documentation of symptoms, associated diagnoses and treatments
- The name of the valve system to be implanted
- Documentation of aortic valve stenosis (e.g., valve area, mean aortic valve gradient)

- In the case of valve-in-valve implantation, documentation that supports determination that patient is not a candidate or is high-risk for open surgery

CROSS REFERENCES

None

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.[1] 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, and include advanced age, male gender, smoking, hypertension, and hyperlipidemia.[1] 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 stage, symptoms of dyspnea, chest pain, and/or dizziness/syncope often occur, and the disorder progresses rapidly.

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 two years.[2] Open surgical replacement of the diseased valve with a bioprosthetic or mechanical valve is an effective treatment for reversing aortic stenosis, and artificial valves have demonstrated good durability for up to 20 years.[2] However, these benefits are accompanied by perioperative mortality of approximately 3% to 4% and substantial morbidity,[2] both of which increase with advancing age.

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.[3] 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.[4] 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.

Transcatheter Aortic Valve Implantation

Transcatheter aortic valve implantation (TAVI), also known as transcatheter aortic valve replacement (TAVR), 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 the stenotic area. This is followed by passage of a bioprosthetic artificial valve across the native aortic valve. The valve is initially compressed to allow passage across the native valve and is then expanded and secured to the underlying aortic valve annulus. The procedure is performed on the beating heart without cardiopulmonary bypass.

REGULATORY STATUS

Multiple manufacturers have transcatheter aortic valve devices with FDA approval:

- Edwards SAPIEN Transcatheter Heart Valve System™ (Edwards Lifesciences)
    - Edwards SAPIEN™ Transcatheter Heart Valve, Model 9000TFX
    - Edwards SAPIEN XT Transcatheter Heart Valve (model 9300TFX) and accessories
    - SAPIEN 3 THV System, a design iteration
    - SAPIEN 3 Ultra THV System, a design iteration
      Note: In August 2019, FDA issued a recall for the Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System (Recall event ID: 83293) due to "reports of burst balloons which have resulted in significant difficulty retrieving the device into the sheath and withdrawing the system from the patient during procedures".

- Medtronic CoreValve System™ (Medtronic CoreValve)
    - Medtronic CoreValve Evolut R System™ (design iteration for valve and accessories)
    - Medtronic CoreValve Evolut PRO System™ (design iteration for valve and accessories, includes porcine pericardial tissue wrap)
    - Medtronic CoreValve Evolut PRO+ System™ (design iteration)

- LOTUS Edge™ Valve System (Boston Scientific)

  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.[5] There are no safety concerns for patents who have the LOTUS Edge™ Valve System currently implanted. Boston Scientific has chosen to retire the entire LOTUS product platform immediately rather than develop and reintroduce an enhanced delivery system. All related commercial, clinical, research and development, and manufacturing activities will cease.

- Portico™ with FlexNav™ (Abbott Medical)

- Navitor™ Transcatheter Aortic Valve Implantation System with FlexNav™ (Abbott Medical)

Other transcatheter aortic valve systems are under development. The following repositionable valves are under investigation:

- JenaValve™ (JenaValve Technology); designed for transapical placement

- Acurate™ aortic valve platform (Boston Scientific); designed for individuals with severe aortic stenosis indicated for TAVR who are at low, intermediate, or high risk of operative mortality.

EVIDENCE SUMMARY

TAVI OUTCOMES IN PATIENTS AT PROHIBITIVE RISK FOR OPEN SURGERY

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. A systematic review sponsored by the Agency for Healthcare Research and Quality (2010, archived) evaluated 84 publications (total n=2,375 patients).[6] 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 systematic review by Figulla (2011) 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.[7] 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 one year was 75.9% (95% confidence interval [CI] 73.3% to 78.4%). This one-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

<u>SAPIEN and SAPIEN XT</u>

The Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve (PARTNER) randomized controlled trial (RCT) was a pivotal multicenter trial of TAVI performed in the United States, Canada, and Germany, using the SAPIEN™ system. Leon (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.[8] To be classified as unsuitable for open surgery, patients had to have a predicted probability of 50% or higher for death or a serious irreversible condition at 30 days post-surgery. This probability was determined by two 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 3,105 patients were screened for aortic valve surgery, and 12% of them were included in the cohort of patients deemed unsuitable for surgery.

In the trial, 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 six-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 than in the TAVI group (30.4 vs. 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 one 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 one death over a one-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 one 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 one year was more than twice as frequent for the TAVI group (10.6% vs. 4.5%, p=0.04). Major bleeding and vascular complications occurred in a substantial percentage of patients undergoing TAVI (22.3% vs. 11.2%, p=0.007) and were significantly higher than in the standard therapy group (32.4% vs. 7.3%, p<0.001).

Quality of life (QoL) outcomes from this trial were reported by Reynolds (2011), and were evaluated using the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score, the 12-Item Short-Form Health Survey (SF-12), and the EuroQoL (EQ-5D).[9] 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, six 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 six 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 from the PARTNER trial were reported by Makkar (2012).[10] Mortality at two 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 two-year period was lower with TAVI (35.0%) than with medical therapy (72.5%, p<0.001).

Svensson (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).[11] For the 358 patients considered inoperable and enrolled in the PARTNER B trial, 237 patients had died at last follow-up. Those randomized to standard therapy exhibited an early peak in mortality that was higher than those randomized to TAVI, and that persisted beyond six 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 (2014) reported on three-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.[12] Analysis of the pooled randomized patients was anticipated in the study protocol. At the three-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 three years (5.5%, HR 3.81, 95% CI 1.26 to 6.26, p=0.012). However, at three 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 three 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 two- and three-year follow-ups, mortality was lower for patients who had undergone TAVI than in those who had standard therapy (at two years: 44.8% vs. 64.3%, at three years: 54.9% vs. 78.0%, all p<0.001).

Webb (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.[13] The trial used a noninferiority design; for its primary endpoint, a composite of all-cause mortality, major stroke, and rehospitalization at one 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 (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 1,204 pairs of patients in the PARTNER trials.[14] 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 one year.

Huded (2022) reported on rehospitalization rates from the PARTNER trial, finding no effect modification by transcatheter versus surgical aortic valve replacement.[15]

Nonrandomized Studies

Many case series of TAVI have been published in the last 10 years, most of which have included patients that were 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, including the series reporting on the pivotal trials leading to devices' approvals.

CoreValve Extreme Risk Study

Popma (2014) published results of the CoreValve Extreme Risk Study pivotal trial, which was designed to evaluate the CoreValve self-expanding valve among patients with severe aortic stenosis who were considered to be at extreme risk (NYHA class ≥II) for SAVR.[16] A patient was judged to be at extreme risk if two cardiac surgeons and one 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 two sources: (1) a weighted meta-analysis of seven 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.

There were 489 patients included in the attempted implant analysis population of 506 patients recruited (11 of whom exited the study before treatment, six 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 one 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 (2015).[17] 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 one and two were 12.3% for all-cause mortality, 7.9% for cardiovascular mortality, and 0.8% for stroke. Baron (2017) reported on three-year results of the QoL data.[18] The QoL improvements following TAVR were largely sustained through three years with clinically meaningful (≥10 points) improvements in the KCCQ overall summary score at three years observed in greater than 83.0%. At five years of follow-up, the Kaplan-Meier rate of death or major stroke was 72.6%, and the KCCQ remained improved compared with pre-TAVI scores.[19]

Osnabrugge (2015) reported on health status outcomes for the 471 patients who underwent TAVI via the transfemoral approach.[20] On average, general and disease-specific QoL scores both showed substantial improvements after TAVI. However, 39% of patients had a poor outcome at six months (22% death, 16% very poor QOL, 1.4% QoL declined).

Reardon (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.[21] 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).

Post-approval Registries

Mack (2013) reported on outcomes after TAVI from 224 hospitals participating in the Edwards SAPIEN device post-FDA approval registry.[22] From November 2011 to May 2013, the registry included 7,710 patients who underwent TAVI placement, of whom 1,559 (20%) patients were considered inoperable and 6,151 (80%) were considered high-risk but operable. Of those considered inoperable, 1,139 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.[23] The study enrolled 1,015 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 three categories of surgical risk based on logistic EuroSCORE values (≤10%, >10% to ≤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 two largest series included in the Agency for Healthcare Research and Quality review[6] (described previously) reported on 646 patients treated with the CoreValve[24] and 339 patients treated with the SAPIEN valve.[25] The CoreValve study by Piazza (2008) was notable in that it used more objective patient selection criteria than is common in this literature.[24] Their criteria for eligibility included: (1) logistic EuroSCORE of 15% or higher, (2) age of 75 or older, or (3) age of 65 or older with liver cirrhosis, pulmonary insufficiency, pulmonary hypertension, previous cardiac surgery, porcelain aorta, recurrent pulmonary emboli, right ventricular insufficiency, previous chest burns, or radiation precluding open surgery, or body mass index of 18 kg/m^2 or less. Procedural success was 97%, and 30-day survival was 92%. The 30-day combined rate of death, MI, or stroke was 9.3%. The Canadian study by Rodes-Cabau (2010) used the SAPIEN valve.[25] 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 eight months.

Additional series have described experiences with TAVI in European centers. Zahn (2011), in a large case series from Germany, reported on 697 patients treated with the CoreValve system.[26] Procedural success was 98.4%, and 30-day mortality was 12.4%. Another large case series from Italy included 663 patients treated with the CoreValve device.[27] Procedural success was 98%, and mortality at one year was 15%.

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

Numerous case series have demonstrated the feasibility and short-term efficacy for TAVI in patients who are not surgical candidates. In the PARTNER B trial, there was a large decrease in all-cause mortality and cardiovascular mortality at one year for TAVI compared with standard therapy. Subsequent publications from this same trial reported that the mortality benefit was maintained at two 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.

TAVI OUTCOMES IN PATIENTS AT HIGH RISK FOR OPEN SURGERY

Systematic Reviews

A meta-analysis of four RCTs was published by Panoulas (2018) to determine whether sex differences had any impact on mortality rates for TAVI and SAVR.[28] The four RCTs comprised of 3,758 patients (2,052 men, 1,706 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 one-year mark; in fact, women undergoing TAVI were found to have a 31% lower mortality rate than women undergoing SAVR, again at the one-year

mark (odds ratio [OR] 0.68, 95% CI 0.50 to 0.94). There was no statistical difference in mortality in men undergoing TAVR versus men undergoing SAVR. An updated meta-analysis by Dagan (2021) identified eight RCTs including 8,040 patients (41.4% female).[29] Similar results were found to the 2018 analysis with lower one-year mortality and improved safety with TAVI compared with SAVR in women.

Villablanca (2016) reported on a meta-analysis and meta-regression of long-term outcomes (more than one year) of TAVI compared with SAVR for severe aortic stenosis.[30] Trial methods were described in the meta-analysis protocol, which was registered with PROSPERO.[30] The review was limited to studies comparing TAVI with surgical repair, with subgroup analyses for high- and intermediate-risk patients. Overall, four RCTs (n=3,806 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[31] and CoreValve High Risk Trial[32]). Results from the subgroup analyses focused on high-risk patients are shown in Table 1.

Table 1. TAVI Versus Surgical Repair in High-Risk Patients

Outcomes	TAVI[a]	Surgical Repair[a]	RR for TAVI vs. Surgical Repair (95% CI)	I^2, %
30-day postprocedure mortality	508/8,552 (5.9%)	804/29,323 (2.7%)	1.02 (0.76 to 1.36)	72.3
All-cause mortality	3,625/8,803 (41.1%)	5,438/29,450 (18.6%)	1.16 (0.87 to 1.53)	96.6
Stroke incidence	191/4,293 (4.4%)	213/4,348 (4.9%)	0.79 (0.66 to 0.95)	0
Myocardial infarction incidence	57/2,820 (2.0%)	59/2,746 (2.1%)	0.91 (0.64 to 1.29)	21.5
Vascular complication incidence	203/2,489 (8.2%)	35/2,682 (1.3%)	5.5 (2.42 to 12.4)	67.5
Residual regurgitation incidence	268/2,831 (9.5%)	36/2,823 (1.3%)	6.3 (4.55 to 8.71)	0
Requirement for permanent pacemaker incidence	527/3,449 (15.3%)	236/3,653 (6.4%)	1.68 (0.94 to 3.00)	83.2
New-onset AF incidence	165/1,192 (13.8%)	376/1,281 (29.4%)	0.38 (0.26 to 0.55)	64.6
Major bleeding incidence	321/2,074 (15.4%)	416/2,298 (18.1%)	0.73 (0.65 to 0.83)	24.2
Acute kidney injury incidence	294/3,446 (8.5%)	396/3,528 (11.2%)	0.73 (0.53 to 1.01)	68.4

Adapted from Villablanca (2016).[30]
AF: atrial fibrillation; CI: confidence interval; RR: relative risk; TAVI: transcatheter aortic valve implantation.
[a] Values are n/N (%).

Earlier systematic reviews focused largely on nonrandomized comparative studies because only one RCT had been published at the time of the reviews (the PARTNER trial). Panchal (2013) reported on results from a meta-analysis of 17 studies that included 4,659 patients: 2,267 treated with TAVI and 2,392 treated with open surgery.[33] 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 4,873

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 three months and three years (HR 0.99, 95% CI 0.83 to 1.2).[34]

Randomized Controlled Trials

SAPIEN PARTNER A Trial

Smith (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.[35] 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 3,105 patients were screened for aortic valve surgery, and 22.5% of them were included in the cohort of patients deemed high-risk for surgery.

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

The primary outcome was death from any cause at one-year follow-up. A second powered endpoint was noninferiority at one year for patients undergoing TAVI by the transfemoral approach. Secondary 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 one 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 one year was similar between groups at one 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 one 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 (2015).[31] At five-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 five-year mortality risk (72.4% for moderate or severe aortic regurgitation vs. 56.6% for mild aortic regurgitation or less, p=0.003).

Reynolds (2012) published QoL results from the PARTNER A trial.[36] 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 one 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 (2014) published a follow-up study from the PARTNER A trial reporting on bleeding complications.[37] 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 (2014) published results of the U.S. CoreValve High Risk Study.[38] 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 two cardiac surgeons and one 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 one 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 one 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 (2015).[32] At that point, the mortality benefits seen with TAVI were maintained.

A three-year follow-up analysis was reported by Deeb (2016), which found sustained improvements in the TAVI-treated group for all-cause mortality, stroke, and MACCE compared with the surgical group.[39] At three 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 three years. The authors noted the improvement in mean aortic valve gradient for both cohorts (TAVR 7.62 mmHg vs. SAVR 11.40 mmHg, p<0.001).

Additional analyses of the U.S. CoreValve High Risk Study have focused on the impact of patient and prosthesis mismatch[40] and health status.[41]

Conte (2017) analyzed both periprocedural and early complications (0-3 days and 4-30 days postoperative, respectively) in patients from the U.S. CoreValve High Risk Study.[42] There were no statistically significant differences in all-cause mortality, stroke, MI, or major infection in either the periprocedural period (0-3 days) or between 4 and 30 days postprocedure. Major vascular complication rate within three 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 (2019) reported five-year follow-up of the CoreValve High Risk Trial and estimated similar five-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 reintervention were uncommon; freedom from valve reintervention was 97.0% for TAVR and 98.9% for SAVR.[43]

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 two different TAVR platforms: the mechanically expanded Lotus valve (which was discontinued in January 2021) and self-expanding CoreValve. Thirty-day and one-year results were reported in the Summary of Safety and Effectiveness compiled by the FDA and two-year results were published by Reardon (2019).[44 45] 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

five years. Patients were required to have an STS-prom risk score of ≥8% or another indicator of high or extreme risk. The mean age was 83 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 one 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 two 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 two years, all-cause death was 21% vs. 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% vs. 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%).

PORTICO IDE

The Portico Re-sheathable Transcatheter Aortic Valve System US Investigational Device Exemption (PORTICO IDE) trial enrolled patients with severe aortic stenosis at high or extreme surgical risk.[46] Patients were randomized to a Portico valve (n=381) or another FDA-approved valve (n=369). The primary efficacy endpoint was a composite of all-cause mortality and stroke at one year, and the primary safety endpoint was a composite of all-cause mortality, disabling stroke, life-threatening bleeding, AKI, or major vascular complications. Overall, the mean age was 83 years with females comprising 52.7% of patients. Additional demographic characteristics were not reported. The primary efficacy endpoint at one year was similar between groups (14.8% in the Portico group vs. 13.4% with other valves, absolute difference 1.5%, 95% CI -3.6 to 6.5). For the composite safety endpoint at 30 days, the event rate was higher with the Portico valve (13.8% vs 9.6%, absolute difference 4.2%, 95% CI -0.4 to 8.8). At two years, the rates of death or disabling stroke were similar between groups.

Nonrandomized Studies

Since the publication of the pivotal RCTs and systematic reviews described previously, a number of nonrandomized studies have compared surgical with TAVR.[47-49] Given the availability of RCT evidence, these studies provide limited additional information on the efficacy of TAVI.

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

The most direct evidence related to the use of TAVI compared to SAVR for aortic stenosis in patients who are at high but not prohibitive risk of surgery comes from two 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 one year and most major secondary outcomes. The noninferiority boundaries for this trial included an upper limit of 7.5% absolute increase in mortality. The reported mortality for the TAVI group was lower than that for the open group, although not significantly better. QoL was also similar at one year between the TAVI and AVR groups. Stroke and TIA were significantly more common for the TAVI

group, occurring at a rate of almost two 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 trial, stroke rates were not higher in patients who underwent TAVI, a requirement for permanent pacemaker was more common in the TAVI group. Follow-up analyses of the U.S. CoreValve High Risk Study showed sustained improvements in the TAVI group for the outcome of all-cause mortality and a number of secondary outcomes. The incidence of pacemaker implantation continued to be higher in TAVI-treated patients.

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

TAVI OUTCOMES IN PATIENTS AT INTERMEDIATE RISK OR LOW RISK FOR OPEN SURGERY

Systematic Reviews

Several systematic reviews and meta-analyses were published in 2017 through 2023,[50-68] including many overlapping RCTs and observational studies.

In a Cochrane review, Kolkailah (2019) evaluated the literature on TAVI versus SAVR for severe aortic stenosis in patients with low surgical risk.[69] The review included four studies (n=2,818) and one 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 (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.[52] 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 2.

Table 2. TAVI Versus Surgical Repair in Low- or Intermediate-Risk Patients

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

Adapted from Garg (2017).[52]
Values are percent unless other noted.
CI: confidence interval; RR: relative risk; TAVI: transcatheter aortic valve implantation.

Zhou (2016) reported on a meta-analysis comparing TAVI with surgical repair in patients at low or intermediate risk of open surgery.[70] Seven studies were included: three RCTs (Nordic Aortic Intervention Trial [NOTION; 2015],[71]Transapical Transcatheter Aortic Valve Implantation vs. Surgical Aortic Valve Replacement in Operable Elderly Patients with Aortic Stenosis [STACCATO; 2012],[72] Leon [2016][73]) and four observational studies (total n=6,214 patients, 3,172 [51.0%] treated with TAVI). The main meta-analytic results are summarized in Table 3. Importantly, this review included a meta-analytic result for mortality at one year.

Table 3. TAVI Versus Surgical Repair in Low- or Intermediate-Risk Patients

Outcomes	TAVI	Surgical Repair	RR for TAVI vs. Surgical Repair (95% CI)	p	I^2
Short-term postprocedure mortality	2.59	3.94	0.63 (0.37 to 1.08)	0.09	56
Short-term cardiovascular mortality	1.96	3.15	0.51 (0.23 to 1.15)	0.11	68
Acute kidney injury incidence	1.92	4.8	0.34 (0.17 to 0.67)	0.002	61
Stroke incidence	3.57	4.90	0.72 (0.56 to 0.92)	0.01	42
Myocardial infarction incidence	0.7	1.7	0.51 (0.23 to 0.69)	<0.001	10
Major vascular complication incidence	7.2	3.6	3.54 (1.42 to 8.81)	0.006	86
Requirement for permanent pacemaker incidence	11.9	6.1	2.79 (1.49 to 5.23)	0.001	88
All-cause mortality (one year)	10.1	12.2	0.82 (0.58 to 1.16)	0.26	67

Adapted from Zhou (2016).[70]
Values are percent unless other noted.
CI: confidence interval; OR: odds ratio; TAVI: transcatheter aortic valve implantation.

Earlier systematic reviews came to similar conclusions.[74 75] Siemieniuk (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.[76]

Overall, the results suggest that for intermediate and low operative risk patients, periprocedural and short-term (one-year) mortality rates do not differ significantly between TAVI and open aortic valve repair. However, like the high- and prohibitive-risk populations, TAVI is associated with higher rates of major vascular complications, paravalvular regurgitation, and need for permanent pacemakers, but lower rates of major bleeding.

RANDOMIZED CONTROLLED TRIALS

Eight RCTs including patients with severe aortic stenosis who were at low and/or intermediate risk for open surgery have been published. The RCTs are summarized in Tables 4 and 5 and the following paragraphs.

Table 4. Characteristics of RCTs Comparing TAVI With SAVR in Patients at Low and Intermediate Surgical Risk

					Interventions		
Study and Trial	Countries	Sites	Dates	Participants	TAVR	SAVR	Sponsor
Nielsen	Denmark	2	Nov	Mean age, 81	n=34	n=36	Participating

					Interventions		
Study and Trial	**Countries**	**Sites**	**Dates**	**Participants**	**TAVR**	**SAVR**	**Sponsor**
(2012)[72] STACCATO			2008-May 2011	years No significant coronary artery disease Any surgical risk (mean STS PROM, 3.3)	Edwards Sapien THV	Conventional open-heart surgery with CPB	hospitals and Danish Heart Foundation
Thyregod (2015)[71] Søndergaard (2016)[77] Thyregod (2019)[78] Søndergaard (2019)[79] NOTION	Denmark, Sweden	3	Dec 2009-Apr 2013	Mean age, 79 years No significant coronary artery disease Any surgical risk (mean STS PROM, 3.0; 82% low-risk)	n=145 Core-Valve	n=135 Conventional open-heart surgery with CPB	Danish Heart Foundation
Reardon (2016)[80] CoreValve U.S. Pivotal	U.S.	45	Feb 2011-Sep 2012	Mean age, 81 years STS score <7[a] (median, 5.3) Symptomatic (NYHA class ≥II)	n=202 Core-Valve	n=181 Conventional open-heart surgery with CPB	Manufacturer
Leon (2016)[73] PARTNER 2A	U.S., Canada	57	Dec 2011-Nov 2013	Mean age, 82 years Symptomatic (NYHA class ≥II) STS PROM ≥4 and ≤8 or STS PROM <4 with coexisting conditions (mean, 5.8)	n=1,011 SAPIEN XT	n=1,021 Conventional surgery	Manufacturer
Reardon (2017)[81] SURTAVI	U.S., Spain, Netherlands, Germany, UK, Canada, Switzerland, Sweden	87	NR	Mean age, 80 years STS PROM ≥4 and <15 (mean, 4.5) Symptomatic (NYHA class ≥II)	n=879 Core-Valve	n=867 Conventional surgery with coronary re-vascularization if needed	Manufacturer
Popma (2019)[82] Forrest (2022)[83] Evolut Low Risk Trial	Australia, Canada, France, Japan, Netherlands, New Zealand, U.S.	86	Mar 2016 - Nov 2018	Mean age, 74 years STS PROM≤ 3 (mean, 1.9) 90% NYHA class ≥II (symptomatic); 10% NYHA class I (asymptomatic)	n=734 CoreValve, Evolut R, or Evolut PRO	n=734 Conventional surgery	Manufacturer

					Interventions		
Study and Trial	**Countries**	**Sites**	**Dates**	**Participants**	**TAVR**	**SAVR**	**Sponsor**
Mack (2019)[84] Leon (2021)[85] PARTNER 3	U.S., Canada, Australia, New Zealand, Japan	71	Mar 2016 - Oct 2017	Mean age, 73 years STS PROM <4 (mean, 1.9) 28% NYHA III or IV	n=503 SAPIEN 3	n=497 Conventional surgery	Manufacturer
Toff (2022)[86] UK TAVI	UK	34	April 2014-April 2018	Mean age, 81 years Median STS PROM, 2.7[b] 43% NYHA III or IV	n=458 SAPIEN 3 (45.1%)	n=455 Conventional surgery	NIHR HTA Programme; University of Leicester

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

[a] Includes analysis of a subset of originally randomized patients

[b] No specified risk threshold for trial inclusion

Table 5. RCTS Comparing TAVI with Surgical Repair in Patients at Low and Intermediate Surgical Risk

Study	**Primary Outcome**	**Results of Primary Outcomes, %**				**All-Cause Mortality (2 years), %**			**New Permanent Pacemaker (2 years), %**		
		TAVI	**Surg**	**TE (95% CI)**	**p**	**TAVI**	**Surg**	**p**	**TAVI**	**Surg**	**p**
Nielsen (2012)[72] STACCATO	Death, stroke, or renal failure at 30 d										
All patients		14.7	2.8	RD (NR)	0.07	NR	NR		NR	NR	
Thyregod (2015)[71], (2019)[78] Søndergaard (2016),[77] (2019)[79] NOTION	Death, stroke, or MI at 1 year										
All patients		13.1	16.3	RD = -3.2	0.43[a]	4.9	7.5	0.38	34.1	1.6	<0.001
Reardon (2016)[80] CoreValve U.S. Pivotal	Death at 2 years										

Study	Primary Outcome	Results of Primary Outcomes, %				All-Cause Mortality (2 years), %			New Permanent Pacemaker (2 years), %		
		TAVI	Surg	TE (95% CI)	p	TAVI	Surg	p	TAVI	Surg	p
STS score ≤7		26.3	15.0	HR (NR)	0.01	See previous columns			27.7	10.5	<0.001
Leon (2016)[73] PARTNER 2A	Death or disabling stroke at 2 years										
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
Trans-femoral 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
Trans-thoracic access		27.7	23.4	HR 1.21 (0.84 to 1.74)		25.2	20.7	0.26	13.1	8.6	0.13
Reardon (2017)[81] Van Mieghem (2022)[87] SURTAVI	Death from any cause or disabling stroke										
All patients at 2 years		12.6	14.0	RD = -1.4 (-5.2 to 2.3)[b]		11.4	11.6	-3.8 to 3.3[b]	25.9	6.6	15.9 to 22.7[b]
All patients at 5 years		31.3	30.8	p = 0.085		30	28.7	0.55	35.8	14.6	<0.001
Popma (2019)[82] Forrest (2022)[83], (2023)[88] (2025)[89] Evolut Low Risk Trial	Death or disabling stroke										
All patients at 2 years		5.3	6.7	RD = -1.4 (−4.9		4.3	6.3	NR	23.8	7.0	NR

Study	Primary Outcome	Results of Primary Outcomes, %				All-Cause Mortality (2 years), %			New Permanent Pacemaker (2 years), %		
		TAVI	Surg	TE (95% CI)	p	TAVI	Surg	p	TAVI	Surg	p
				to 2.1)[b]							
All patients at 3 years		7.4	10.4	HR= 0.7 (0.49 to 1), p= 0.051		6.3	8.3	0.16	23.2	9.1	<0.001
All patients at 5 years		15.5	16.4	p= 0.47		13.5	14.9	0.39	27.0	11.3	<0.001
Mack (2019)[84] Leon (2021)[85] PARTNER 3	Death, stroke, or rehospital-ization at 1 year										
All patients		8.5	15.1	RD = -6.6 (−10.8 to −2.5)[b]		11.5	17.4		NR		
Toff (2022)[86] UK TAVI	Death at 1 year										
All patients		4.6	6.6	RD = -2.0 (-∞ to 1.2)[c]	<0.001	NR			14.2	7.3	<0.001

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.
[a] Superiority
[b] Bayesian credible interval
[c] Noninferiority with 97.5% confidence interval

Mixed Risk Populations Including Intermediate- and Low-Risk Patients

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 (2012).[72] 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 (2016) reported on an analysis of patients from the U.S. Pivotal High Risk Trial who had STS score less than 7.0% at baseline.[80] 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 two years for TAVR versus SAVR in the subgroup with STS score less than 7.0 was 15% (95% CI 9% to 20%) vs. 26% (95% CI 20% to 33%, p=0.01). The rates of stroke at two years for TAVR versus SAVR were 11% versus 15% (p=0.50).

Thyregod (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.[71] 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 one 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 5. 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 one-year follow-up (29.5% vs. 15.0%, p=0.01).

In a two-year follow-up of the NOTION trial, Søndergaard (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.[77] For the composite rate of death at two 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 two 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 five years of follow-up were reported by Thyregod (2019).[78] 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 (2019) compared the durability of TAVR versus SAVR after six years of follow-up from NOTION. At six years, the rates of all-cause mortality were similar for TAVR (42.5%) and SAVR (37.7%) patients. The rate of moderate to severe structural valve deterioration was higher for SAVR than TAVR (24.0% vs. 4.8%, p < 0.001) and there were no differences in nonstructural valve deterioration (57.8% vs. 54.0%), bioprosthetic valve failure (6.7% vs. 7.5%) or endocarditis (5.9% vs. 5.8%).[79] At eight years of follow-up, Jørgensen

(2021) found no significant difference between TAVI and SAVR in the composite outcome of mortality, stroke, or MI.[90]

Toff (2022) published one-year results from an investigator-initiated, publicly funded, pragmatic RCT in the United Kingdom (UK TAVI) that compared clinical outcomes for 913 patients aged ≥80 years, or aged ≥70 years with low-to-intermediate surgical risk, with severe, symptomatic aortic stenosis randomized to TAVI or SAVR.[86] For the primary outcome (all-cause mortality at one year), TAVI was noninferior to SAVR (4.6% vs. 6.6%, adjusted absolute risk difference, -2.0%, one-sided 97.5% CI -∞ to 1.2%, p<0.001) based on a prespecified margin of 5%. The adjusted hazard ratio for death from any cause was 0.69 (95% CI 0.38 to 1.26, p=0.23). No significant differences in cardiovascular deaths or strokes (fatal or nonfatal) were found between groups. While TAVI was associated with significantly shorter hospital stay and fewer major bleeding events, it was also associated with more vascular complications (p<0.001), conduction disturbances requiring pacemaker implantation (p=0.01), and mild or moderate aortic regurgitation (p<0.001). Trial follow-up is planned for five years.

Including Intermediate-Risk Only

Reardon (2017) published two-year results from an RCT (SURTAVI trial) that compared clinical outcomes for 1,746 patients at intermediate surgical risk randomized to TAVR or SAVR.[81] For the primary outcome (composite death at two years), an improvement was observed in the TAVR-treated group, compared with surgery (12.6% of TAVR patients vs. 14.0% of SAVR patients [95% credible interval -5.2% to 2.3%], posterior probability >0.999). Rates of death, MI, and disabling stroke were comparable between groups, as were secondary outcomes that included echocardiographic measurement of aortic valve gradient and paravalvular regurgitation (data reported in the supplemental material). More patients were assigned to the CoreValve bioprosthesis (n=724) than received Evolut R bioprosthesis (n=137), which might have affected the results; also, a considerable number of patients withdrew consent before surgery, resulting in an as-treated population of 1660. Finally, the authors acknowledged a gap in knowledge of how baseline characteristics of patients who received surgery differed from those who did not. The authors noted the low 30-day surgical mortality ratio (0.38, observed-to-expected) and the similarity of this rate between groups (2.2% of the TAVR patients vs. 1.7% of surgical patients). Five-year follow-up of the SURTAVI trial reported by Van Mieghem (2022) showed no difference in disabling stroke or death from any cause between groups (31.3% of the TAVI patients vs. 30.8% of the SAVR, p=0.85), but reported that the rate of new pacemaker implantation was significantly higher in TAVI than in SAVR (35.8% vs. 14.6%, p<0.001).[87]

Leon (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).[73] Eligible patients had degenerative aortic valve stenosis, with NYHA functional class II or higher, and were in STS PROM score of 4 or greater (or <4 if determined by a heart team to have an “intermediate-risk patient profile with important comorbidities not represented in the STS Risk Calculator algorithm.”) The trial used a noninferiority design, with a primary composite endpoint of death from any cause or disabling stroke (score of ≥2 on the modified Rankin Scale) at two years and a noninferiority margin of 1.2 (i.e., noninferiority was considered met if upper bound of two-sided CI for the RR for the primary outcome was <1.2). A total of 2032 patients were randomized to TAVI (n=1,011) or surgical repair (n=1,021), with 1,550 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 5. 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 five-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).[91] Overall, more patients in the TAVI group had at least mild paravalvular aortic regurgitation (33.3% vs. 6.3%), experienced repeat hospitalizations (33.3% vs. 25.2%), and underwent aortic valve reinterventions (3.2% vs. 0.8%). Improvement in health status at five years was similar between the groups.

Including Low-Risk Only

Popma (2019) reported results of prespecified, interim analyses of the multinational Evolut Low Risk Trial, a noninferiority trial conducted from 2016 to 2018 comparing TAVR (n=734) to SAVR (n=734) in patients who had severe aortic stenosis and were at low surgical risk (STS-PROM ≤3%).[82] Patients with bicuspid aortic valves were excluded. Patients assigned to TAVR were treated with one of three Medtronic self-expanding, supra-annular bioprostheses (CoreValve, Evolut R, or Evolut PRO). Preliminary analyses were performed when 850 patients had reached 12-month follow-up. Long-term follow-up is scheduled to continue for 10 years. The primary outcome was a composite of death or disabling stroke at 24 months performed using Bayesian methods. At the time of the preliminary analysis, 149 patients had reached the 24 months visit. The 24-month estimated incidence of the primary outcome was 5.3% in the TAVR group and 6.7% in the SAVR group (risk difference -1.4%, 95% Bayesian credible interval −4.9 to 2.1, posterior probability of noninferiority >0.999). Several 30-day outcomes were also reported. The incidence at 30 days of disabling stroke (0.5% vs. 1.7%), bleeding complications (2.4% vs. 7.5%), 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±14.2 in the TAVR group vs. 78.6±18.9 in the SAVR group). Forrest (2022) published two-year outcomes.[83] Follow-up data was available for 97.7% in the TAVI group and 92.3% in the SAVR group. The Kaplan-Meier estimate of all-cause mortality or disabling stroke at two years was 4.3% and 6.3% in the TAVI and SAVR groups, respectively (p=0.084). The number of patients requiring new permanent pacemaker implantation was significantly higher with TAVI (23.8% vs. 7.0%). Similar results were found at three years follow-up. Forrest (2023) published three-year outcomes that showed a non-significant difference in all-cause mortality or disabling stroke in the TAVI (7.4%) and SAVR (10.4%) group (HR 0.7, 95% CI 0.49 to 1, p=0.051). The rate of permanent pacemaker implantation remained higher in TAVI than in redo-SAVR (23.2% vs. 9.1%, p<0.001).[88] At five years, there was no significant difference in the primary outcome (5.5% for TAVR vs. 16.4% for surgery (p=0.47), but a significantly higher rate of permanent pacemaker implantation with TAVI (27.0% vs. 11.3%, p<0.001).[89]

Mack (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.[84] Patients bicuspid aortic valves were excluded. The primary

outcome was a composite of death, stroke, or rehospitalization at one year. Follow-up is designed to continue for at least 10 years. Primary analyses were performed and reported in the as-treated population (n=496 in the TAVR, n=454 in SAVR) but sensitivity analyses of the primary outcome performed in the intention-to-treat population with multiple imputations for missing data were reportedly consistent with the primary analysis. The number of participants that did not receive the assigned treatment was higher in the SAVR group (7 vs. 43). The most common reported reason was refusal to undergo surgery or the choosing to undergo surgery at a non-trial site. The estimated incidence of the primary outcome at one year was significantly lower in TAVR versus SAVR (8.5% vs. 15.1%, risk difference -6.6%, 95% CI −10.8 to −2.5, p<0.001 for noninferiority). All components of the composite (death, stroke, and hospitalization) individually favored TAVR at 30 days and one 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 (three days vs. seven 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 one year was higher with TAVR (29.4% vs. 2.1%). In an analysis specific to the echocardiographic findings of the PARTNER 3 trial, Pibarot (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).[92] Mean transvalvular gradient (13.7 ±5.6 vs. 11.6 ±5.0 mmHg, p=0.12) and aortic valve area (1.72 ±0.37 vs. 1.76 ±0.42 cm^2, p=0.12) were similar between groups at one year. In another analysis specific to atrial fibrillation (n=781), Shahim (2021) found lower early postoperative atrial fibrillation in patients following TAVI compared with SAVR (19.5% vs. 36.6%, p<0.0001).[93] At two-year follow-up, Leon (2021) reported continued improvement of the composite primary endpoint with TAVI versus SAVR (11.5% vs. 17.4%, HR 0.63, 95% CI 0.45 to 0.88, p=0.007); however, there was no significant difference in death or stroke between TAVI and SAVR.[85]

Study Limitations

The purpose of the study limitation tables (see Tables 6 and 7) 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 6. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Nielsen (2012)[72] STACATTO	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 (2015)[71] NOTION	4: Included patients with any surgical risk				

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Follow-Up[e]
Reardon (2016)[81] 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 (2016)[73] PARTNER 2A	4: 12% of the study population had an STS risk score > 8				
Reardon (2017)[81] SURTAVI					
Popma (2019)[82] Evolut Low Risk Trial					
Mack (2019)[84] PARTNER 3				4: Rehospital-ization was included in composite primary outcome	
Toff (2022)[86] UK TAVI	1. Proportion of patients with low vs. intermediate risk unclear; median STS risk score 2.7				

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 limitations assessment.

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

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

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

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

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

Table 7. Study Design and Conduct Limitations

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
Nielsen (2012)[72] STACCATO		1: Patients and study staff not blinded		1: Study terminated early with only 70 participants		
Thyregod (2015)[71] NOTION		1: Patients and study staff not blinded 2,3: Unclear if outcome adjudication was blinded				
Reardon (2016)[80] 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 (2016)[73] PARTNER 2A		1: Patients and study staff not blinded		1: High frequency of withdrawals in patients assigned to undergo surgery		
Reardon (2017)[81] SURTAVI		1: Patients and study staff not blinded 2,3: Unclear if outcome adjudication was blinded		1: High frequency of withdrawals in patients assigned to undergo surgery		
Popma (2019)[82] Evolut Low Risk Trial		1: Patients and study staff not blinded		1: High frequency of withdrawals in patients assigned to undergo surgery		3: Incomplete reporting of confidence intervals

Study	Allocation[a]	Blinding[b]	Selective Reporting[c]	Data Completeness[d]	Power[e]	Statistical[f]
						and/or p-values
Mack (2019)[84] 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		
Toff (2022)[86] UK TAVI		1: Patients and study staff not blinded				

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

Section Summary: TAVI Outcomes in Patients at Intermediate- or Low-Risk for Open Surgery

Intermediate-Risk

Most participants in five RCTs were intermediate risk, and two 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 three of the five RCTs including the two 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 two procedures.

Low-Risk

The NOTION and UK TAVI trials were 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 one year was numerically but not statistically significantly lower in the TAVR group compared to SAVR and after five 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 publicly sponsored UK TAVI trial, TAVI was noninferior to SAVR with respect to all-cause mortality at one year. 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, acute kidney injury, 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 one 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 ≤75-years-old and does not exclude patients with bicuspid aortic valves. Jørgensen (2024) reported one-year results for this study, which randomized 370 patients in a 1:1 ratio to TAVI or SAVR.[94] There was no significant difference between groups for primary endpoint of the study, a composite of all-cause mortality, stroke, or rehospitalization (10.2% for TAVI vs. 7.1% for SAVR, HR 1.4; 95% CI 0.7 to 2.9, p=0.3). The study included 100 patients with bicuspid valves, and found that compared with patients with tricuspid valves, there was a higher rate of the primary endpoint with TAVR compared to surgery (14.3% for TAVR and 3.9% for SAVR for bicuspid valves vs. 8.7% for TAVR and 8.3% for SAVR for tricuspid valves).

TAVI 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.

Systematic Reviews

Aedma (2022) conducted an umbrella or meta-meta-analysis evaluating the efficacy and safety of valve-in-valve (ViV) TAVI compared to redo-surgical aortic valve replacement (redo-SAVR).[95] Nine analyses were included for review. ViV TAVI was associated with a significantly lower risk of 30-day mortality (OR 0.60, 95% CI 0.53 to 0.68, p<0.00001) and

procedural mortality (OR 0.52, 95% CI 0.27 to 0.98, p=0.04). No significant differences in one-year mortality or hospital readmissions were identified. ViV TAVI was also associated with a lower risk several complications, including stroke (OR 0.71, 95% CI 0.59 to 0.84, p<0.001), major bleeding (OR 0.44, 95% CI 0.35 to 0.57, p<0.000001), acute kidney injury (OR 0.57, 95% CI 0.43 to 0.75, p<0.0001), and pacemaker implantation (OR 0.67, 95% CI 0.52 to 0.86, p<0.002). No association of acute myocardial infarction with ViV TAVI and redo-SAVR was found (OR 1.15, 95% CI 0.84 to 1.59, p=0.38); however, ViV TAVI was associated with a higher risk of vascular complications (OR 2.70, 95% CI 1.58 to 4.62, p<0.0003).

Raschpichler (2022) published a meta-analysis of nonrandomized studies comparing ViV TAVI with redo-SAVR.[96] A total of 15 studies with 8,881 patients were identified for analysis, which included 4,458 patients (50.2%) treated with ViV TAVI and 4,423 patients (49.8%) treated with redo-SAVR. Short-term mortality (<30 days) was 2.8% in patients undergoing ViV TAVI compared with 5.0% in patients undergoing redo-SAVR (RR 0.55, 95% CI 0.34 to 0.91). Midterm mortality (up to five years) was not significantly different between groups (HR 1.27, 95% CI 0.72 to 2.25). The rate of acute kidney failure was lower following ViV (RR 0.54, 95% CI 0.33 to 0.88); however, prosthetic aortic valve regurgitation (RR 4.18, 95% CI 1.88 to 9.3, p=0.003) and severe patient-prosthesis mismatch (RR 3.12, 95% CI 2.35 to 4.1, p<0.001) were significantly more frequent. Additionally, the transvalvular gradient was significantly higher following ViV procedures (standard mean difference 0.44, 95% CI 0.15 to 0.72, p=0.008). There were no significant differences between groups with respect to stroke, myocardial infarction, or pacemaker implantation. The authors concluded that the early safety advantages of ViV should be weighed against a potential midterm benefit of redo-SAVR. The authors also noted that given the likely selection bias in individual studies, an adequately powered multicenter randomized trial with sufficiently long follow-up in patients with low-to-intermediate surgical risk is warranted.

A subsequent time-to-event analysis of all-cause mortality in ViV TAVI versus redo-SAVR in 10 studies conducted by Sá (2023) similarly found a short-term protective effect with ViV TAVI in the first 44 days (HR 0.67, 95% CI 0.49 to 0.93, p=0.017).[97] A HR reversal was observed after 197 days favoring redo-SAVR (HR 1.53, 95% CI 1.22 to 1.93, p<0.001). Additionally, a statistically significant association of patient-prosthesis mismatch with all-cause mortality during follow-up for ViV TAVI was identified via Cox regression modeling (p<0.001).

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.[98] The review included three systematic reviews and meta-analysis[99-101] and eight 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 one month to one year. Two systematic reviews and meta-analysis 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 six observational studies reported no statistically significant difference between valve-in-valve TAVI and redo SAVR in perioperative mortality (5% vs. 6%, RR 0.78, 95% CI 0.33 to 1.84), late mortality (median one-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 two 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.

Begun (2023) published a retrospective analysis of ViV TAVI compared to TAVI in a native valve using the Danish National Patient Registry from 2008 to 2020.[102] A total of 5,823 patients with native valve TAVI and 247 with ViV TAVI were identified with a median age of 81 years. All-cause mortality was reported at 30 days, one year, and five years post-procedure with values of 2.4%, 9.7% and 28.7% in the ViV TAVI group and 2.7%, 10.3%, and 33.8% in the native TAVI group; no significant between group differences were observed for hazard ratios at any follow-up assessment. The cumulative five-year risk of death was similar with 42.5% (95% CI 34.2% to 50.6%) in patients with ViV TAVI and 44.8% (95%% CI 43.2% to 46.4%) in patients with TAVI in a native valve. Overall, the number of rehospitalizations from any cause and from cardiovascular causes was not significantly lower in the group of patients with ViV TAVI compared with native-valve TAVI at 30 days, one-year, and five-years post-procedure.

Van Steenbergen (2022) reported on outcomes of ViV TAVI and redo-SAVR via a propensity score-matched analysis of data from the Netherlands Heart Registry collected between 2014 and 2018 from 16 cardiac centers.[103] Patients with concomitant coronary procedures such as percutaneous coronary interventions or coronary artery bypass grafting were eligible for inclusion. A total of 653 high-risk patients were identified, including 374 treated with ViV TAVI and 279 with redo-SAVR; following propensity score-matching, 165 pairs were included for analysis. EuroSCORE I surgical risk was significantly higher for ViV TAVI patients compared to redo-SAVR (19.4, IQR 13.3 to 27.9, vs. 13.8, IQR, 8.3 to 21.9, p<0.01). The primary endpoint of composite 30-day all-cause mortality and in-hospital postoperative stroke was not significantly different for ViV TAVI and redo-SAVR (OR 1.30, 95% CI 0.57 to 3.02). Additionally, no significant differences in procedural, 30-day, and one-year all-cause mortality rates or incidence of in-hospital post-operative stroke, pacemaker implantation, and redo procedures within one year were identified. Study interpretation is limited by its retrospective nature, small sample size, and possible selection bias.

Kaneko (2021) evaluated the safety and efficacy of ViV TAVI amongst patients treated from 2015 to 2020 with SAPIEN 3 valves in the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies Registry.[104] A total of 145,917 SAPIEN 3 TAVI patients were identified in the database, for which 3% (n=4,276) underwent transfemoral ViV TAVI and had adequate baseline data. The mean age of this cohort was 73.9 years of age, with a mean STS score of 6.9. Overall mortality at 30 days was 2.4%, with cardiac death occurring in 1.2% of patients. At one-year follow-up, mortality was 10.8%. Stroke occurred in 1.4% of patients, and major vascular complications occurred in 0.9%. New pacemaker implantation was required in 2.1% of patients. Moderate or severe aortic regurgitation was observed in 0.9% of patients at 30-day follow-up and 1.3% at one-year post-ViV-TAVI. When stratified based on STS score (low score <4%, intermediate score 4% to 8%, high score >8%),

30-day mortality was 0.9% in the low score group, 2.2% in the intermediate score group, and 4.3% in the high-score group. A stratified analysis found that the lower and intermediate STS score groups had significantly lower mortality rates than the high score group (p<0.0001). Similarly, one-year mortality rates were also lower in the low-score (5.7%) and intermediate-score (9.3%) groups compared to the high-score group (17.9%, p<0.0001).

Tam (2020) reported data from the CorHealth Ontario Cardiac Registry for patients undergoing ViV TAVI and redo-SAVR. A total of 558 patients (ViV TAVI, n=214 and redo-SAVR, n=344) were included in the unmatched analysis. A propensity-matched subset of patients with 131 individuals in each group was constructed based on 27 clinically relevant baseline characteristics that were not balanced in the unmatched population.[105] In the matched cohort, patients treated with ViV TAVI had better early outcomes for mortality (Absolute risk difference [ARD] -7.5, 95% CI -12.6% to -2.3%), permanent pacemaker implantation (ARD -9.8%, 95% CI -16.1% to -3.4%), and blood transfusion rate (ARD -63.1%, 95% CI -76.2% to -50.1%) than patients in the redo-SAVR group. No differences in all-cause of hospital readmission rates 30 days post-treatment were observed between groups. The median follow-up period was 3.2 years (interquartile range [IQR], 1.6 to 5.1 years), with a maximum follow-up of 10.4 years. At five-year follow-up, survival was significantly higher for ViV TAVI (76.8%, 95% CI 67.8 to 86.9%) than redo-SAVR (66.8%, 95% CI 58.3% to 76.6%, p=0.046) in the matched cohort, but no significant difference was observed in the unmatched cohort. No differences in the cumulative incidence of late all-cause readmission or freedom from late major adverse cardiac events (death, stroke, or aortic valve reintervention) were observed.

Hirji (2020) published a retrospective comparison of 30-day outcomes of ViV TAVI compared to redo-SAVR drawn from a large U.S. multicenter National Readmission Database.[106] The authors identified 6,815 eligible patients who underwent ViV-TAVI (n=3,443) or redo-SAVR (n=3,372), but this cohort varied significantly in mean age and the prevalence of co-morbid conditions at baseline. A matched cohort of 2,181 participants per group was created, which was balanced across baseline patient characteristics and had a mean age of 73 years. In the unmatched analysis, VIV TAVI patients had significantly lower 30-day mortality (2.8% vs. 5.0%, OR 0.55, 95% CI 0.33 to 1.91), 30-day morbidity (66.4% vs. 79%, OR 0.52, 95% CI 0.41 to 0.66), and rates of major bleeding complications (35.8% vs. 49.9%, OR 0.56, 95% CI 0.44 to 0.71) than redo-SAVR. However, no between-group differences were noted in the rate of all-cause 30-day readmission, post-operative stroke, renal failure, permanent pacemaker placement, or complete heart block. Findings from the propensity-matched analysis were similar, with ViV TAVI having lower odds of 30-day mortality (OR 0.41, 95% CI 0.23 to 0.74), 30-day morbidity (OR 0.53, 95% CI 0.43 to 0.72), and major bleeding (OR 0.66, 95% CI 0.51 to 0.85).

Following the National Institute for Health and Care Excellence review, three-year results from the PARTNER 2 valve-in-valve registry were published by Webb (2019).[98] The registry included 365 patients who had valve-in-valve[100 101] procedures with a mean age of 79 (± 10) years and mean STS-PROM score of 9.1% (±4.7). The estimated incidence of all-cause mortality at three years was 32.7%. Aortic valve re-replacement was performed in 1.9% by three years. From baseline to year three, 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 three years (p<0.0001). QoL as measured by the KCCQ overall score also increased from baseline to three years (43.1 to 73.1, p<0.0001).

Hahn (2022) published five-year follow-up outcomes from the PARTNER 2 registry.[107] The Kaplan-Meier rates of all-cause mortality, any stroke, and all neurological events (all strokes and transient ischemic attacks) in patients with high surgical risk were 50.6%, 10.5%, and 13.8%, respectively. The incidence of structural valve deterioration, related hemodynamic valve deterioration, or bioprosthetic valve failure was 6.6%. Aortic valve re-replacement was performed in 14 patients (6.3%). Reasons for reintervention included stenosis (n=6) and combined aortic insufficiency/paravalvular regurgitation (n=3). Improvements in NYHA functional class and KCCQ overall score were maintained at five years. Patients receiving a 23-mm SAPIEN XT valve were found to have a significantly increased risk of mortality compared to patients who received a 26-mm SAPIEN XT valve (HR 1.55, 95% CI 1.09 to 2.20, p=0.01).

PRACTICE GUIDELINE SUMMARY

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.[108] Both groups issued a joint focused update in 2017.[109] In 2020, a new full guideline was published that replaces the 2014 revision and 2017 focused update.[110] These guidelines made the following recommendations on the timing of intervention and choice of surgical or transcatheter intervention for treatment of aortic stenosis (see Table 8).

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 8. Recommendations on Surgical or Transcatheter Intervention for Aortic Stenosis

Recommendation	COR	LOE
Timing of Intervention		
“In adults with severe high-gradient AS (Stage D1) and symptoms of exertional dyspnea, heart failure, angina, syncope, or presyncope by history or on exercise testing, AVR is indicated."	I	A
“In asymptomatic patients with severe AS and a left ventricular ejection fraction <50% (Stage C2), AVR is indicated."	I	B
“In asymptomatic patients with severe AS (Stage C1) who are undergoing cardiac surgery for other indications, AVR is indicated."	I	B
"In symptomatic patients with low-flow, low-gradient severe AS with reduced left ventricular ejection fraction (Stage D2), AVR is recommended."	I	B
"In symptomatic patients with low-flow, low-gradient severe AS with reduced left ventricular ejection fraction (Stage D3), AVR is recommended if AS is the most likely cause of symptoms."	I	B

Recommendation	COR	LOE
“In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when an exercise test demonstrates decreased exercise tolerance (normalized for age and sex) or a fall in systolic blood pressure of ≥10 mmHg from baseline to peak exercise."	IIa	B
“In asymptomatic patients with very severe AS (defined as an aortic velocity of ≥5 m/s) and low surgical risk, AVR is reasonable."	IIa	B
“In apparently asymptomatic patients with severe AS (Stage C1) and low surgical risk, AVR is reasonable when the serum B-type natriuretic peptide level is >3 times normal."	IIa	B
"In asymptomatic patients with high-gradient severe AS (Stage C1) and low surgical risk, AVR is reasonable when serial testing shows an increase in aortic velocity ≥0.3 m/s per year."	IIa	B
"In asymptomatic patients with severe high-gradient AS (Stage C1) and a progressive decrease in left ventricular ejection fraction on at least 3 serial imaging studies to <60%, AVR may be considered.	IIb	B
"In patients with moderate AS (Stage B) who are undergoing cardiac surgery for other indications, AVR may be considered.	IIb	C
Choice of SAVR Versus TAVI for Patients for Whom a Bioprosthetic AVR is Appropriate		
"For symptomatic and asymptomatic patients with severe AS and any indication for AVR who are <65 years of age or have a life expectancy >20 years, SAVR is recommended."	I	A
"For symptomatic patients with severe AS who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either SAVR or transfemoral TAVI is recommended after shared decision-making about the balance between expected patient longevity and valve durability."	I	A
"For symptomatic patients with severe AS who are >80 years of age or for younger patients with a life expectancy of <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to SAVR."	I	A
"In asymptomatic patients with severe AS and a left ventricular ejection fraction <50% who are ≤80 years of age and have no anatomic contraindication to transfemoral TAVI, the decision between TAVI and SAVR should follow the same recommendations as for symptomatic patients in the 3 recommendations above."	I	B
"For asymptomatic patients with severe AS and an abnormal exercise test, very severe AS, rapid progression, or an elevated B-type natriuretic peptide, SAVR is recommended in preference to TAVI."	I	B
"For patients with an indication for AVR for whom a bioprosthetic valve is preferred but valve or vascular anatomy or other factors are not suitable for transfemoral TAVI, SAVR is recommended."	I	A
"For symptomatic patients of any age with severe AS and a high or prohibitive surgical risk, TAVI is recommended if predicted post-TAVI survival is >12 months with an acceptable quality of life."	I	A
"For symptomatic patients with severe AS for whom predicted post-TAVI or post-SAVR survival is <12 months or for whom minimal improvement in quality of life is expected, palliative care is recommended after shared decision-making, including discussion of patient preferences and values."	I	C
"In critically ill patients with severe AS, percutaneous aortic balloon dilation may be considered as a bridge to SAVR or TAVI."	IIb	C
Intervention for Prosthetic Valve Stenosis		
"In patients with symptomatic severe stenosis of a bioprosthetic or mechanical prosthetic valve, repeat surgical intervention is indicated unless surgical risk is prohibitive."	I	B

Recommendation	COR	LOE
"For severely symptomatic patients with bioprosthetic aortic valve stenosis and high or prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a Comprehensive Valve Center."	IIa	B
"For patients with significant bioprosthetic valve stenosis attributable to suspected or documented valve thrombosis, oral anticoagulation with a VKA is reasonable."	IIa	B
Prosthetic Valve Regurgitation		
"In patients with intractable hemolysis or HF attributable to prosthetic transvalvular or paravalvular leak, surgery is recommended unless surgical risk is high or prohibitive."	I	B
"In asymptomatic patients with severe prosthetic regurgitation and low operative risk, surgery is reasonable."	IIa	B
"In patients with prosthetic paravalvular regurgitation with the following: 1) either intractable hemolysis or NYHA class III or IV symptoms and 2) who are at high or prohibitive surgical risk and 3) have anatomic features suitable for catheter-based therapy, percutaneous repair of paravalvular leak is reasonable when performed at a Comprehensive Valve Center."	IIa	B
"For patients with severe HF symptoms caused by bioprosthetic valve regurgitation who are at high to prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a Comprehensive Valve Center."	IIa	B

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

SUMMARY

TAVI

There is enough research to show that transcatheter aortic valve implantation (TAVI) can improve health outcomes for individuals with heart failure who have severe symptomatic aortic stenosis. For patients who are not surgical candidates due to excessive surgical risk, trial results have shown decreased mortality for the TAVI patients at one year compared with medical care, but an increased risk of stroke and vascular complications. For patients who are surgical candidates, trials have shown similar or better outcomes for TAVI compared to open surgical procedures. Therefore, TAVI may be considered medically necessary for patients that meet the policy criteria.

TAVR

There is not enough research to show that transcatheter aortic valve replacement (TAVR) can improve health outcomes for individuals with bioprosthetic valves who have valve dysfunction and aortic stenosis or regurgitation compared with open repair. Studies comparing TAVR to surgical repair and have reported similar mortality, stroke, and survival rates for the two procedures, however there is a lack of high-quality trial data. Therefore, TAVR may be considered medically necessary for high- or prohibitive-risk surgical patients but is otherwise considered investigational.

Bicuspid Aortic Valves

There is not enough research to show that transcatheter aortic valve implantation or replacement can improve health outcomes for patients for patients with bicuspid valves. Individuals with bicuspid aortic valves were excluded from the large trials that evaluated

transcatheter aortic valve implantation (TAVI) and transcatheter aortic valve replacement (TAVR), due to an increased risk of complications. Further study is needed to evaluate the long-term health outcomes and identify which patients may benefit from these procedures. Therefore, TAVI and TAVR are considered investigational for patients with bicuspid aortic valves.

Other Indications and Devices

There is not enough research to show that transcatheter aortic valve implantation or replacement can improve health outcomes for patients without heart failure symptoms and severe aortic stenosis. There is also a lack of evidence regarding non-FDA-approved devices. Therefore, these are considered investigational.

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CODES

Codes	Number	Description
CPT	33361	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach
	33362	;open femoral artery approach
	33363	;open axillary artery approach
	33364	;open iliac artery approach
	33365	;transaortic approach (eg, median sternotomy, mediastinotomy)
	33366	;transapical exposure (eg, left thoracotomy)
	33367	;cardiopulmonary bypass support with percutaneous peripheral arterial and venous cannulation (eg, femoral vessels) (List separately in addition to code for primary procedure)
	33368	;cardiopulmonary bypass support with open peripheral arterial and venous cannulation (eg, femoral, iliac, axillary vessels) (List separately in addition to code for primary procedure)
	33369	;cardiopulmonary bypass support with central arterial and venous cannulation (eg, aorta, right atrium, pulmonary artery) (List separately in addition to code for primary procedure)
HCPCS	None	

Date of Origin: *December 2018*