DRAFT

BlueCross BlueShield of Alabama

Name of Policy:
Transcatheter Aortic-Valve Implantation for Aortic Stenosis

Policy #: 483
Category: Surgery

Latest Review Date: May 2018
Policy Grade: B

Background/Definitions:

As a general rule, benefits are payable under Blue Cross and Blue Shield of Alabama health plans only in cases of medical necessity and only if services or supplies are not investigational, provided the customer group contracts have such coverage.

The following Association Technology Evaluation Criteria must be met for a service/supply to be considered for coverage:

1. *The technology must have final approval from the appropriate government regulatory bodies;*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes;*
3. *The technology must improve the net health outcome;*
4. *The technology must be as beneficial as any established alternatives;*
5. *The improvement must be attainable outside the investigational setting.*

Medical Necessity means that health care services (e.g., procedures, treatments, supplies, devices, equipment, facilities or drugs) that a physician, exercising prudent clinical judgment, would provide to a patient for the purpose of preventing, evaluating, diagnosing or treating an illness, injury or disease or its symptoms, and that are:

1. *In accordance with generally accepted standards of medical practice; and*
2. *Clinically appropriate in terms of type, frequency, extent, site and duration and considered effective for the patient's illness, injury or disease; and*
3. *Not primarily for the convenience of the patient, physician or other health care provider; and*
4. *Not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of that patient's illness, injury or disease.*

Description of Procedure or Service:

Transcatheter aortic valve implantation (TAVI; also known as transcatheter aortic valve replacement or TAVR) is a potential treatment for patients with severe aortic stenosis (AS). Many patients with aortic stenosis are elderly and/or have multiple medical comorbidities, thus indicating a high, often prohibitive risk, for surgery. This procedure is being evaluated as an alternative to open surgery, or surgical aortic valve replacement (SAVR), for high-risk patients with AS and as an alternative to non-surgical therapy for patients with a prohibitive risk for surgery.

Aortic Stenosis

Aortic stenosis (AS) 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 (AoV) is the most common etiology in North America and Europe, while rheumatic fever is the most common etiology in developing countries. Congenital abnormalities of the AoV, most commonly a bicuspid valve, increase the risk for aortic stenosis, but AS can also occur in a normal aortic valve. Risk factors for calcification of a congenitally normal valve mirror those for atherosclerotic vascular disease, including advanced age, male gender, smoking, hypertension, and hyperlipidemia. Thus, the pathogenesis of calcific AS is thought to be similar to that of atherosclerosis, i.e. deposition of the atherogenic lipids and infiltration of inflammatory cells, followed by progressive calcification.

The natural history of AS involves a long asymptomatic period, with slowly progressive narrowing of the valve until the stenosis reaches the severe stage. At this time, symptoms of dyspnea, chest pain, and/or dizziness/syncope often occur and the disorder progresses rapidly. Treatment of AS is primarily surgical; involving replacement of the diseased valve with bio-prosthetic or mechanical valve by open heart surgery.

Disease Burden

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

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

Unmet Needs

Many patients with severe, symptomatic AS are poor operative candidates. Approximately 30% of patients presenting with severe AS dos not undergo open surgery due to factors such as advanced age, advanced left ventricular dysfunction, or multiple medical comorbidities. For

patients who are not surgical candidates, medical therapy can partially alleviate the symptoms of AS, but does not affect the underlying disease progression. Percutaneous balloon valvuloplasty can be performed, but this procedure has less than optimal outcomes. 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 (MI), and aortic regurgitation. In addition, restenosis can occur rapidly and there is no improvement in mortality. As a result, there is a large unmet need for less invasive treatments for AS in patients who are at increased risk for open surgery.

Treatment
TAVI has been developed in response to this unmet need, and was originally intended as an alternative treatment for patients in whom surgery is not an option due to prohibitive surgical risk, or for patients who are 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 in order to open up the stenotic area. This is followed by passage of a bioprosthetic artificial valve across the native aortic valve. The valve is initially compressed to allow passage across the native valve, and is then expanded and secured to the underlying aortic-valve annulus. The procedure is performed on the beating heart without the need for cardiopulmonary bypass.

Policy:

Effective for dates of service on and after May 1, 2018:

Transcatheter aortic valve replacement with an FDA-approved transcatheter heart valve system, performed via an approach consistent with the device's FDA-approved labeling, meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for patients with native valve aortic stenosis when **ALL** of the following conditions are present:

- Severe aortic stenosis* with a calcified aortic annulus; **AND**
- NYHA [New York Heart Association] heart failure Class II,III or IV symptoms; **AND**
- Left ventricular ejection fraction >20%; **AND**
- Patient is not an operable candidate for open surgery, as judged by at least two cardiovascular specialists (cardiologist and/or cardiac surgeon); or patient is an operable candidate but is at high or intermediate risk for open surgery**.

Transcatheter aortic valve replacement with a transcatheter heart valve system approved for use for **repair of a degenerated bioprosthetic valve meets** Blue Cross and Blue Shield's medical criteria for coverage when all of the following conditions are present:

- Failed (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve; **AND**
- NYHA heart failure class II, III or IV symptoms; **AND**
- Left ventricular ejection fraction greater than 20%; **AND**
- Patient is not an operable candidate for open surgery, as judged by at least 2 cardiovascular specialists (cardiologist and/or cardiac surgeon); or patient is an operable candidate but is at high risk for open surgery**.

*For the use of the Sapien or CoreValve device, severe aortic stenosis is defined by one or more of the following criteria:

- An aortic valve area of less than or equal to 1 cm^2
- 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/sec

**FDA definition of intermediate risk is:

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

**FDA definition of high risk for open surgery:

- Society of Thoracic Surgeons predicted operative risk score of ≥8%; or
- Judged by a heart team, which includes an experienced cardiac surgeon and a cardiologist, to have an expected mortality risk of ≥15% for open surgery.

**FDA definition of extreme risk or inoperable for open surgery:

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

Transcatheter aortic valve replacement does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for all other indications.

Effective for dates of service on and after August 30, 2016 through April 30, 2018:
Transcatheter aortic valve replacement with an FDA-approved transcatheter heart valve system, performed via an approach consistent with the device's FDA-approved labeling, meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for patients with native valve aortic stenosis when **ALL** of the following conditions are present:

- Severe aortic stenosis* with a calcified aortic annulus; **AND**
- NYHA [New York Heart Association] heart failure Class II,III or IV symptoms; **AND**
- Left ventricular ejection fraction >20%; **AND**
- Patient is not an operable candidate for open surgery, as judged by at least two cardiovascular specialists (cardiologist and/or cardiac surgeon); or patient is an operable candidate but is at high risk for open surgery**.

Transcatheter aortic valve replacement with a transcatheter heart valve system approved for use for **repair of a degenerated bioprosthetic valve meets** Blue Cross and Blue Shield's medical criteria for coverage when all of the following conditions are present:

- Failed (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve; **AND**
- NYHA heart failure class II, III or IV symptoms; **AND**
- Left ventricular ejection fraction greater than 20%; **AND**
- Patient is not an operable candidate for open surgery, as judged by at least 2 cardiovascular specialists (cardiologist and/or cardiac surgeon); or patient is an operable candidate but is at high risk for open surgery**.

*For the use of the Sapien or CoreValve device, severe aortic stenosis is defined by one or more of the following criteria:

- An aortic valve area of less than or equal to 1 cm^2
- 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/sec

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- Judged by a heart team, which includes an experienced cardiac surgeon and a cardiologist, to have an expected mortality risk of ≥15% for open surgery.

**FDA definition of extreme risk or inoperable for open surgery:

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

Transcatheter aortic valve replacement does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for all other indications.

Effective for dates of service on or after October 9, 2014 and prior to August 30, 2016:
Transcatheter aortic valve replacement with an FDA-approved transcatheter heart valve system, performed via an approach consistent with the device's FDA-approved labeling, meets Blue Cross and Blue Shield of Alabama's medical criteria for coverage for patients with aortic stenosis when **ALL** of the following conditions are present:

- Severe aortic stenosis* with a calcified aortic annulus; **AND**
- NYHA [New York Heart Association] heart failure Class II,III or IV symptoms; **AND**
- Left ventricular ejection fraction >20%; **AND**
- Patient is not an operable candidate for open surgery, as judged by at least two cardiovascular specialists (cardiologist and/or cardiac surgeon); or patient is an operable candidate but is at high risk for open surgery**.

*For the use of the Sapien or CoreValve device, severe aortic stenosis is defined by one or more of the following criteria:

- An aortic valve area of less than or equal to 1 cm^2
- An aortic valve area index of less than or equal to 0.6 cm^2/m^2
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**FDA definition of extreme risk or inoperable for open surgery:

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

Transcatheter aortic valve replacement does not meet Blue Cross and Blue Shield of Alabama's medical criteria for coverage and is considered **investigational** for all other indications, including but not limited to:

- patients with a degenerated bio-prosthetic valve ("Valve-in-Valve" implantation)

Blue Cross and Blue Shield of Alabama does not approve or deny procedures, services, testing, or equipment for our members. Our decisions concern coverage only. The decision of whether or not to have a certain test, treatment or procedure is one made between the physician and his/her patient. Blue Cross and Blue Shield of Alabama administers benefits based on the member's contract and corporate medical policies. Physicians should always exercise their best medical judgment in providing the care they feel is most appropriate for their patients. Needed care should not be delayed or refused because of a coverage determination.

Key Points:

The most recent literature review covered the period from through February 2, 2018.

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

The literature evaluating transcatheter aortic valve implantation (TAVI) has reported on three potential populations: (1) patients who are not surgical candidates, (2) patients who are at high risk for surgery but still considered to be surgical candidate, and (3) patients who are low- or intermediate-risk for surgery.

TAVI Outcomes in Patients at Prohibitive Risk for Open Surgery

Systematic Reviews

Systematic reviews on the question of whether TAVI improves outcomes for patients who are not suitable candidates for open surgery consist of summaries of case series. An Agency for Healthcare Research and Quality (AHRQ) -sponsored systematic review in 2010 reviewed 84 publications enrolling 2375 patients. 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 (AE) rates were reported in the larger case series, with an estimated 30-day rate of major cardiovascular AEs and stroke of 8%.

A second systematic review was published in 2011 by Figulla et al. This review included studies that enrolled symptomatic patients with severe aortic stenosis, had a mean age of 75 years or older, reported on ten or more patients, and had a follow-up duration of 12 months or more. A total of 12 studies met these criteria and were compared with a group of eleven 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% (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 (RCTs)

Sapien and Sapien XT

The PARTNER trial was a pivotal multicenter RCT of TAVI performed in the United States, Canada, and Germany, using the SAPIEN™ heart-valve system. Leon et al reported results of patients from this trial with severe aortic stenosis who were not candidates for open surgery, referred to as the PARTNER B trial. To be classified as unsuitable for open surgery, patients had to have a predicted probability of 50% or higher for death or a serious irreversible condition at 30 days postsurgery. This probability was determined by 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 3105 patients were screened for aortic valve surgery, and 12% of these were eventually included in the cohort of patients deemed unsuitable for surgery.

A total of 358 patients were randomized to TAVI or usual care. TAVI was performed by the transfemoral approach under general anesthesia. Standard therapy was determined by the 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 that was not participating in the trial. The primary outcome was death from any cause over the course of the trial (median follow-up, 1.6 years). A “co-primary” end point was the composite of time to death from any cause or time to repeat hospitalization related to aortic stenosis or TAVI. Secondary end points were cardiovascular mortality, New York Heart Association (NYHA) functional class, the rate of hospitalizations due to aortic stenosis or TAVI, the six-minute walk test, valve performance as measured by echocardiography, and procedural complications (myocardial infarction [MI], stroke, acute kidney injury [AKI], vascular complications, bleeding).

The mean age of enrolled patients was 83.2 years. There were some baseline imbalances in the patient population indicating that the standard therapy group may have had a higher severity of illness. Standardized scores of surgical risk were higher in the standard therapy group. The Logistic EuroSCORE was significantly higher in the standard therapy group compared with the TAVI group (30.4±19.1 vs 26.4±17.2, p=0.04) and the STS score was numerically higher but did

not reach statistical significance (12.1±6.1 vs 11.2±5.8, 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%).

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 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 percent 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 six-minute walk test 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 percent of patients undergoing TAVI and were significantly higher than in the standard therapy group (22.3% vs 11.2%, p=0.007; and 32.4% vs. 7.3%, p<0.001, respectively).

Quality of life (QOL) outcomes from this trial were reported by Reynolds et al in 2012. QOL outcomes 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). 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 the follow-up time points of 30 days, six months, and 12 months, the change in the QOL scores was greater for the TAVI group. At 30 days, the mean difference in the KCCQ 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 26.0 points (95% CI, 18.7 to 33.3; p<0.001) at 12 months. Changes in the SF-12 and EQ-5D measures showed similar patterns.

Two-year outcomes were reported from the PARTNER trial by Makkar in 2012. 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 in the TAVI group compared with medical therapy (31.0% vs 62.4%, p<0.001). The rate of hospitalization over the two-year period was lower in the TAVI group compared with medical therapy (35.0% vs 72.5%, p<0.001).

In 2014, Svensson et al reported detailed mortality outcomes for both arms of the PARTNER trial: the PARTNER B RCT previously described that compared surgical repair with TAVI in

prohibitive surgical risk patients, and the PARTNER A RCT that compared surgical repair with TAVI in high surgical risk patients, described next. For the 358 patients who were considered inoperable and enrolled in the PARTNER B RCT, at last follow-up, 237 patients had died. Those randomized to standard therapy exhibited an early peak in mortality that was higher than those randomized to TAVI and 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).

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

In 2015, Webb et al 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. The trial used a noninferiority design; for its primary end point, a composite of all-cause mortality, major stroke, and rehospitalization at 1 year in the intention-to-treat population, the relative risk between the SAPIEN and SAPIEN XT groups was 0.99 (p<0.002), which met the criteria for noninferiority.

Case Series and Cohort Studies

Many case series of TAVI have been published in the last ten years, the majority of which have included patients who are 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 some overlap in these series with patients who are surgical candidates, but the distinction cannot be easily made for the reported studies.

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

CoreValve

In 2014, Popma et al published results of the CoreValve Extreme Risk 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 for surgical aortic valve replacement. The

study included patients with severe aortic stenosis and NYHA Class II or greater symptoms who were considered to be at extreme risk for open aortic valve repair. A patient was judged to be 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 end point 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.

Four hundred eighty-nine patients were included in the attempted implant analysis population of 506 patients recruited (eleven of whom exited the study prior to treatment, six of whom did not complete the procedure with iliofemoral access). The Kaplan-Meier rate of the primary end point (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).

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

Two-year results from the CoreValve Extreme Risk Pivotal trial were reported by Yakubov et al in 2015. The Kaplan-Meier rate of all-cause mortality or major stroke was 38.0% (upper bound of 95% CI, 42.6%). The incremental rates between year 1 and year 2 were 12.3% for all-cause mortality, 7.9% for cardiovascular mortality, and 0.8% for stroke. Baron et al (2017) reported on

3-year results of the QOL data. The QOL improvements following TAVR were largely sustained through 3 years with clinically meaningful (>10 point) improvements in the KCCQ overall summary score at 3 years observed in greater than 83.0%.

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

Post approval Registries

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

Additional Case Series

The ADVANCE study was a prospective nonrandomized study with central adjudication of end points and adverse events to evaluate the CoreValve in individuals with severe symptomatic aortic stenosis who were considered inoperable or at higher risk for surgical aortic valve replacement. The study enrolled 1015 patients, of whom 996 were implanted, most (88.4%) by the iliofemoral approach, with 9.5% and 2.1% by the subclavian and direct aortic approaches, respectively. For the study's primary end point of major adverse cardiac and cerebrovascular events (MACCE; 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%) and 4.5% (95% CI 2.9% to 6.1%) at 30 days and 12 months. A new permanent pacemaker was implanted in 26.3% (95% CI, 23.5% to 29.1%) and 29.2% (95% CI, 25.6% to 32.7%) at 30 days and 12 months of follow-up. Patients were grouped into 3 categories of surgical risk based on logistic EuroSCORE values (≤10%, >10% but ≤20%, and >20%). Thirty-day survival did not differ significantly across risk groups, but 12-month rates of MACCE, all-cause mortality, cardiovascular mortality, and death from any cause or major stroke were higher for higher surgical risk patients.

The two largest series included in the AHRQ review described previously reported on 646 patients treated with the Medtronic CoreValve™ and 339 patients treated with the Edwards SAPIEN™ valve. The CoreValve™ study by Piazza et al (2008) was notable in that it used more objective patients' selection criteria that are common in this literature. Their criteria for eligibility included the following:

1. Logistic EuroScore ≥15%;
2. Age ≥75 or;
3. Age ≥65 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 BMI≤18kg/m^2.

Procedural success was 97% and 30-day survival was 92%. The 30-day combined rate of death, MI or stroke was 9.3%. The study by Rodes-Cabou et al (2010) was performed in Canada and used Edwards SAPIEN™ valve. This study had subjective inclusion criteria, relying on the judgement of the participating surgeons to determine eligibility for TAVI. The procedure 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 describe experiences with TAVI in European centers. Zahn et al (2011) reported on a larger case series was from Germany and reported on 697 patients treated with the CoreValve™ system. Procedural success was 98.4% and 30-day mortality was 12.4%. Another large case series (2011) from Italy included 663 patients treated with the CoreValve™ device. 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 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 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 judgment of the cardiovascular surgeons and/or cardiologists. It is not known whether this type of decision making by surgeons and cardiologists is reliable across the range of practicing clinicians.

TAVI Outcomes in Patients at High Risk for Open Surgery
Systematic Reviews
A meta-analysis of 4 RCTs was published by Panoulas et al (2018) to determine whether sex differences had any impact on mortality rates for TAVI and SAVR. The 4 RCTs comprised of 3758 patients (2052 men, 1706 women); all patients had severe aortic stenosis. The study revealed that among women undergoing TAVI, a significantly lower mortality rate was found than in women undergoing SAVR at the 1- year mark; in fact, women undergoing TAVI were

found to have a 31% lower mortality rate than women undergoing SAVR, again at the 1-year mark (odds ratio [OR], 0.68; 95% CI, 0.50 to 0.94). There was no statistical difference in mortality in men undergoing TAVR vs men undergoing SAVR.

In 2016, Villablanca et al reported on a meta-analysis and meta-regression of long-term outcomes (>1 year) of TAVI compared with surgical AVR for severe aortic stenosis. Trial methods were described in the meta-analysis protocol, which was registered with PROSPERO. The review was limited to studies comparing TAVI and surgical repair, with subgroup analyses for high- and intermediate-risk patients. Overall, 4 RCTs (n=3806 patients) and 46 observational studies (n=40,441 patients) were included, with a median follow-up of 21.4 months. Two of the RCTs were conducted in high-risk patients, and are described in detail below (PARTNER 1 [Mack et al, 2015] and CoreValve High Risk Trial [Reardon et al, 2015]). Results from the subgroup analyses focused on high- risk patients are shown in Table 1.

Table 1: TAVI vs Surgical Repair in High-Risk Patients (Villablanca et al, 2016)

Outcomes	TAVI[a]	Surgical Repair[a]	RR for TAVI vs Surgical Repair (95% CI)	I^2
30-day postprocedure mortality	508/8552 (5.9%)	804/29323 (2.7%)	1.02 (0.76 to 1.36)	72.3%
All-cause mortality	3625/8803 (41.1%)	5438/29,450 (18.6%)	1.16 (0.87 to 1.53)	96.6%
Stroke incidence	191/4293 (4.4%)	213/4348 (4.9%)	0.79 (0.66 to 0.95)	0%
Myocardial infarction incidence	57/2820 (2.0%)	59/2746 (2.1%)	0.91 (0.64 to 1.29)	21.5%
Vascular complication incidence	203/2489 (8.2%)	35/2682 (1.3%)	5.5 (2.42 to 12.4)	67.5%
Residual regurgitation incidence	268/2831 (9.5%)	36/2823 (1.3%)	6.3 (4.55 to 8.71)	0%
Requirement for permanent pacemaker incidence	527/3449 (15.3%)	236/3653 (6.4%)	1.68 (0.94 to 3.00)	83.2%
New-onset AF incidence	165/1192 (13.8%)	376/1281 (29.4%	0.38 (0.26 to 0.55)	64.6%
Major bleeding incidence	321/2074 (15.4%)	416/2298 (18.1%)	0.73 (0.65 to 0.83)	24.2%
Acute kidney injury incidence	294/3446 (8.5%)	396/3528 (11.2%)	0.73 (0.53 to 1.01)	68.4%

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

Earlier systematic reviews focused largely from nonrandomized comparative studies, because only one RCT had been published at the time of the reviews (the PARTNER trial). Panchal et al (2013) reported results from a meta-analysis of 17 studies that included 4659 patients, 2267 treated with TAVI, and 2392 treated with open surgery. Patients in the TAVI group were more severely ill, as evidenced by a EuroSCORE for predicted 30-day mortality that was higher by a mean of 3.7 points compared with patients undergoing open surgery. On combined analysis, there were no differences between groups on 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 (relative risk [RR]=1.42; 95% CI, 1.20 to 1.67; p<0.001). In a similar meta-analysis (2013) that included 17 studies reporting on 4873 patients, there were no differences between TAVI and open surgery in early mortality (odds ratio [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).

Randomized Controlled Trials (RCTs)

Sapien PARTNER A Trial

Smith et al (2011) published results from the cohort of patients in the PARTNER trial of the SAPIEN valve who were high-risk for open surgery, but still suitable candidates. The inclusion and exclusion criteria were generally the same as 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%, as determined by a cardiac surgeon and cardiologist using clinical judgment. An STS score of ≥10 was included as a guide for high-risk, but a STS score threshold was not a required criterion for enrollment. The executive committee of the PARTNER trial reviewed all patient selection decisions and approved the classification of patients as high risk for surgery. A total of 3105 patients were screened for aortic-valve surgery, and 22.5% of these were eventually included in the cohort of patients deemed high risk for surgery.

A total of 699 patients were randomized to TAVI or surgical aortic valve repair. The primary hypothesis was that TAVI was non-inferior to open aortic valve replacement (AVR), using a one-sided non-inferiority 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 either 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 non-inferiority at one year for the patients undergoing TAVI by the transfemoral approach. Secondary endpoints were cardiovascular mortality, NYHA functional class, rehospitalizations, the six-minute walk test, valve performance as measured by echocardiography, and procedural complications (MI, stroke, acute kidney injury, vascular complications, and bleeding). The mean age of enrolled patients was 83.6 years in the TAVI group and 84.5 years in the open AVR group. Other baseline demographics and clinical characteristics were generally well-balanced, except for a trend toward an increased percent of patients in the TAVI group with a creatinine level >2.0 (11.1% vs. 7.0%, p=0.06).

Death from any cause at one year following enrollment was 24.2% for the TAVI group compared to 26.8% for the open AVR group (p=0.44 for difference between groups). The upper limit of the 95% CI for the difference between groups was a 3.0% excess mortality in the TAVI group, which was well within the non-inferiority boundary of 7.5%. Thus the criterion of non-inferiority was met, with a p-value of 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 compared with 26.4% mortality in the open AVR group (p=0.002 for non-inferiority). The secondary outcomes of cardiovascular mortality (14.3% vs. 13.0%, p=0.63) and rehospitalizations (18.2% vs. 15.5%, p=0.38) were not significantly different for the TAVI versus open AVR groups. The percentage of patients in NYHA class I or II at one year was similar between groups at one year, as was the improvement in the six-minute walk test. 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 CABG, 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%, p=0.04). Vascular complications occurred in 18.0% percent 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 compared to TAVI (25.7% vs. 14.7%, p=0.01).

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

Reynolds et al published QOL results from the PARTNER A trial in 2012. 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 surgical AVR 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 et al published a follow-up study from the PARTNER A trial reporting on bleeding complications. 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 patients treated with surgery (22.7%) had major bleeding complications within 30 days of the procedure, compared with 27 (11.3%) of those treated with transfemoral TAVI and nine (8.8%) of those treated with transapical TAVI (p<0.001).

The U.S. CoreValve High Risk Study

In 2014, Adams et al published results of the U.S. CoreValve High Risk Study. This was an RCT comparing surgical aortic valve replacement with TAVI using a self-expanding transcatheter aortic valve prosthesis (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 aortic valve replacement. 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 after 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 an attempted implantation. For the study's primary outcome, the rate of death from any cause at one year was lower in the TAVI group than in the surgical group (14.2% vs 19.1%; absolute risk reduction,

4.9%; upper boundary of 95% CI, -0.4, which was less than the predefined non-inferiority margin of 7.5% point difference between the groups; non-inferiority, 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 post-procedure than the surgical group; 8.8% for the TAVI group compared with 12.6% for the surgical group (p=0.10).

Two-year follow-up results from the U.S. CoreValve High Risk study were published in 2015 by Reardon et al. At that point, the mortality benefits seen with TAVI continued to be present.

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

Additional analyses of the CoreValve study have focused on the impact of patient and prosthesis mismatch (Zorn et al, 2016).

Nonrandomized Comparative Studies

Since the publication of the pivotal RCTs and systematic reviews described previously, a number of nonrandomized studies have compared surgical and transcatheter aortic valve repair. Given the availability of RCT evidence, these studies provide limited additional information about 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 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 surgical AVR reported no differences between TAVI and open AVR in terms of mortality at one year and most major secondary outcomes. The non-inferiority boundaries for this trial included an upper limit of 7.5% absolute increase in mortality, but in actuality, the reported mortality for the TAVI group was lower than for the open group, although not significantly different. 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 for generalizability of results given that 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, in contrast to the PARTNER A RCT, stroke rates were not higher in patients who underwent TAVI, a requirement for permanent pacemaker was more common in the TAVI group. Follow-up analyses of the U.S. CoreValve High Risk Study showed sustained improvements in the TAVI group for the outcome of all-cause mortality and a number of secondary outcomes. The incidence of pacemaker implantation continued to be higher in TAVI-treated patients.

TAVI Outcomes in Patients at Low or Intermediate Risk for Open Surgery

Most research on TAVI has focused on its use as an alternative to open surgery in patients at least with a high risk for surgery. Five RCTs were identified that evaluated the use of TAVI in patients who were not necessarily at high risk of open surgery.

Systematic Reviews

Several systematic reviews and meta-analyses were published in 2017 and 2018, including many overlapping RCTs and observational studies.

Garg et al (2017) included all 5 RCTs published through 2017, and therefore the next paragraph will focus on that review. Garg et al (2017) published a systematic review and meta-analyses that included RCTs and prospective observational studies comparing TAVI with SAVR published between January 2000 and March 2017 including low-to-intermediate surgical risk patients with severe aortic stenosis. Five RCTs (n=4425 patients) were included and are discussed in the following section. The meta-analytic results pooling the RCTs are shown in Table 2.

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

Outcomes	TAVI	Surgical Repair	RR for TAVI vs Surgical Repair (95% CI)	p	r^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). Values are percent unless other noted. CI: confidence interval; RR: relative risk; TAVI: transcatheter aortic valve implantation.

In 2016, Zhou et al reported on a meta-analysis comparing TAVI with surgical repair in patients at low or intermediate risk of open surgery. Seven studies were included, 3 RCTs (NOTION [2015], STACCATO [2012], Leon et al [2016]), and 4 observational studies (total N=6214 patients; n=3172 [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 vs Surgical Repair in Low- or Intermediate-Risk Patients (from Zhou et al, 2016)

Outcomes	TAVI	Surgical Repair	OR for TAVI vs Surgical Repair (95% CI)	p	I^2
Short-term post-procedure mortality	2.59%	3.94%	0.63 (0.37 to 1.08)	0.09	56%
Short-term cardiovascular mortality	1.96%	3.15%	0.51 (0.23 to 1.15)	0.11	68%
Acute kidney injury incidence	1.92%	4.8%	0.34 (0.17 to 0.67)	0.002	61%
Stroke incidence	3.57%	4.90%	0.72 (0.56 to 0.92)	0.01	42%
Myocardial infarction incidence	0.7%	1.7%	0.51 (0.23 to 0.69)	<0.001	10%
Major vascular complication incidence	7.2%	3.6%	3.54 (1.42 to 8.81)	0.006	86%
Requirement for permanent pacemaker incidence	11.9%	6.1%	2.79 (1.49 to 5.23)	0.001	88%
All-cause mortality (1 year)	10.1%	12.2%	0.82 (0.58 to 1.16)	0.26	67%

CI: confidence interval; OR: odds ratio; TAVI: transcatheter aortic valve implantation.

Earlier systematic reviews came to similar conclusions.

Overall, the results suggest that, for intermediate and low operative risk patients, periprocedural and short-term (1-year) mortality rates do not differ significantly between TAVI and open aortic valve repair. However, similar to the high- and prohibitive-risk populations, TAVI is associated with higher rates of major vascular complications, paravalvular regurgitation, and need for permanent pacemakers, but lower rates of major bleeding.

Randomized Controlled Trials

Five 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		
Author; Study	**Countries**	**Sites**	**Dates**	**Participants**	**TAVR**	**SAVR**	**Sponsor**
Nielsen et al (2012); STACATTO	Denmark	2	Nov 2008-May 2011	• Mean age, 81 y • No significant coronary artery disease • Any surgical risk (mean STS-PROM, 3.3)	• n=34 Edwards Sapien THV	• n=36 • Conventional open heart surgery with CPB	Participating hospitals and Danish Heart Foundation
Thyregod et al (2015) , Søndergaard et al (2016); NOTION (NCT01057173)	Denmark, Sweden	3	Dec 2009-Apr 2013	• Mean age, 79 y • No significant coronary artery disease • Any surgical	• n=145 • CoreValve	• n=135 • Conventional open heart surgery with CPB	Danish Heart Foundation

				risk (mean STS-PROM, 3.0; 82% low-risk)			
Reardon et al (2016); CoreValve U.S. Pivotal (NCT01240902)	U.S.	45	Feb 2011-Sep 2012	• Mean age, 81 y • STS score	• n=202 • CoreValve	• n=181 • Conventional open heart surgery with CPB	Manufacturer
Leon et al (2016); PARTNER 2A (NCT01314313)	U.S., Canada	57	Dec 2011-Nov 2013	• Mean age, 82 y • Symptomatic (NYHA class >II) • STS-PROM >4 and <8 or • STS-PROM	• n=1011 • SAPIEN XT	• n=1021 • Conventional surgery	Manufacturer
Reardon et al (2017); SURTAVI (NCT01586910)	U.S., Netherlands, Germany, UK, Spain, Switzerland, Sweden, Canada	87		• Mean age, 80 y • STS-PROM ≥4 and	• n=879 • Core	• n=867 • Conventional	Manufacturer

CPB: cardiopulmonary bypass; NYHA: New York Heart Association; RCT: randomized controlled trial; SAVR: surgical aortic valve replacement; STS-PROM: Society of Thoracic Surgeons predicted risk of mortality score; TAVI: transcatheter aortic valve implantation; TAVR: transcatheter aortic valve replacement; THV: Transcatheter heart valve a Includes analysis of a subset of originally randomized patients

In 2016, Leon et al reported results of a multicenter noninferiority RCT 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). Eligible patients had degenerative aortic valve stenosis, with NYHA functional class II or higher, and were in STS Risk Score of 4 or greater (or <4 if determined by a heart team to have an "intermediate-risk patient profile with important comorbidities not represented in the STS Risk Calculator algorithm.") The trial used a noninferiority design, with a primary composite end point of death from any cause or disabling stroke (score of ≥2 on the modified Rankin Scale) at 2 years and a noninferiority margin of 1.2 (i.e., noninferiority was considered met if upper bound of 2-sided CI for the relative risk for the primary outcome was <1.2).

A total of 2032 patients were randomized to TAVI (n=1011) or surgical repair (n=1021), with 1550 considered suitable for transfemoral placement (76.3%) and 482 (23.7%) requiring transthoracic access. At baseline, the mean STS Risk Score was 5.8%; 81.3% had a score between 4% and 8%. The primary outcome results and select additional results of the trial are summarized in Table 5. In addition, similar to other TAVI trials, the frequency and severity of paravalvular regurgitation was higher after TAVI than in surgical repair. The presence paravalvular regurgitation was associated with all-cause mortality during follow-up (HR for moderate or severe paravalvular regurgitation vs none or trace, 2.85; 95% CI, 1.57 to 5.21; p<0.001).

Table 5: RCTs Comparing TAVI and Surgical Repair in Intermediate or Unselected Risk

Study	Primary Outcome	Results of Primary Outcomes, %				All-Cause Mortality (2 y), %			New Permanent Pacemaker (2 y), %		
		TAVI	Surg	TE (95% CI)	p	TAVI	Surg	p	TAVI	Surg	p
Nielsen et al (2012)	Death from any cause, stroke, or renal failure at 30 d										
All patients		14.7	2.8	RD (NR)	0.07	NR	NR		NR	NR	
Reardon et al (2016)	Death from any cause at 2y										
STS score <7		26.3	15.0	HR (NR)	0.01	See previous columns	See previous columns	See previous columns	27.7	10.5	<0.001
Leon (2016)	Death from any cause or disabling stroke (2 y)										
All patients		19.3	21.1	0.92 (0.75 to 1.08)		16.7	18.0	0.45	11.8	10.9	0.29
Transfemoral access		16.8	20.4	0.79 (0.62 to 1.00)		14.2	17.2	0.11	11.4	10.8	0.71
Transthoracic access		27.7	23.4	1.21 (0.84 to 1.74)		25.2	20.7	0.26	13.1	8.6	0.13
Reardon et al (2017)	Death from any cause or disabling stroke at 2y										
All patients		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]
Thyregod (2015)	Death from any cause, stroke, or MI at 1 y										
All patients		13.1	16.3	-3.2 (p=0.43)[a,b]	0.43[a]	4.9	7.5	0.38	34.1	1.6	<0.001

CI: confidence interval; HR: hazard ratio; RD: risk difference; MI: myocardial infarction; NR: not reported; Surg: surgical repair; TAVI: transcatheter aortic valve implantation; TE: treatment effect. a Superiority. b Bayesian credible interval.

In 2015, Thyregod et al reported results of the NOTION RCT trial, which compared TAVI to surgical repair in 280 patients with severe aortic stenosis who were 70 years old or older, regardless of predicted risk of death after surgery. Patients randomized to TAVI underwent implantation of the CoreValve self-expanding prosthesis by the femoral (preferred) or subclavian route. The study was powered to detect an absolute risk reduction of 10% or a relative risk reduction of 66.7% in primary outcome at 1 year. At baseline, 81.8% of the study population were considered to be at low risk (STS 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 II or III acute kidney injury (0.7% vs 6.7%, p=0.01), and new onset or worsening atrial fibrillation (16.9% vs 57.8%, p<0.001). Both groups showed improvements in NYHA functional class. However, more TAVI-treated patients were in NYHA functional class II at 1 year follow up (29.5% vs 15.0%, p=0.01).

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

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

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

Reardon et al (2017) published 2-year results from an RCT (SURTAVI trial) that compared clinical outcomes for 1746 patients at intermediate surgical risk randomized to transcatheter aortic valve replacement (TAVR) or SAVR. For the primary outcome (composite death at 2 years), an improvement was observed in the TAVR-treated group, compared with surgery (12.6% of TAVR patients vs 14.0% of SAVR patients [95% credible interval, -5.2% to 2.3%]; posterior probability, >0.999). Rates of death, MI, and disabling stroke were comparable between groups, as were secondary outcomes that included echocardiographic measurement of aortic valve gradient and paravalvular regurgitation (data reported in the supplemental material). More patients were assigned to the CoreValve bioprosthesis (n=724) than received Evolut R bioprosthesis (n=137), which might have affected the results; also, a considerable number of

patients withdrew consent before surgery, resulting in an as-treated population of 1660. Finally, the authors acknowledged a gap in knowledge of how baseline characteristics of patients who received surgery differed from those who did not. The authors noted the low 30-day surgical mortality ratio (0.38; observed-to-expected) and the similarity of this rate between groups (2.2% of the TAVR patients vs 1.7% of surgical patients).

Noncomparative Studies

The literature search focused on studies describing issues unique to the risk-benefit tradeoff for TAVI in individuals at intermediate or low surgical risk.

In 2016, Fanning et al reported on a prospective observational study evaluating clinical and subclinical (magnetic resonance imaging [MRI]) neurologic injury in 40 individuals at intermediate surgical risk who were undergoing TAVI with the Edwards SAPIEN XT valve. Following the procedure, 60 patients had new lesions on diffusion weighted imaging (DWI), suggestive of acute ischemia.

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

Five RCTs have evaluated TAVI in patients in low or intermediate risk for open surgery.

Intermediate Risk

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

Low Risk

Limited data are available comparing TAVI with SAVR in patients at low risk for open surgery. The NOTION trial was the only trial with predominantly low surgical risk patients. The STACCATO trial also included some patients at low surgical risk. One systematic review of these 2 RCTs and 4 observational studies with propensity score matching comparing TAVI with SAVR in patients at low surgical risk reported that the 30-day and in-hospital mortality rates were similar for TAVI (2.2%) and SAVR (2.6%). However, TAVI was associated with increased risk of mortality with longer follow-up (median 2 years; 17.2% vs 12.7%). TAVI was associated with reduced risk of bleeding and renal failure and an increase in vascular complications and pacemaker implantation compared with SAVR.

TAVI Outcomes for "Valve-in-Valve" Approach

TAVI has been used through a "valve-in-valve" replacement approach for patients with degenerated bioprosthetic valves or failed TAVI. The evidence on outcomes after the use of TAVI for "valve-in-valve" replacement consists of case series. The largest case series published to date is from the Global Valve-in-Valve registry. The most recent results from this registry have been reported through May 2013, including 459 patients. Included patients were from 38 cardiac centers and had a prior surgical bioprosthetic valve replacement that had failed. Failure was due to stenosis in 181 (39.4%) patients, regurgitation in 139 (30.3%), or a combination in 139 (30.3%). The balloon-expandable and self-expandable devices were used in 246 (53.6%) and 213 (46.4%) patients, respectively. At 30 days, mortality was 7.6% (35/459), with a higher mortality rate in patients with failure due to stenosis (10.5% vs 4.3% in the regurgitation group and 7.2% in the combined group; p=0.04). The overall 1-year mortality rate was 16.8%, with a higher mortality rate in the stenosis group than the other 2 groups (23.4% vs 8.8% in the regurgitation group and 16.1% in the combined group; p=0.01). At 1 year, 86.2% of patients were in NYHA functional class I or II.

Other case series are smaller and generally from a single center. A case series from Europe using the Medtronic CoreValve enrolled 27 patients from one cardiology center. There were two deaths within 30 days. Improvements in the aortic valve gradient and the degree of regurgitation were noted. AEs included stroke (7.4%), kidney failure (7.4%), life-threatening bleeding (7.4%), and access site complications (11.1%). Another case series from Europe treated 18 patients with a degenerated bioprosthetic valve and symptoms due to valve dysfunction. Implantation was successful in 17/18 patients. Complications included AKI in three of 18 patients, major bleeding in four of 18 patients, and major access site complications in one of 18 patients. At a median follow-up of eleven months, mortality was 5.6% and symptoms were improved with all patients in NYHA class II or lower. A 2014 series from Australia including 12 patients who underwent valve-in-valve replacement of a degenerated bioprosthetic valve reported successful valve implantation for all patients, with 1 case complicated by cardiac arrest during bioprosthetic valve predilation. No periprocedural deaths, MIs, neurologic events, or major vascular complications occurred. After 1624 and 1319 days, 2 patients had died. The remaining patients had a median survival of 581 days, and all were in NYHA class I or II functional status.

Smaller case series have reported on valve-in-valve implantation for patients with failed TAVI. For example, a publication from Canada reported on 21 patients with transcatheter valve failure due to aortic regurgitation. The procedure was successful in 19 of 21 patients; the remaining two patients required conversion to open surgery. Mortality at 30 days was 14.3% and at one year was 24%. Aortic regurgitation was absent in four patients, mild in 13 patients, and moderate in two patients.

In 2014, Raval et al reported results from a systematic review of multiple types of valve-in-valve replacement procedures, including 31 studies that reported outcomes after transcatheter aortic valve-in-valve replacement, 13 of which were case reports. Pooled analyses of study results are not reported, but the authors report a relatively high rate (90%-90%) of success for valve-in-valve TAVI procedures for series that report procedural success.

Section Summary: Outcomes for TAVI for "Valve-in-Valve" Approach
The evidence related to the use of TAVI for valve-in-valve replacement after failed TAVI or degenerated bioprosthetic valve consists case series (the largest of which included 459 patients), and one systematic review of available case series. These studies report high rates of technical success of valve implantation, but often also report high rates of short-term complications. At 1 year postprocedure, reported mortality rates are often high, but high proportions of patients have improvement in heart failure-related symptoms.

Adverse Events and Complications Following TAVI
Summary of Complications
Conte et al (2017) analyzed both periprocedural and early complications (0-3 days and 4-30 days postoperative, respectively) in patients from the U.S. CoreValve High Risk Study. 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%, p<0.001) were significantly higher with SAVR.

A 2013 meta-analysis of complications associated with TAVI was published by Khatri et al. This analysis included all publications with at least 100 patients that had data on at least one type of complication. A total of 49 studies enrolling 16,063 patients were identified. The most common AE was heart block requiring a pacemaker insertion, which occurred in 13.1% of patients. Vascular complications occurred in 10.4% of patients. The third most common complication was acute renal failure requiring therapy in 4.9% of patients, and stroke was reported in 2.9% of patients. Other complications included moderate to severe aortic regurgitation in 4.5%, valve embolization in 1.3%, MI in 1.1% and coronary obstruction in 0.8%.

Giordana et al (2014) published a meta-analysis of predictors of all-cause mortality after TAVI. The authors included 25 studies with 8874 patients who underwent TAVI for severe symptomatic aortic stenosis that reported predictors of mortality at 30 days or at mid-term follow-up. Most patients (51.1%) underwent the procedure via the transfemoral approach, with 33.7% and 1.7% receiving a transapical or direct aortic/subclavian approach, respectively. A Sapien balloon-expandable valve was used in 5392 patients (60.8%), while a CoreValve self-expandable valve was used in 1899 patients (21.4%). Three studies did not report the type of valve implanted. At 30 days, 663 patients died (7.5%), 712 developed AKI (8.02%), 1224 (13.8%) developed major bleeding, 782 (8.8%) developed major vascular complications, and 1106 (12.5%) required pacemaker implantation. At mid-term follow-up (median 365 days), 1917 patients (21.6%) had died. The strongest predictors of 30-day mortality were higher AKI stage (≥2; OR=18.0; 95% CI, 6.25 to 52), pre-procedural hospitalization for at least one week (OR=9.36; 95% CI, 2.55 to 35); periprocedural acute myocardial infarction (OR=8.54; 95% CI, 2.57 to 33.52); and preprocedural increased pro-brain natriuretic peptide (BNP) levels (OR=5.35; 95% CI, 1.74 to 16.5). The strongest predictors of mid-term mortality were increased pro-BNP levels (OR=11; 95% CI, 1.51 to 81), Stage III AKI (OR=6.80; 95% CI, 2.55 to 15.66), left ventricular ejection fraction less than 30% (OR=6.67; 95% CI, 3.5 to 12.76), and periprocedural acute myocardial infarction (OR=6.52; 95% CI, 2.34 to 18.14).

Some studies have specifically reported on one or more complications in large numbers of patients. Representative studies of this type will be reviewed here.

Vascular Access Complications
The most common complications following TAVI are vascular complications related to the access site. Van Miegham et al pooled results from prospective databases on 986 patients undergoing transfemoral TAVI from five clinical centers in Europe. The rate of major vascular complications was 14.2%. Major bleeding occurred at a rate of 17.8% and life-threatening/disabling bleeding occurred at a rate of 11%. Czerwinska-Jelonkiewicz et al reported vascular complication rates for 89 consecutive patients treated at a single institution; 44 patients had vascular complications, 17 of which (20.5% of the total) were considered major incidents.

Acute Kidney Injury
AKI is also relatively common following TAVI. In 218 patients treated at one academic medical center in the United States, Stage II or higher AKI occurred in 8.3% (18/218). Half of the patients with AKI (9/18) required dialysis. Mortality at 30 days (44.4% vs 3.0%, $p<0.001$) and one year (55.6% vs 16.0%, $p<0.001$) was much higher in patients with AKI compared with those without AKI. In a similar study of 248 patients from an academic center in Europe, Stage II or higher AKI was more common, occurring in 35.9% of patients (89/248). Mortality was also increased at 30 days (13.5% vs 3.8%, $p<0.001$) and at one year (31.5% vs 15.0%, $p<0.001$) for patients with AKI.

Permanent Pacemaker Requirement
A pacemaker requirement due to conduction abnormalities is another relatively frequent complication following TAVI, and predictors and rates of permanent pacemaker requirement have been a focus of a number of studies.

Siontis et al (2014) conducted a meta-analysis to determine predictors of permanent pacemaker implantation after TAVI. The authors included 41 studies that made available individual patient-level data, which included 11,210 patients treated with TAVI, of whom 17% required a permanent pacemaker after aortic valve implantation. Between 2% and 51% of patients across the individual studies required a permanent pacemaker. For the patients receiving the Medtronic CoreValve, the median rate of permanent pacemaker placement was 28% (interquartile range, 24%-35%), whereas for those receiving the Edwards Sapien valve, the median permanent pacemaker placement rate was 6% (interquartile range, 5%-7%). In pooled analyses, factors significantly associated with permanent pacemaker requirement after TAVI included male sex (RR=1.23; $p<0.01$); baseline first-degree atrioventricular block (RR=1.52, $p<0.01$); and intraprocedural atrioventricular block (RR=3.49; $p<0.01$).

Several studies that were not included in the Siontis review have addressed the need for permanent pacemaker placement after TAVI. Gensas et al (2014) reported rates and predictors of permanent pacemaker requirements after TAVI in patients enrolled in a multicenter Brazilian registry. Four hundred eighteen patients were treated with TAVI between 2008 and 2012. The authors reported outcomes for 353 who survived the procedure and who did not have a previous permanent pacemaker. About a quarter (25.2%) of patients required a permanent pacemaker by

30 days post-procedure. In multivariable analysis, CoreValve device (vs Sapien XT; OR=4.24, 95% CI, 1.56 to 11.49; p<0.000), baseline right bundle branch block (OR=4.41, 95% CI, 2.20 to 8.82; p<0.001), and requirement for balloon pre-dilatation of the aortic valve (OR=1.75; 95% CI, 1.02 to 3.02; p=0.04) were independent predictors of a requirement for permanent pacemaker.

As previously described, Abdel-Wahid et al (2014) reported results of an RCT comparing the CoreValve and the Sapien valves and found that patients in the balloon-expandable group less frequently required placement of a new permanent pacemaker (17.3% vs 37.6%, p=0.001).

Lenders et al (2014) compared permanent pacemaker requirement rates based on depth of implantation for patients treated with the CoreValve device. Two hundred thirty-two patients were treated with a CoreValve device, some with a newer-generation delivery catheter (the Accutrak; N=112) and some with an older-generation delivery catheter (N=120). Groups were similar at baseline. The mean depth of implantation was 8.4 in the non-Accutrak group and 7.1 in the Accutrack group (p=0.034). In patients without a permanent pacemaker before valve implantation, 33 patients in the non-Accutrak group (32.3%) received a permanent pacemaker after implantation, compared with 21 in the Accutrak group (21.4%; p=0.094). Among all patients, the mean depth of implantation was significantly lower (lower in relation to a reference line connecting the lower edges of the three aortic valve cusps) in patients who required a new permanent pacemaker compared with those who did not (8.9 mm vs 6.9 mm; p=0.002).

Boerlage-Van Dijk et al reported predictors of cardiac conduction abnormalities in 121 patients who received a CoreValve implant at a single center between October 2007 and June 2011. For the analysis of new left bundle branch block, 34 patients were excluded because of preprocedural left bundle branch block or a ventricular-paced rhythm. For the analysis of permanent pacemaker implantation, 16 patients were excluded, ten patients because of preprocedural pacemaker implantation, five because they died before the required observation period for possible pacemaker indication, and one because the patient needed a pacemaker implantation due to a sick sinus syndrome, which was not related to TAVI and was discovered in the observation period after TAVI. After the TAVI procedure, 23 patients (21.9%) required pacemaker implantation, most commonly due to total atrioventricular block (N=21; 91.3%). Forty-seven patients developed a new left bundle branch block after the TAVI procedure, which was temporary in 19%. Significant predictors of pacemaker requirement were mitral annular calcification and pre-existing right bundle branch block, while prosthesis size and prosthesis depth were significant predictors of new left bundle branch block.

In another series reporting on predictors of cardiac conduction abnormalities after CoreValve implantation, Kim et al (2015) reported on 117 patients without preexisting permanent pacemakers who underwent CoreValve placement, of whom 12 (19.7%) required a pacemaker postimplantation. In multivariable analysis, the strongest predictors of pacemaker requirement were the perimeter stretching index (OR=1.548; 95% CI, 1.239 to 1.935; p<0.001) and the device depth (OR=1.262; 95% CI, 1.034 to 1.543, p=0.02).

Section Summary: Adverse Events and Complications Following TAVI

In addition to complication rates that are reported in randomized and nonrandomized studies evaluating outcomes after TAVI, two meta-analyses and a number of cohort studies have

reported specifically on complications after TAVI, particularly vascular access complications, AKI, and need for permanent pacemaker. Given the high requirements for new permanent pacemakers after TAVI, particularly with the CoreValve, studies have focused on predictors of new conduction abnormalities, identifying the use of a CoreValve device (versus the Edwards SAPIEN device), insertion depth, and pre-existing right bundle branch block as significant predictors of pacemaker requirement.

Summary of Evidence

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

For individuals who have severe symptomatic aortic stenosis who are at high risk for open surgery who receive TAVI, the evidence includes 2 RCTs comparing TAVI with surgical repair in individuals at high risk for surgery, multiple nonrandomized comparative studies and systematic reviews of these studies. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related mortality and morbidity. For patients who are high risk for open surgery, but are operable candidates, the PARTNER A trial reported non-inferiority for survival at one year for the balloon-expandable valve compared to open surgery. In this trial, TAVI patients also had higher risks for stroke and vascular complications. Nonrandomized comparative studies of TAVI versus open surgery in high-risk patients have reported no major differences in mortality or in rates of stroke between the two procedures. Since the publication of the PARTNER A trial, the CoreValve High Risk study demonstrated noninferiority for survival at one and two years for the self-expanding prosthesis. This study reported no significant differences in stroke rates between the groups. In an RCT directly comparing the self-expandable to the balloon-expandable valve among surgically high-risk patients, the devices had similar 30-day mortality outcomes, although the self-expandable valve was associated with higher rates of residual aortic regurgitation and requirement for a new permanent pacemaker. Evidence from this and nonrandomized studies suggest that TAVI with a self-expanding device is associated with higher rates of requirements for permanent pacemakers postprocedure. However, survival rates appear to be similar between device types, and the evidence does not clearly support the superiority of 1 device over another in all patients. Two sex-specific studies were also identified

in a literature search with the objective of observing mortality rates in women undergoing TAVI or SAVR. Results were varied, and further study is needed. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have severe symptomatic aortic stenosis who are at intermediate risk for open surgery who receive TAVI, the evidence includes 3 RCTs comparing TAVI with surgical repair including individuals at intermediate surgical risk, two RCTs only in patients with intermediate risk, and multiple systematic reviews and nonrandomized cohort studies. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related mortality and morbidity. Five RCTs have evaluated TAVI in patients with intermediate risk for open surgery. Three of them, which included over 4000 patients combined, reported noninferiority of TAVI vs SAVR for the composite outcome measures (generally including death and stroke). A subset analysis of patients (n=383) with low and intermediate surgical risk from a fourth trial reported higher rates of death at 2 years for TAVI vs SAVR. The final study (N=70) had an unclear hypothesis and reported 30-day mortality rates favoring SAVR (15% vs 2%, p=0.07) but used a transthoracic approach. The rates of adverse events differed between groups, with bleeding, cardiogenic shock, and acute kidney injury higher in patients randomized to open surgery and permanent pacemaker requirement higher in patients randomized to TAVI. Subgroup analyses of meta-analyses and the transthoracic arm of the Leon et al RCT has suggested that the benefit of TAVI may be limited to patients who are candidates for transfemoral access. Although several RCTs have 2 years of follow-up postprocedure, it is uncertain how many individuals require reoperation. The evidence is sufficient to determine that the technology results in a meaningful improvement in net health outcomes.

For individuals who have severe symptomatic aortic stenosis who are at low risk for open surgery who receive TAVI, the evidence includes two RCTs comparing TAVI with surgical repair in individuals selected without specific surgical risk criteria but including patients at low surgical risk, systematic reviews, and nonrandomized cohort studies. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related mortality and morbidity. Limited data are available comparing SAVR with TAVI in patients who had severe aortic stenosis with low risk for open surgery. A systematic review including the low surgical risk patients of these 2 RCTs, and 4 observational studies, with propensity score matching, reported that the 30-day and in-hospital mortality rates were similar for TAVI (2.2%) and SAVR (2.6%). However, TAVI was associated with increased risk of mortality with longer follow-up (median, 2 years; 17.2% vs 12.7%). TAVI was associated with reduced risk for bleeding, renal failure and, an increase in vascular complications and pacemaker implantation compared with SAVR. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have valve dysfunction and aortic stenosis or regurgitation after aortic valve replacement who receive transcatheter aortic “valve-in-valve” replacement, the evidence includes case series (largest included 459 patients) and systematic reviews of the available case series. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related mortality and morbidity. These case series report high rates of technical success of valve implantation, and improvement in heart-failure symptoms for most patients. However, the studies also reported high rates of short-term complications and high rates of mortality at 1 year postprocedure. Clinical input obtained in 2016 supported the use of transcatheter aortic “valve-

in-valve" replacement for individuals who have degeneration of a surgically implanted aortic valve and who are at high or prohibitive risk for open repair.

Practice Guideline and Position Statements

American Heart Association and American College of Cardiology

In 2014, the American Heart Association and the American College of Cardiology published guidelines for the management of valvular heart disease. Both groups issued a joint focused update in 2017. These guidelines make the following recommendations regarding the choice of surgical or transcatheter intervention for treatment of aortic stenosis:

- Class I recommendations:
  - Surgical AVR [aortic valve replacement] is recommended in patients who meet an indication for AVR with low or intermediate surgical risk (Level of Evidence: A).
  - For patients in whom TAVR [transcatheter aortic valve replacement] or high-risk surgical AVR is being considered, members of a Heart Valve Team should collaborate to provide optimal patient care (Level of Evidence: C).
  - TAVR is recommended for symptomatic patients with severe AS and high risk for SAVR, depending on patient-specific procedural risks, values and preferences.
  - TAVR is recommended for symptomatic patients with severe AS, a prohibitive risk for SAVR and a predicted post-TAVR survival >12 mo (Level of Evidence: A).
- Class IIa recommendations:
  - TAVR is a reasonable alternative to SAVR for symptomatic patients with severe AS and intermediate surgical risk, depending on patient-specific procedural risks, values and preferences" (Level of Evidence B)
  - For severely symptomatic patients with bioprosthetic stenosis or regurgitation at high or prohibitive risk for reoperation, and in whom improvement in hemodynamics is anticipated, valve-in-valve TAVR is reasonable" (Level of Evidence: B).
- Class IIb recommendations:
  - Percutaneous aortic balloon dilation may be considered as a bridge to surgical or transcatheter AVR in severely symptomatic patients with severe AS (Level of Evidence: C).
- Class III recommendations (no benefit):
  - TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS (Level of Evidence: B).

European Society for Cardiology and European Association for Cardio-Thoracic Surgery

The European Society for Cardiology and the European Association for Cardio-Thoracic Surgery (2017) published joint guidelines on the management of valvular heart disease. These guidelines made the following recommendations on the use of TAVI.

- Class I recommendations:
    - TAVI is recommended in patients who are not suitable for SAVR as assessed by the Heart Team. (Level of Evidence B)
    - In patients who are at increased surgical risk (STS or EuroSCORE II ≥4% or logistic EuroSCORE I ≥10% or other risk factors not included in these scores such as frailty, porcelain aorta, sequelae of chest radiation), the decision between SAVR and TAVI should be made by the Heart Team according to the individual patient characteristics, with TAVI being favored in elderly patients suitable for transfemoral access. (Level of Evidence B)

U.S. Preventive Services Task Force Recommendations
Transcatheter aortic valve implantation is not a preventive service.

Key Words:

Transcatheter aortic valve implantation, TAVI, The Edwards SAPIEN heart-valve system™, Medtronic CoreValve ReValving System™, SAPIEN XT™, porcine bioprosthetic valve, SAPIEN™ heart-valve system, aortic valve replacement, AVR, catheter-delivered prosthetic aortic heart valve, aortic valve replacement, transcatheter aortic valve replacement, TAVR, Edwards SAPIEN™ transcatheter heart valve, valve-in-valve, Sapien 3

Approved by Governing Bodies:

Two manufacturers have transcatheter aortic valve devices with Food and Drug Administration (FDA) approval. Regulatory status data for these devices are listed in Table 6.

Table 6. FDA-approved Transcatheter Aortic Valve Device Systems

Device and Indication	Manufacturer	Date Cleared	PMA
Edwards SAPIEN Transcatheter Heart Valve System ™	Edwards Lifesciences		P100041
• Severe native aortic valve stenosis determined to be inoperable for open aortic valve replacement (transfemoral approach)		11/11	
• Expanded to include high-risk aortic stenosis (transapical approach)		10/12	
• Expanded to include replacement of bioprosthetic valve in high risk for death or severe complications of repeat surgery		06/17	
• Expanded to include severe aortic stenosis with intermediate surgical risk		08/16	
Edwards SAPIEN XT Transcatheter Heart Valve (model 9300TFX) and accessories			P130009
• Severe native aortic valve stenosis at high or greater risk for open		07/14	

surgical therapy			
• Expanded to include failure of bioprosthetic valve in high or greater risk for open surgical therapy		10/15	P130009/S034
• Expanded to include severe aortic stenosis with intermediate surgical risk		08/16	
Medtronic CoreValve System™			P130021
• Severe native aortic stenosis at extreme risk or inoperable for open surgical therapy		01/14	
• Expanded to include high risk for open surgical therapy		06/16	P130021/S002
• Expanded to include intermediate risk for open surgical therapy		07/17	P130021/S033
Medtroinc CoreValve Evolut R System™	Medtronic CoreValve		P130021/S014
• Design iteration for valve and accessories		06/15	
• Expanded to include intermediate risk for open surgical therapy		07/17	P130021/S033
Medtronic CoreValve Evolut PRO System™			P130021/S029
• Design iteration for valve and accessories		03/17	
• Expanded to include intermediate risk for open surgical therapy		07/17	P130021/S033

FDA: Food and Drug Administration; PMA: postmarket approval

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

- Lotus™ Aortic Valve Replacement System (Boston Scientific, Marlborough, MA)
- Portico™ Transcatheter Aortic Valve (St. Jude Medical, St. Paul, MN)
- JenaValve™ (JenaValve Technology, Munich); designed for transapical placement

Several embolic protection devices, which are designed to collect embolic debris distal to the transcatheter aortic valve implantation apparatus and to prevent ischemic stroke, are under investigation. No devices have FDA approval for use in the United States. Examples include the TriGuard (Keystone Heart) and the Sentinel Cerebral Protection System (Claret Medical).

Benefit Application:

Coverage is subject to member's specific benefits. Group specific policy will supersede this policy when applicable.
ITS: Home Policy provisions apply.
FEP: Special benefit consideration may apply. Refer to member's benefit plan. FEP does not consider investigational if FDA approved and will be reviewed for medical necessity.

Current Coding:

CPT Codes:

33361	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach **(Effective 01/01/2013)**
33362	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open femoral artery approach **(Effective 01/01/2013)**
33363	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open axillary artery approach.
33364	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open iliac artery approach **(Effective 01/01/2013)**
33365	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transaortic approach (e.g., median sternotomy, mediastinotomy) **(Effective 01/01/2013)**
33366	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transapical exposure (e.g., left thoracotomy) **(Effective 01/01/2014)**
33367	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with percutaneous peripheral arterial and venous cannulation (e.g., femoral vessels) (List separately in addition to code for primary procedure) **(Effective 01/01/2013)**
33368	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with open peripheral arterial and venous cannulation (e.g., femoral, iliac, axillary vessels) (List separately in addition to code for primary procedure) **(Effective 01/01/2013)**
33369	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with central arterial and venous cannulation (e.g., aorta, right atrium, pulmonary artery) (List separately in addition to code for primary procedure) **(Effective 01/01/2013)**

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Policy History:

Medical Policy Group, September 2011**(2):** New policy
Medical Policy Administration Committee, September 2011
Available for comment September 22 through November 7, 2011
Medical Policy Panel, December 2011
Medical Policy Group, January 2012 **(2):** Policy, Key Points, Governing Bodies, References updated, Key Words
Medical Policy Administration Committee, January 2012
Available for comment January 30 – March 14, 2012
Medical Policy Group, November 2012: 2013 Coding Updates – Added Codes 33361, 33362, 33364, 33365, 33367, 33368, 33369; deleted 0256T, 0257T, 0258T, 0259T; verbiage change 0318T: all effective 1/1/2013
Medical Policy Panel, December 2012
Medical Policy Group, March **(2):** Coverage indications added for patients who are at high risk for open surgery using the transfemoral approach, and patients who are at high risk for open surgery using the transapical approach. Investigational statement added for treatment of degenerated bio-prosthetic valve or failed TAVI (Valve-in-Valve approach), and for vascular approaches other than transfemoral or transapical. Key Points and References updated to support references. Approved Governing Bodies updated with information on the Edwards SAPIEN™ transcatheter heart valve. Key words updated.
Medical Policy Administration Committee, April 2013
Available for comment April 18 through June 5, 2013
Medical Policy Group, December 2013 **(3):** 2014 Coding Update – added code 33366 to current coding (effective 1/1/14); moved code 0318T to previous coding (deleted effective 01/01/2014)
Medical Policy Panel, October 2014
Medical Policy Group, October 2014 **(3):** 2014 Updates to Description, Key Points, Governing Bodies & References; Policy section updated to expand coverage statement to include "Transcatheter aortic valve replacement with an FDA-approved transcatheter heart valve system, performed via an approach consistent with the device's FDA-approved labeling"
Medical Policy Administration Committee, November 2014
Available for comment October 24 through December 4, 2014
Medical Policy Group April 2015 **(4)**: Update to Approved Governing Bodies, Key Words and References. Added FDA approved use of CoreValve for valve-in-valve replacements. No change to policy statement.
Medical Policy Group, June 2015 **(4)**: Updates to Approved by Governing Bodies, Key Words, and References. No change to policy statement.
Medical Policy Panel, August 2016
Medical Policy Group, August 2016 **(4)**: Updates to Description, Key Points, Approved Governing Bodies, Coding and References. From policy section, removed "Effective for dates of service January 1, 2012 through June 5, 2013" and Effective for dates of service prior to January

1, 2012". Also in the Policy section, valve in valve procedures updated to meet medical criteria for coverage with certain criteria.
Medical Policy Administration Committee, September 2016
Available for comment August 30 through October 14, 2016
Medical Policy Group, December 2016: 2017 Annual Coding Update. Added new cpt codes 93591 and 93592 to Current Coding.
Medical Policy Panel, February 2017
Medical Policy Group, March 2017 **(4):** Updates to Key Points, Approved by Governing Bodies, and References. No change to policy statements. Removed CPT codes 93591 and 93592, codes do not apply to this policy.
Medical Policy Panel, April 2018
Medical Policy Group, May 2018 **(4):** Updates to Description, Policy, Key Points, Approved by Governing Bodies, Coding and References. Updated policy statement to allow coverage for patients who are intermediate risk for open surgery. Removed policy statements for dates of service June 6, 2013 through October 8, 2014. Removed Previous coding section (codes 0256T – 0259T, and 0318T). CPT codes were deleted in 2013.
Medical Policy Administrative Committee: May 2018
Available for comment May 3 through June 17, 2018
