Transcatheter Aortic Valve Implantation for Aortic Stenosis

Policy # 00406
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Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services May Be Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider transcatheter aortic valve replacement (TAVR) with an FDA-approved transcatheter heart valve system, performed via an approach consistent with the device’s FDA-approved labeling, for patients with native valve aortic stenosis to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility will be met for transcatheter aortic valve replacement (TAVR), with an FDA-approved transcatheter heart valve system, performed via an approach consistent with the device’s FDA-approved labeling for patients with native valve aortic stenosis when all of the following conditions are present:

- Severe aortic stenosis with a calcified aortic annulus; AND
- New York Heart Association (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 two cardiovascular specialists (cardiologist and/or cardiac surgeon); or patient is an operable candidate but is at high risk for open surgery.

Based on review of available data, the Company may consider transcatheter aortic valve replacement (TAVR) with a transcatheter heart valve system approved for use for repair of a degenerated bioprosthetic valve to be eligible for coverage.

Patient Selection Criteria
Coverage eligibility will be met for transcatheter aortic valve replacement (TAVR) with a transcatheter heart valve system approved for use for repair of a degenerated bioprosthetic valve when all of the following are present:

- Failure (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 (see Policy Guidelines section).

Note: FDA definition of high risk for open surgery:
- Society of Thoracic Surgeons predicted operative risk score of 8% or higher; or
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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% or higher 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.

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

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers transcatheter aortic valve replacement (TAVR) to be investigational for all other indications.

The use of transcatheter aortic valve replacement (TAVR) when patient selection criteria are not met is considered investigational.*

Background/Overview
Transcatheter aortic valve implantation (also known as transcatheter aortic valve replacement) is a potential treatment for patients with severe aortic stenosis. 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 for high-risk patients with aortic stenosis and as an alternative to nonsurgical therapy for patients with a prohibitive risk for surgery.

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

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

Burden of Illness
Aortic stenosis 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 people older than 65 years of age have evidence of significant aortic stenosis, increasing up to 8% of people by age 85 years. In the Helsinki Aging Study, a population-based study of 501 patients aged 75 to 86 years, the prevalence of severe aortic stenosis by echocardiography was estimated to be 2.9%. In the United States, more than 50,000 aortic valve replacements are performed annually due to severe aortic stenosis.

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

Unmet Needs
Many patients with severe, symptomatic aortic stenosis are poor operative candidates. Approximately 30% of patients presenting with severe aortic stenosis do not undergo open surgery due to factors such as advanced age, advanced left ventricular dysfunction, or multiple medical comorbidities. For patients who are not surgical candidates, medical therapy can partially alleviate the symptoms of aortic stenosis but does not affect the underlying disease progression. Percutaneous balloon valvuloplasty can be performed, but this procedure has less than optimal outcomes. 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 aortic stenosis in patients who are at increased risk for open surgery.

Transcatheater Aortic Valve Implantation
Transcatheter aortic valve implantation has been developed in response to this unmet need and is 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 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.
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Two transcatheter aortic valve devices have Food and Drug Administration (FDA) approval. The Edwards SAPIEN Transcatheter Heart Valve System is a tri-leaflet bioprosthetic porcine valve contained within a stainless steel frame. This device first received FDA approval in 2011, with expanded indications granted in 2012 and 2013.

The CoreValve ReValving System and the second-generation Evolut R system are porcine bioprosthetic valves sewn within a self-expanding nitinol frame, which received FDA approval in 2014. The CoreValve is most commonly inserted via the transfemoral artery approach, but can also be inserted via a non-iliofemoral approach (subclavian artery or direct aortic access). The Evolut R system incorporates a repositionable valve and an in-line catheter design, reducing the diameter of the device delivery system.

Several embolic protection devices, which are designed to collect embolic debris distal to the TAVI 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, Caesarea, Israel) and the Sentinel Cerebral Protection System (Claret Medical, Santa Rosa, CA).

FDA or Other Governmental Regulatory Approval
U.S. Food and Drug Administration (FDA)
In November 2011, the SAPIEN Transcatheter Heart Valve System™‡ (Edwards LifeSciences, Irvine, CA) was originally approved by the U.S. FDA through the premarket approval process for patients with severe aortic stenosis who are not eligible for open-heart procedures and have a calcified aortic annulus. Approval was granted for both the transfemoral and transapical approach. For the transfemoral approach, patient indications were broadened to include patients at high risk for open surgery. For the transapical approach, approval was granted for patients at high risk for open surgery. In September 2012, FDA expanded the indications for the transapical approach to include both inoperable patients and patients at high risk for open surgery. As a result, the SAPIEN Transcatheter Heart Valve System is approved for both high-risk and inoperable patients when used either by the transapical or transfemoral approach. In June 2014, the next-generation SAPIEN XT Transcatheter Heart Valve (model 9300TFX) was approved by FDA for use with the NovaFlex+ delivery system. In October 2015, FDA expanded the indication for the SAPIEN valve to include treatment of a failed surgical bioprosthesis (TAV-in-SAV or “valve-in-valve”).

In August 2016, the SAPIEN XT valve and introducers were approved with an expanded indication to include individuals at intermediate surgical risk for open aortic valve replacement (ie, predicted risk of surgical mortality ≥3% at 30 days based on the Society of Thoracic Surgeons [STS] Risk Score and other clinical comorbidities unmeasured by the STS Risk Calculator). The earlier generation Sapien devices also received the expanded indication for intermediate surgical risk patients.

In January 2014, the CoreValve™‡ Transcatheter Aortic Valve Replacement System (Medtronic, Minneapolis, MN) was approved by FDA through the premarket approval process for patients with symptomatic heart disease due to severe native calcific aortic stenosis and with native aortic annulus diameters between 18 and 29 mm who are judged by a heart team, including a cardiac surgeon, to be at extreme risk or inoperable for open surgical therapy.10 In June 2014, FDA expanded the indications for the CoreValve to include patients at high risk for open surgery. FDA labeling indicates that the device can be
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delivered via femoral, subclavian/axillary, or ascending aortic access. In March 2015, FDA further expanded the indications for the CoreValve to include treatment of a failed surgical bioprosthesis (TAV-in-SAV or “valve-in-valve”). A second-generation CoreValve device, the CoreValve Evolut R System, received FDA approval in June 2015.

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
- Direct Flow Medical Transcatheter Aortic Valve System (Direct Flow Medical, Santa Rosa, CA).

Centers for Medicare and Medicaid Services (CMS)
The Centers for Medicare and Medicaid Services (CMS) published a decision memo on the use of TAVR in May 2012. This memo indicated that CMS covers TAVI when used according to FDA indications when the following conditions are met:
- Device has FDA approval
- Two cardiac surgeons agree with indications for the procedure
- The patient is “under the care of a heart team” and the hospital meets qualifications for performing TAVR.

The memo also stated that TAVR could be covered for non-FDA-approved indications under the Coverage with Evidence Development (CED) program. The following is a summary of the main conditions required for CED:
- TAVI is performed within a clinical study that has the following characteristics:
- “The clinical study must adhere to the … standards of scientific integrity and relevance to the Medicare population.”
- The study must address quality of life and adverse events at follow-up periods of 1 year or longer.

Rationale/Source
The evidence on TAVI consists of many uncontrolled case series, 2 pivotal randomized controlled trials (RCTs), the PARTNER trial and the CoreValve High Risk Study, and an RCT directly comparing the CoreValve and the SAPIEN devices. These studies report on 2 potential populations for TAVI: (1) patients who are not surgical candidates and (2) patients who are high risk for surgery but still considered to be surgical candidates. The evidence on these 2 groups of patients will be discussed separately.

Outcomes for TAVI in Patients Who are 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
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 10 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 11 studies that treated severe aortic stenosis with nonsurgical therapy. The procedural success in these studies ranged from 86% to 100%, and the 30-day mortality ranged from 5.3 to 23%. The combined mean survival rate at 1 year was 75.9% (confidence interval [CI], 73.3 to 78.4). This 1-year survival rate compared favorably with medical therapy, which was estimated to be 62.4% (95% CI, 59.3 to 65.5).

Randomized Controlled Trials

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 the PARTNER 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 2 surgeon investigators using clinical judgment and the Society of Thoracic Surgery (STS) risk score. The executive committee of the PARTNER trial reviewed all patient selection decisions and approved the classification of patients as unsuitable for surgery. A total of 3105 patients were screened for aortic valve surgery, and 12% of 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 “coprimary” 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 6-minute walk test, valve performance as measured by echocardiography, and procedural complications (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),
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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 1 year after enrollment was lower for the TAVI group (30.7% vs 49.7%, p<0.001). This represents a 19% absolute risk reduction, a 38.2% relative risk reduction, and a number needed to treat of 5.3 to prevent 1 death over a 1-year follow-up. Most secondary outcomes also favored the TAVI group. Cardiovascular death was lower in the TAVI group (19.6% vs 44.1%, p<0.001). The composite of all-cause mortality and repeat hospitalizations was reached by 42.5% of the patients in the TAVI group compared with 70.4% in the standard therapy group. Symptoms and functional status were also superior in the TAVI group. The percent of patients in NYHA class I or II at 1 year was higher for the TAVI group (74.8% vs 42.0%, p<0.001), and there was a significant improvement in the 6-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 1 year was more than twice as frequent for the TAVI group (10.6% vs 4.5%, p=0.04). Major bleeding and vascular complications occurred in a substantial 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, 6 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 6 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 in 2012. Mortality at 2 years was 43.3% in the TAVI group compared with 68.0% in the medical therapy group (hazard ratio [HR], 0.58; 95% CI, 0.36 to 0.92; p=0.02). Cardiovascular mortality was also lower in the TAVI group compared with medical therapy (31.0% vs 62.4%, p<0.001). The rate of hospitalization over the 2-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 prolonged beyond 6 months. Compared with standard therapy, the estimated net lifetime benefit added by transfemoral TAVI was 0.50 years (90% CI, 0.30 to 0.67).
In 2014, Kapadia et al reported on 3-year outcomes for prohibitive-risk patients (N=358) randomized to standard therapy or TAVI in the PARTNER trial, 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 (15.7%) than in the standard therapy group at 3 years (5.5%; HR=3.81; 95% CI, 1.26 to 6.26; p=0.012). However, at 3 years, the incidence of the composite of death or stroke was significantly lower in the TAVI group (57.4% vs 80.9%; HR=0.60; 95% CI, 0.46 to 0.77; p<0.001). Survivors at 3 years who had undergone TAVI were more likely to have NYHA class I or II symptoms than those who had received standard therapy. In the pooled sample, at the 2- and 3-year follow-ups, mortality was lower for patients who had undergone TAVI than in those who had standard therapy (2 years: 44.8% vs 64.3%; 3 years: 54.9% vs 78.0%; all p<0.001).

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/Cohort Studies
Many case series of TAVI have been published in the last 10 years, most 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 from the reported studies. Some of the larger and/or prospective case series are discussed next. Included are the series that have reported on the pivotal trials leading to devices approvals (ie, Popma et al [2014] and Reardon et al [2014]) or on postapproval registries (ie, Mack et al [2013]). In addition, series that discuss the longer term durability of the TAVI devices are included.

CoreValve Extreme Risk Pivotal Trial
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 2 cardiac surgeons and 1 interventional cardiologist at the clinical site estimated a 50% or greater risk for mortality or irreversible morbidity at 30 days with surgical repair. The study’s primary 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
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based on 2 sources: a weighted meta-analysis of 7 balloon aortic valvuloplasty studies, which yielded a rate of 12-month all-cause mortality or major stroke of 42.7% (95% CI, 34.0% to 51.4%). This estimate was adjusted based on the lower 95% confidence bound of 43% in the standard therapy arm of inoperable patients in the PARTNER trial.

Four hundred eighty-nine patients were included in the attempted implant analysis population of 506 patients recruited (11 of whom exited the study prior to treatment, 6 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 1 year following enrollment was 24.3%, while the rate of major stroke at 12 months was 4.3%. These rates are comparable or better than those seen in the TAVI arm of the PARTNER pivotal trial, although patients in the PARTNER pivotal trial had a higher baseline STS score (12.1% in the PARTNER trial vs 10.3% in the CoreValve Extreme Risk trial).

Two-year results from the CoreValve Extreme Risk Pivotal Trial were reported by Yakubov et al in 2015.25 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 years 1 and 2 were 12.3% for all-cause mortality, 7.9% for cardiovascular mortality, and 0.8% for stroke.

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 QOL scores both showed substantial improvements after TAVI. However, 39% of patients had a poor outcome at 6 months (22% death, 16% very poor QOL, 1.4% QOL declined).

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 postprocedure, 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).

Postapproval 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 nontransfemoral access. In-hospital mortality was 5.4% and 7.1% for the inoperable patients who underwent TAVI via transfemoral and nontransfemoral access, respectively. Thirty-day clinical outcomes were reported for 694 inoperable patients; of those, 30-day mortality was 6.7% and 12.6% for patients who underwent TAVI via transfemoral and nontransfemoral access, respectively.

**Additional Case Series**

The prospective nonrandomized ADVANCE study had central adjudication of end points and adverse events to evaluate the CoreValve implants in individuals with severe symptomatic aortic stenosis who were considered inoperable or at higher risk for surgical AVR. 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; a composite of all-cause mortality, MI, stroke, or reintervention), rates were 8.0% (95% CI, 6.3% to 9.7%) at 30 days and 21.2% (95% CI, 18.4% to 24.1%) at 12 months. The all-cause mortality rate was 4.5% (95% CI, 3.2% to 5.8%) at 30 days and 17.9% (95% CI, 15.2% to 20.5%) at 12 months. Overall, strokes occurred in 3.0% (95% CI, 2.0% to 4.1%) at 30 days and in 4.5% (95% CI, 2.9% to 6.1%) at 12 months. A new permanent pacemaker was implanted in 26.3% (95% CI, 23.5% to 29.1%) and in 29.2% (95% CI, 25.6% to 32.7%) at 30 days and 12 months of follow-up, respectively. Patients were grouped into 3 categories of surgical risk based on logistic EuroSCORE values (<10%, >10% but ≤20%, and >20%). Thirty-day survival did not differ significantly across risk groups, but 12-month rates of MACCE, all-cause mortality, cardiovascular mortality, and death from any cause or major stroke were higher for higher surgical risk patients.

The 2 largest series included in the AHRQ review 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 was notable in that it used more objective patient selection criteria than is common in this literature. Their criteria for eligibility included the following: (1) logistic EuroSCORE of 15% or higher, (2) age of 75 or older, or (3) age of 65 or older with liver cirrhosis, pulmonary insufficiency, pulmonary hypertension, previous cardiac surgery, porcelain aorta, recurrent pulmonary emboli, right ventricular insufficiency, previous chest burns or radiation precluding open surgery, or body mass index of 18 kg/m² or less. Procedural success was 97% and 30-day survival was 92%. The 30-day combined rate of death, MI, or stroke was 9.3%. The study by Rodes-Cabou et al was performed in Canada and used Edwards SAPIEN valve. This study had subjective inclusion criteria, relying on the judgment of the participating surgeons to determine eligibility for TAVI. The procedural success rate was 93.3%, and the 30-day mortality was 10.4%. The authors also reported a mortality rate of 22.1% at a median follow-up of 8 months.

Additional series have described experiences with TAVI in European centers. In the largest series identified, with up to 6 years of follow-up, Ludman et al reported on 3980 TAVI procedures in the United Kingdom, using data from a national registry linked to National Health Service outcomes. One-, 2-, 5-, and 6-year survival rates were 81.7%, 72.8%, 46.9%, and 37.3%, respectively. Zahn et al, in a large case series from Germany, reported on 697 patients treated with the CoreValve system. Procedural success was 98.4%, and
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30-day mortality was 12.4%. Another large case series from Italy included 663 patients treated with the CoreValve device. Procedural success was 98%, and mortality at 1 year was 15%.

Section Summary
Numerous case series have demonstrated the feasibility and short-term efficacy for TAVI in patients who are not surgical candidates. In the PARTNER B trial, there was a large decrease in all-cause mortality and cardiovascular mortality at 1 year for TAVI compared with standard therapy. Subsequent publications from this same trial reported that the mortality benefit was maintained at 2 years and that QOL was improved for the TAVI group. Baseline 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 overestimation of the mortality benefit.

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.

Outcomes for TAVI in Patients Who Are at High Risk for Open Surgery

Systematic Reviews

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 (from Villablanca et al, 2016)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>TAVI (RR for TAVI vs Surgical Repair (95% CI))</th>
<th>Surgical Repair (RR for TAVI vs Surgical Repair (95% CI))</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day postprocedure mortality</td>
<td>508/8552 (5.9%) (41.1%)</td>
<td>804/29323 (2.7%) (18.6%)</td>
<td>1.02 (0.76 to 1.36) (0.64 to 1.29)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>3625/8803 (4.1%)</td>
<td>5438/29,450 (18.6%)</td>
<td>1.16 (0.87 to 1.53)</td>
</tr>
<tr>
<td>Stroke incidence</td>
<td>191/4293 (4.4%)</td>
<td>213/4348 (4.9%)</td>
<td>0.79 (0.66 to 0.95)</td>
</tr>
<tr>
<td>Myocardial infarction incidence</td>
<td>57/2820 (2.0%)</td>
<td>59/2746 (2.1%)</td>
<td>0.91 (0.64 to 1.29)</td>
</tr>
<tr>
<td>Vascular complication incidence</td>
<td>203/2489 (8.2%)</td>
<td>35/2682 (1.3%)</td>
<td>5.5 (2.42 to 12.4)</td>
</tr>
</tbody>
</table>
Residual regurgitation incidence

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>TAVI</th>
<th>Surgical Repair</th>
<th>RR for TAVI vs Surgical Repair (95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requirement for permanent pacemaker incidence</td>
<td>527/3449 (15.3%)</td>
<td>236/3653 (6.4%)</td>
<td>1.68 (0.94 to 3.00)</td>
<td>83.2%</td>
</tr>
<tr>
<td>New-onset AF incidence</td>
<td>165/1192 (13.8%)</td>
<td>376/1281 (29.4%)</td>
<td>0.38 (0.26 to 0.55)</td>
<td>64.6%</td>
</tr>
<tr>
<td>Major bleeding incidence</td>
<td>321/2074 (15.4%)</td>
<td>416/2298 (18.1%)</td>
<td>0.73 (0.65 to 0.83)</td>
<td>24.2%</td>
</tr>
<tr>
<td>Acute kidney injury incidence</td>
<td>294/3446 (8.5%)</td>
<td>396/3528 (11.2%)</td>
<td>0.73 (0.53 to 1.01)</td>
<td>68.4%</td>
</tr>
</tbody>
</table>

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

Randomized Controlled Trials

**PARTNER A Trial**

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

A total of 699 patients were randomized to TAVI or surgical aortic valve repair. The primary hypothesis was that TAVI was noninferior to open AVR, using a 1-sided noninferiority boundary of 7.5% absolute difference in mortality at 1 year. Patients were first evaluated to determine if they were eligible for TAVI via the transfemoral approach. Four hundred ninety-two patients were eligible for transfemoral TAVI; the remaining
207 were categorized as the transapical placement cohort. Within each cohort (transfemoral and transapical), patients were randomized to surgical aortic valve repair (n=351) or TAVI (n=348).

The primary outcome was death from any cause at 1-year follow-up. A second powered end point was noninferiority at 1 year for patients undergoing TAVI by the transfemoral approach. Secondary end points were cardiovascular mortality, NYHA functional class, rehospitalizations, 6MWT, valve performance as measured by echocardiography, and procedural complications (MI, stroke, AKI, vascular complications, bleeding). Mean age of enrolled patients was 83.6 years in the TAVI group and 84.5 years in the open AVR group. Other baseline demographics and clinical characteristics were generally well-balanced, except for a trend toward an increased percentage of patients in the TAVI group with a creatinine level greater than 2.0 (11.1% vs 7.0%, p=0.06).

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

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

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

Reynolds et al 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
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significant improvements in all QOL measures over the 12 months following treatment. The TAVI group had superior improvement at 1 month on the KCCQ (mean difference, 9.9; 95% CI, 4.9 to 14.9; p<0.001), but this difference was no longer present at 6 or 12 months. A similar pattern of results was reported for the SF-12 and EQ-5D measures.

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

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

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

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

Nonrandomized Comparative Studies
Since publication of the pivotal RCTs and systematic reviews described previously, a number of nonrandomized studies (all published in 2015) have compared surgical and transcatheter aortic valve repair. Given the availability of RCT evidence, these studies provide limited additional information on the efficacy of TAVI.
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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 2 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 1 year and most major secondary outcomes. The noninferiority boundaries for this trial included an upper limit of 7.5% absolute increase in mortality, but, in actually, the reported mortality for the TAVI group was lower than that for the open group, although not significantly better. QOL was also similar at 1 year between the TAVI and AVR groups. Stroke and TIA were significantly more common for the TAVI group, occurring at a rate of almost 2 times that reported for open surgery. Other secondary outcomes were similar between groups, except for higher rates of vascular complications in the TAVI group and higher rates of major bleeding in the open surgery group. As in the first PARTNER cohort, there is concern about the generalizability of results because the patient selection process relied largely on the judgment of surgeons and cardiologists participating in the trial. The U.S. CoreValve High Risk Study reported that TAVI was noninferior to open surgical repair. Although, unlike the PARTNER A RCT, stroke rates were not higher in patients who underwent TAVI, a requirement for permanent pacemaker was more common in the TAVI group.

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 with at least a high risk of surgery. Two RCTs identified have evaluated the use of TAVI in patients not at high risk of open surgery.

Systematic Reviews

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 2.

Table 2: TAVI vs Surgical Repair in Low- or Intermediate-Risk Patients (from Zhou et al, 2016)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>TAVI</th>
<th>Surgical Repair</th>
<th>OR for TAVI vs Surgical Repair (95% CI)</th>
<th>p</th>
<th>f</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term postprocedure mortality</td>
<td>2.59%</td>
<td>3.94%</td>
<td>0.63 (0.37 to 1.08)</td>
<td>0.09</td>
<td>56%</td>
</tr>
<tr>
<td>Short-term cardiovascular mortality</td>
<td>1.96%</td>
<td>3.15%</td>
<td>0.51 (0.23 to 1.15)</td>
<td>0.11</td>
<td>68%</td>
</tr>
<tr>
<td>Acute kidney injury incidence</td>
<td>1.92%</td>
<td>4.6%</td>
<td>0.34 (0.17 to 0.67)</td>
<td>0.002</td>
<td>61%</td>
</tr>
<tr>
<td>Stroke incidence</td>
<td>3.57%</td>
<td>4.30%</td>
<td>0.72 (0.56 to 0.92)</td>
<td>0.01</td>
<td>42%</td>
</tr>
<tr>
<td>Myocardial infarction incidence</td>
<td>0.7%</td>
<td>1.7%</td>
<td>0.51 (0.23 to 0.69)</td>
<td>&lt;0.001</td>
<td>10%</td>
</tr>
<tr>
<td>Major vascular complication incidence</td>
<td>7.2%</td>
<td>3.6%</td>
<td>3.54 (1.42 to 8.81)</td>
<td>0.006</td>
<td>86%</td>
</tr>
<tr>
<td>Requirement for permanent pacemaker incidence</td>
<td>11.9%</td>
<td>6.1%</td>
<td>2.79 (1.49 to 5.23)</td>
<td>0.001</td>
<td>88%</td>
</tr>
<tr>
<td>All-cause mortality (1 year)</td>
<td>10.1%</td>
<td>12.2%</td>
<td>0.82 (0.58 to 1.16)</td>
<td>0.26</td>
<td>67%</td>
</tr>
</tbody>
</table>

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

In 2016, Siemieniuk et al reported on a systematic review and meta-analysis comparing TAVI with surgical repair in patients at low or intermediate risk of open surgery, with the aim of evaluating valve durability and...
need for reinterventions. Inclusion criteria were RCTs comparing TAVI and surgical repair in patients with severe aortic stenosis and a mean STS Risk Score of 8% or less. Reviewers identified 4 RCTs (Leon et al [2016], Adams et al [2014], NOTION [2015], STACCATO [2012]) and data published in 5 secondary reports. The longest follow-up was 36 months in the US CoreValve High Risk Study pivotal trial. Transfemoral, but not transapical, TAVI outcomes tended to favor TAVI in terms of mortality and incidence of stroke and AKI. However, patients in the TAVI group were more likely to require reinterventions at latest follow-up (HR=3.25; 95% CI, 1.29 to 8.14; I²=0%).

In 2016, Kondur et al reported on a meta-analysis comparing TAVI with surgical repair in patients at low or intermediate risk of open surgery. A total of 5 studies were included, 3 RCTs (NOTION, STACCATO [described below], Reardon et al (2015) [described above]), and 2 prospective observational cohort studies (from the multicenter OBSERVANT and SURTAVI registries, reported by Tamburino et al [2015] and Piazza et al [2013], respectively). The studies included a total of 3199 participants (1618 [50.6%] treated with TAVI), with a mean follow-up of 1.05 years. The main results of the meta-analysis are summarized in Table 3.

Table 3: TAVI vs Surgical Repair in Low- or Intermediate-Risk Patients (from Kondur et al, 2016)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>TAVI</th>
<th>Surgical Repair</th>
<th>OR for TAVI vs Surgical Repair (95% CI)</th>
<th>p</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day post-procedure mortality</td>
<td>4.3%</td>
<td>4.4%</td>
<td>0.99 (0.71 to 1.39)</td>
<td>0.97</td>
<td>1%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>15.5%</td>
<td>16.3%</td>
<td>0.92 (0.70 to 1.21)</td>
<td>0.55</td>
<td>37%</td>
</tr>
<tr>
<td>Stroke incidence</td>
<td>6.9%</td>
<td>7.5%</td>
<td>0.90 (0.66 to 1.23)</td>
<td>0.52</td>
<td>44%</td>
</tr>
<tr>
<td>Myocardial infarction incidence</td>
<td>2.2%</td>
<td>2.8%</td>
<td>0.78 (0.47 to 1.31)</td>
<td>0.36</td>
<td>0%</td>
</tr>
<tr>
<td>Major vascular complication incidence</td>
<td>7.0%</td>
<td>1.0%</td>
<td>7.00 (3.81 to 12.87)</td>
<td>&lt;0.001</td>
<td>60%</td>
</tr>
<tr>
<td>Moderate or severe paravalvular regurgitation incidence</td>
<td>8.4%</td>
<td>1.5%</td>
<td>6.10 (3.66 to 10.16)</td>
<td>&lt;0.001</td>
<td>0%</td>
</tr>
<tr>
<td>Requirement for permanent pacemaker incidence</td>
<td>21.6%</td>
<td>7.5%</td>
<td>4.07 (1.98 to 8.34)</td>
<td>&lt;0.001</td>
<td>77%</td>
</tr>
<tr>
<td>Major bleeding incidence</td>
<td>36.7%</td>
<td>57.4%</td>
<td>0.33 (0.25 to 0.43)</td>
<td>&lt;0.001</td>
<td>12%</td>
</tr>
<tr>
<td>Acute kidney injury incidence</td>
<td>4.6%</td>
<td>11.9%</td>
<td>0.35 (0.10 to 1.22)</td>
<td>0.10</td>
<td>40%</td>
</tr>
</tbody>
</table>

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

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

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
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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 (ie, 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 4. 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 4: RCTs Comparing TAVI and Surgical Repair in Intermediate or Unselected Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Outcome</th>
<th>Primary Outcomes</th>
<th>All-Cause Mortality (2 y)</th>
<th>New Permanent Pacemaker (2 y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leon (2016)</td>
<td>Death from any cause or disabling stroke (2 y)</td>
<td>TAVI 19.3% Surg 21.1% HR (95% CI) 0.92 (0.75 to 1.08)</td>
<td>TAVI 16.7% Surg 18.0% p 0.45 11.8% p 0.29</td>
<td>TAVI 11.8% Surg 10.9% p 0.71</td>
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<tr>
<td>Transfemoral</td>
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<td>access</td>
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<td>Transthoracic</td>
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<td>access</td>
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<tr>
<td>Thyregod (2015)</td>
<td>Death from any cause, stroke, or MI at 1 y</td>
<td>TAVI 27.7% Surg 23.4% HR (95% CI) 0.84 (0.62 to 1.00)</td>
<td>TAVI 25.2% Surg 20.7% p 0.26 13.1% p 0.13</td>
<td>TAVI 13.1% Surg 10.8% p 0.29</td>
</tr>
<tr>
<td>All patients</td>
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In 2015, Thyregod et al reported results of the NOTION RCT, which compared TAVI to surgical repair in 280 patients with severe aortic stenosis who were 70 years 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 trial 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 was considered to be at low risk (STS Risk Score <4). Some of the main findings from NOTION are summarized in Table 4.

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 AKI (0.7% vs 6.7%, p=0.01), and new onset or worsening atrial fibrillation (16.9% vs 57.8%, p<0.001) than surgical repair patients, all respectively. Both groups showed improvements in NYHA functional class. However, more TAVI-treated patients were in NYHA functional class II at 1-year follow-up (29.5% vs 15.0%, p=0.01).
A previous RCT, the STACCATO trial, was designed to compare transapical TAVI with the SAPIEN valve to 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 trial 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.

**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**

Two RCTs (1 investigator-initiated) have evaluated TAVI in patients in low or intermediate risk for open surgery, and both reported no significant differences in their composite outcome measure between groups. The rates of adverse events differed between groups, with bleeding, cardiogenic shock, and AKI higher in patients randomized to open surgery and permanent pacemaker requirement higher in patients randomized to TAVI. Subgroup analyses of meta-analyses and the transthoracic arm of the Leon et al RCT suggested that the benefit of TAVI may be limited to patients who are candidates for transfemoral access. In addition, given the limited follow-up beyond a year postprocedure, it is uncertain how many individuals require reoperation.

**LONG-TERM FOLLOW-UP**

A limited body of research is available on the durability of TAVI devices over the long term. Some longer term outcome data come from follow-up on the available RCTs, and some comes from device registry studies, particularly from Europe.

In 2016, Gilard et al reported on scheduled follow-up from the FRANCE-2 registry, a prospective registry of all TAVI procedures performed in France, which included 4201 patients enrolled between 2010 and 2012 at the time of the report. Balloon expandable devices were used in 2774 (66.0%) patients and self-expandable devices in 1413 (33.7%). At a median follow-up of 3.8 years, with clinical follow-up data available for 90.0% of patients, 3-year all-cause mortality was 42.0% (95% CI, 40.5% to 43.5%) and cardiovascular mortality was 17.5% (95% CI, 16.4% to 18.7%). Most severe events (eg, hospital readmission) occurred in the first 30 days postprocedure; 90.0% of patients surviving to 3 years were in NYHA functional class I or II.

In the largest series identified, with up to 6 years of follow-up, Ludman et al (2015) reported on 3980 TAVI procedures in the United Kingdom, using data from a national registry linked to National Health Service outcomes. One-, 2-, 5-, and 6-year survival rates were 81.7%, 72.8%, 46.9%, and 37.3%, respectively.
COMPARISSONS OF DIFFERENT TAVI DEVICES
As of 2014, there were 2 FDA-approved TAVI devices, one of which relies on a self-expanding mechanism and one which relies on a balloon-expanding mechanism. A relatively small body of evidence has addressed whether different TAVI devices are associated with different outcomes.

Systematic Reviews
In 2014, Athappan et al published results from a systematic review and meta-analysis evaluating the risk of stroke for patients undergoing TAVI using the transfemoral with transapical access approaches between the self-expanding (CoreValve) valve design and the balloon-expandable (SAPIEN) valve design. Reviewers identified 25 multicenter studies and 33 single-center studies that met selection criteria, including 3 randomized comparisons, all from the PARTNER study. At 30 days postprocedure, there were no differences in stroke rates. In multicenter studies, the incidence of stroke 30 days postprocedure was 2.4% (95% CI, 1.9% to 3.2%) for centers using the self-expanding valve and 3.0% (95% CI, 2.4% to 3.7%) for centers using the balloon-expanding valve. In pooled analysis, there was no difference in the in-hospital/30-day stroke rates between the self-expanding and balloon-expanding valve groups (pooled OR=1.03; 95% CI, 0.78 to 1.35). Findings were similar for single-center studies. Stroke rates improved with increasing center experience with TAVI.

Randomized Controlled Trials
In 2014, Abdel-Wahab et al published results of the CHOICE RCT, which directly compared the CoreValve self-expandable valve with the SAPIEN balloon-expandable valve among patients at high risk for surgery with severe aortic stenosis. Two hundred forty-one patients were randomized, 121 to the balloon-expandable valve group and 120 to the self-expandable valve group. The trial’s primary end point was device success, a technical composite end point including (1) successful vascular access, delivery, and deployment of the device and successful retrieval of the delivery system; (2) correct positioning of the device in the proper anatomic location; (3) intended performance of the prosthetic heart valve; and (4) only 1 valve implanted in the proper anatomic location. Device success occurred in 116 (95.9%) of 121 of patients in the balloon-expandable group compared with 93 (77.7%) of 120 patients in the self-expandable valve group (RR=1.24; 95% CI, 1.12 to 1.37). This difference was driven largely by differences in rates of residual aortic regurgitation, which occurred in 4.1% of the balloon-expandable valve group and 18.3% of the self-expandable valve group (RR=0.23; 95% CI, 0.09 to 0.58; p<0.001). Cardiovascular mortality at 30 days and bleeding and vascular complications did not differ significantly between groups. Patients in the balloon-expandable group less frequently required placement of a new pacemaker (17.3% vs 37.6%, p=0.001).

One-year follow-up results from the CHOICE trial were published in 2015. Clinical follow-up at 1 year was available for 100% of patients in the balloon-expandable valve group and 97% of those in the self-expandable valve group. From 30 days to 1 year, there were 16 and 9 additional deaths in the balloon-expandable and self-expandable valve groups, respectively. At 1 year, there was no significant difference in all-cause mortality between the balloon expandable (17.4%) and self-expandable (12.8%) groups (RR=1.35; 95% CI, 0.73 to 2.5; p=0.037). Similarly, there were no significant between-group differences in cardiovascular mortality or stroke frequency. The cumulative rate of new pacemaker implantation at 1 year postprocedure, however, was higher in the self-expandable valve group (38.0%) than the balloon-
The evolution of aortic regurgitation did not differ between groups over time, although paravalvular aortic regurgitation and total aortic regurgitation remained less common in the self-expandable valve group (paravalvular aortic regurgitation: 1.1% vs 12.1%; p=0.005; total aortic regurgitation: 1.1% vs 13.1%; p=0.02).

Nonrandomized Comparative Studies

In 2014, Van Belle et al compared rates of postprocedural aortic regurgitation for TAVI with balloon-expandable or self-expandable valves, using data from a large, national French registry of patients undergoing TAVI from January 2010 to October 2011. Significant postprocedural aortic regurgitation (≥grade 1) has been associated with worse long-term outcomes. For this analysis, the authors included 1872 (67.6%) patients who received a balloon-expandable valve and 897 (32.4%) who received a self-expandable valve. Postprocedural aortic regurgitation greater than grade 1 occurred in 15.8% of all patients, and in 21.5% of patients who received a self-expandable valve (vs 13.0% of those who received a balloon-expandable valve; p<0.001); this difference remained significant after controlling for potential confounding factors.

Dworakowski et al (2014) used data from a registry of TAVI procedures in the United Kingdom (the UK TAVI Registry) to compare differences between balloon-expandable and self-expandable valves in terms of paraprosthetic aortic regurgitation post-TAVI. The analysis included 2440 patients enrolled at 25 U.K. centers, 52.7% and 47.2% of whom received a balloon-expandable or a self-expandable device, respectively. Ten percent of patients had moderate or severe post-TAVI paraprosthetic aortic regurgitation. The use of a self-expanding valve was associated with paraprosthetic aortic regurgitation, with 13.6% of those with a self-expanding valve experiencing moderate or severe aortic regurgitation (vs 7.6% of those with balloon-expandable valve; p<0.001). However, overall mortality did not differ between valves. In regression modeling, moderate- to-severe aortic regurgitation was a significant predictor of mortality in patients treated with a balloon-expandable valve (HR=1.97; 95% CI, 1.47 to 2.61), but not in patients treated with a self-expanding valve (HR=1.13; 95% CI, 0.83 to 1.51). The authors noted that the basis for this difference in aortic regurgitation–related mortality risk is not well understood.

Kasel et al (2014) prospectively compared sequential patients treated at a single institution with the CoreValve and SAPIEN devices. Patients treated with TAVI from December 2007 to April 2010 received the CoreValve device; those treated after April 2010 received the SAPIEN device. The study included 50 patients treated with transfemoral TAVI with each device; of 185 patients considered candidates for TAVI, the first 25 of those treated in the 2007-2010 period were excluded to avoid a learning curve effect. In addition, 60 of those who were treated with transapical TAVI in the post-2010 period were excluded. SAPIEN- and CoreValve-treated patients differed at baseline in relation to sex, history of dyslipidemia, previous cardiovascular surgery, previous chest irradiation, STS Risk Score, and presence of rhythm disturbances. Device implantation success rates were similar between groups (98% with the SAPIEN valve vs 90% with the CoreValve; p=0.20). For the primary end point of Valve Academic Research Consortium–combined safety events, in multivariable analysis, the SAPIEN device was associated with significantly fewer AEs (OR=0.21; 95% CI, 0.05 to 0.84; p=0.03). More patients treated with the CoreValve required a permanent pacemaker placement (38% vs 8%; p<0.001).
Section Summary: Comparisons of Different TAVI Devices
A single RCT that compared TAVI devices with different mechanisms (self-expanding [CoreValve] valves vs balloon-expandable [SAPIEN] valves) reported no significant differences in cardiovascular mortality at 30 days postprocedure. However, the balloon-expandable valve was associated with higher rates of device success due to lower rates of paraprosthetic regurgitation and with lower rates of permanent pacemaker requirement. These findings are supported by results from nonrandomized comparisons between the 2 currently available types of TAVI devices.

COMPARISONS OF ALTERNATIVE TAVI APPROACHES
Most patients treated with TAVI, and all patients enrolled in the PARTNER B trial, received the valves using the transfemoral approach. Other approaches, such as the transapical approach, have been used in patients with inadequate femoral access. There is limited evidence comparing outcomes for different approaches. In the PARTNER A trial, slightly less than one-third of procedures were performed transapically, and there were no substantial differences in outcomes between approaches. The SAPIEN transcatheter heart-valve system has FDA approval for use by the transfemoral and transapical approach. The CoreValve device has FDA approval for use by the transfemoral, transsubclavian/transaxillary, and transaortic approaches.

Systematic Reviews
A meta-analysis of 20 nonrandomized studies comparing outcomes from the transfemoral and transapical approaches was published by Li et al in 2013. This analysis included 20 studies, 19 of which were prospective and 1 of which was retrospective. There were 4267 patients treated by the transfemoral approach and 2242 patients treated by the transapical approach. Patients treated transfemorally had a lower 30-day mortality (7.5% vs 11.3%). There were no differences between groups in incidence of stroke (3.8% vs 4.0%) or heart block requiring pacemaker (8.5% vs 7.5%).

Garcia et al (2014) conducted a meta-analysis comparing 30-day outcomes after TAVI using transfemoral, transapical, and transsubclavian approaches. Reviewers included 7 studies with 2636 patients (1526 treated transfemorally, 882 treated transapically, 228 treated transsubclavianly). Compared with transfemoral access, transapical access was associated with higher odds of 30-day mortality (OR=1.54; 95% CI, 1.09 to 2.16; p=0.01); all patients studied received the SAPIEN valve. Compared with transfemoral access, transsubclavian access was associated with no significant difference in 30-day mortality (OR=0.64; 95% CI, 0.31 to 1.32; p=0.23), but was associated with a decreased risk of vascular complications (OR=0.53; 95% CI, 0.29 to 0.95; p=0.03).

A third meta-analysis (2014) compared the transfemoral and transapical approaches in patients ineligible for open surgery who underwent TAVI. Seventeen studies with a total of 2978 patients (1465 treated transfemorally, 1513 treated transapically) were included. Similar to the findings reported by Garcia and Li, 30-day all-cause mortality was lower after transfemoral TAVI than after transapical TAVI (pooled OR=0.59; 95% CI, 0.45 to 0.76; p<0.001). In the overall population, all-cause mortality did not differ significantly between groups. However, after modulating by logistic EuroSCORE, 1-year all-cause mortality was significantly lower with the transfemoral approach than with the transapical (OR not reported; p=0.001).
A fourth meta-analysis comparing outcomes after transfemoral and transapical TAVI was reported by Liu et al (2016). They included 9 observational studies with a total of 1123 patients (666 treated transfemorally, 457 treated transapically). Patients did not differ significantly by logistic EuroSCORE, although details of how the analysis accounted for the EuroSCORE were not given. In this review, there was no significant difference between treatment approaches in 30-day or 1-year mortality.

**Nonrandomized Comparative Studies**

Some nonrandomized, comparative studies have evaluated outcomes for the transfemoral approach and alternative approaches. In many, direct comparisons between approaches are difficult given the potential for confounding by between-group differences in patients’ underlying disease severity and/or frailty. Studies that compared subgroups of patients who are matched based on propensity score methods help reduce, but not eliminate, this confounding.

Prospective comparisons are available from analyses of PARTNER trial data. Blackstone et al (2015) reported a subanalysis of the PARTNER-I trial comparing outcomes between the transfemoral and the transapical approaches, with propensity score matching of patients to control for some underlying differences in patients treated with the 2 approaches. Included was a total of 2621 high-risk or inoperable patients who underwent transapical TAVI (n=1100) or transfemoral TAVI (n=1521) as part of PARTNER A, PARTNER B, or their continued access studies. Groups differed at baseline, particularly for presence of peripheral artery disease. Patients in the 2 groups were matched based on a propensity score, leading to 501 well-matched pairs. Patients in the matched group treated with a transapical approach had higher in-hospital mortality than those treated with a transfemoral approach (7.4% vs 2.8%, p=0.001), but did not have a significantly different risk of stroke (2.8% vs 3.2%, p=0.7), all respectively. The probability of death after transapical versus transfemoral TAVI differed the most early after the procedure: 9.1% versus 3.7% at 30 days; 19% versus 12% at 6 months; 26% versus 19% at 1 year; 37% versus 33% at 2 years; and 47% versus 45% at 3 years, all respectively. The difference in mortality rates was statistically significant (p=0.01) early after surgery but not after about 4 months postsurgery.

Before the Blackstone publication comparing outcomes transfemoral and transapical TAVI, Dewey et al (2013) used data from the transapical cohort of the PARTNER trial combined with data from patients who underwent transapical TAVI in the continued-access study to report outcomes after transapical procedures. Included in their analysis were 104 patients who underwent transapical TAVI as part of the PARTNER trial, 92 patients who had been in the transapical cohort in the PARTNER trial and were randomized to conventional surgical valve repair, and 975 patients who underwent transapical TAVI as part of the continued-access registry. Thirty-day and in-hospital mortality were similar across groups: 10.6% for patients who received transapical TAVI as part of the PARTNER trial; 12.0% for patients who underwent surgical valve repair; and 8.8% for patients who received transapical TAVI as part of the continued-access registry (p=0.54). Compared with those who received transapical TAVI as part of the PARTNER trial (10.8%), those in the continued-access registry had a lower rate of stroke at 1 year (3%; p=0.004).

Another study (2015) used data from a prospective single-center registry to compare outcomes for patients who underwent TAVI by a transfemoral (n=587) or a transapical (n=413) approach. Decisions about the access route were based on interdisciplinary consensus by members of the heart team. In the full cohort of
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1000 patients, patients undergoing TAVI by the transapical route were less often female and had less pulmonary hypertension, but were more likely to have peripheral arterial disease, coronary artery disease, carotid stenosis, and recurrent cardiac surgery. In the full cohort, 30-day mortality, rates of periprocedural MI, and rates of stroke or TIA did not differ significantly between groups. However, those undergoing TAVI by the transfemoral route were more likely to have major vascular complications (17.5% vs 2.4%; OR=0.12; 95% CI, 0.06 to 0.22; p<0.001), major bleeding (6.6% vs 5.6%; OR=0.46; 95% CI, 0.24 to 0.87; p=0.01), a new pacemaker requirement (15.7% vs 10.7%; OR=0.64; 95% CI, 0.44 to 0.94; p=0.02), and moderate aortic insufficiency (3.9% vs 1.2%; OR=0.3; 95% CI, 0.11 to 0.80; p=0.01), all respectively. In a cohort of 708 patients matched by propensity score to adjust for between-group differences, the risk of major vascular complications and moderate aortic insufficiency remained higher in those treated transfemorally, but the differences in rates of major bleeding and new pacemaker requirement were no longer statistically significant.

Multiple retrospective studies have compared outcomes from TAVI with different access routes. They have generally reported higher rates of mortality with transapical TAVI.

Section Summary: Comparisons of Alternative TAVI Approaches
The most direct evidence on TAVI approaches relates to the transapical approach, compared with the more commonly used transfemoral approach. This evidence includes a subgroup analysis from the PARTNER RCT, nonrandomized comparative studies, and systematic reviews of these studies. In the RCT, there was no mortality difference between the 2 approaches. Nonrandomized studies varied by whether the transapical approach was associated with a higher mortality. Patients treated by the transapical approach were more severely ill, with a higher predicted mortality at baseline. It is not possible to determine whether reported mortality differences are due to noncomparability of groups or due to the specific approach. There is very little evidence on other approaches such as the transaxillary, transaortic, and transiliac.

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 who 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 vs 7.2% in the combined group; p=0.04). At 30 days, 35 (7.6%) patients had died. Patients in the stenosis group had a higher 30-day mortality rate (10.5% vs 4.3% in the regurgitation group vs 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 (23.4%) than the other 2 groups (8.8% in the regurgitation group vs 16.1% in the combined group; p=0.01). At 1 year, 86.2% of patients were in NYHA functional class I or II.
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Other case series are smaller and generally from a single center. A 2012 case series from Europe using the CoreValve enrolled 27 patients from 1 cardiology center. There were 2 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 2012 case series from Europe treated 18 patients with a degenerated bioprosthetic valve and symptoms due to valve dysfunction. Implantation was successful in 17 of 18 patients. Complications included AKI in 3 of 18 patients, major bleeding in 4 of 18 patients, and major access site complications in 1 of 18 patients. At a median follow-up of 11 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, respectively, 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 2012 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 2 patients required conversion to open surgery. Mortality at 30 days was 14.3% and was 24% at 1 year. Aortic regurgitation was absent in 4 patients, mild in 13 patients, and moderate in 2 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 evaluated outcomes after transcatheter aortic valve-in-valve replacement, 13 of which were case reports. Pooled analyses of study results are not reported, but the reviewers reported a high rate (90%-93%) of success for valve-in-valve TAVI procedures for series that report procedural success.

Section Summary: TAVI Outcomes for “Valve-in-Valve” Approach
The evidence related to the use of TAVI for valve-in-valve replacement after failed TAVI or degenerated bioprosthetic valve consists of case series (the largest of which included 459 patients) and a systematic review of the available case series. These series have reported high rates of technical success of valve implantation, but often have also reported 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.

COMPLICATIONS AFTER TAVI
Summary of Complications
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 and with data on at least 1 type of complication. Forty-nine studies (total N=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,
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followed by moderate-to-severe aortic regurgitation in 4.5%, stroke in 2.9%, valve embolization in 1.3%, MI in 1.1%, and coronary obstruction in 0.8%.

Giordana et al (2014) published a meta-analysis on predictors of all-cause mortality after TAVI. They 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 (51.1%) patients 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 (60.8%) patients, while a CoreValve self-expandable valve was used in 1899 (21.4%) patients. Three studies did not report the type of valve implanted. At 30 days, 663 (7.5%) patients died, 712 (8.02%) developed AKI, 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 (21.6%) patients had died. The strongest predictors of 30-day mortality were higher AKI stage (≥2; OR=18.0; 95% CI, 6.25 to 52), preprocedural hospitalization for at least 1 week (OR=9.36; 95% CI, 2.55 to 35), periprocedural acute MI (OR=8.54; 95% CI, 2.57 to 33.5), 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 3 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 MI (OR=6.52; 95% CI, 2.34 to 18.14).

Some studies have specifically reported on 1 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 related to the access site. Van Mieghem et al (2012) pooled results from prospective databases on 986 patients undergoing transfemoral TAVI from 5 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 at a rate of 11%. Czerwinska-Jelonkiewicz et al (2014) reported vascular complication rates for 89 consecutive patients treated at a single institution; 44 patients had vascular complications, 17 (20.5%) of which were considered major incidents.

**Acute Kidney Injury**

AKI is relatively common following TAVI. In 218 patients treated at 1 U.S. academic medical center, stage 2 or higher AKI occurred in 8.3% (18/218). Half the patients with AKI (9/18) required dialysis. Mortality at 30 days (44.4% vs 3.0%, p<0.001) and 1 year (55.6% vs 16.0%, p<0.001) were much higher in patients with AKI than in those without AKI, respectively. In a similar study of 248 patients from an academic center in Europe, stage 2 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 1 year (31.5% vs 15.0%, p<0.001) for patients with AKI.
Permanently Required Pacemaker

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. Reviewers 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 CoreValve, the median rate of permanent pacemaker placement was 28% (interquartile range, 24%-35%), whereas for those receiving the 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 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 had not had a previous permanent pacemaker. A quarter (25.2%) of patients required a permanent pacemaker by 30 days postprocedure. 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 predilatation 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-Wahab et al (2014) reported results of an RCT comparing the CoreValve and SAPIEN valve 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 CoreValve. Two hundred thirty-two patients were treated with CoreValve, 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. Mean depth of implantation was 8.4 mm in the non-AccuTrak group and 7.1 mm in the AccuTrak group (p=0.034). In patients without a permanent pacemaker before valve implantation, 33 (32.3%) patients in the non-AccuTrak group received a permanent pacemaker after implantation, compared with 21 (21.4%) in the AccuTrak group (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 3 aortic valve cusps) in patients who required a new permanent pacemaker (8.9 mm) compared with those who did not (6.9 mm; p=0.002).
Boerlage-Van Dijk et al (2014) reported on 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, 10 patients because of preprocedural pacemaker implantation, 5 because they died before the required observation period for possible pacemaker indication, and 1 because the patient needed a pacemaker implantation due to a sick sinus syndrome, which was unrelated to TAVI and discovered during observation after TAVI. After the TAVI procedure, 23 (21.9%) patients 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 preexisting 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 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: Complications After TAVI

In addition to complication rates reported in randomized and nonrandomized studies evaluating outcomes after TAVI, 2 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 (vs the SAPIEN device), insertion depth, and preexisting 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 transcatheter aortic valve implantation (TAVI), the evidence includes 1 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 1 year compared with 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'
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The evidence is sufficient to determine that the technology results in a prespecified objective performance goal. 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 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 and are surgical candidates, the PARTNER A trial reported noninferiority for survival at 1 year for the balloon-expandable valve compared with open surgery. In this trial, TAVI patients also had higher risks for stroke and vascular complications. Nonrandomized comparative studies of TAVI versus open surgery in high-risk patients have reported no major differences in rates of mortality or stroke between the 2 procedures. Since publication of the PARTNER A trial, the CoreValve High Risk Trial demonstrated noninferiority for survival at 1 year for the self-expanding prosthesis. This trial reported no significant differences in stroke rates between groups. In an RCT directly comparing the self-expandable with the balloon-expandable valve among surgically high-risk patients, the devices had similar 30-day mortality outcomes, although the self-expandable valve was associated with higher rates of residual aortic regurgitation and need for a new permanent pacemaker. Evidence from RCT and nonrandomized studies has suggested that TAVI with a self-expanding device is associated with higher rates for permanent pacemakers postprocedure. However, survival rates appear to be similar between device types, and the evidence does not clearly support the superiority of 1 device over another in all patients. 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 low or intermediate risk for open surgery who receive TAVI, the evidence includes 2 RCTs comparing TAVI with surgical repair in individuals selected without specific surgical risk criteria, 1 RCT 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. Two RCTs, 1 investigator-initiated, have evaluated TAVI in patients in low or intermediate risk for open surgery, and both reported no significant differences in their composite outcome measure between groups. 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. In addition, given the limited follow-up beyond a year postprocedure, it is uncertain how many individuals require reoperation. 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 repair who receive transcatheter aortic “valve-in-valve” implantation, the evidence includes case series (largest included 459 patients) and systematic reviews of case series. Relevant outcomes are overall survival, symptoms, morbid events, and treatment-related mortality and morbidity. These case series have reported high rates of technical success of valve implantation, and improvement in heart failure symptoms for most patients. However, they have also reported high rates of short-term complications and high rates of
mortality at 1 year postprocedure. There is a lack of evidence comparing valve-in-valve replacement with alternative treatment approaches. The evidence is insufficient to determine the effects of the technology on health outcomes.

References
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03/06/2014 Medical Policy Committee review
03/19/2014 Medical Policy Implementation Committee approval. New policy.
03/05/2015 Medical Policy Committee review
03/20/2015 Medical Policy Implementation Committee approval. Added “FDA approved” to the eligible for coverage statement. Updated rationale/source and references.
08/03/2015 Coding update: ICD10 Diagnosis code section added; ICD9 Procedure code section removed.
03/05/2015 Medical Policy Committee review
03/20/2015 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
05/05/2016 Medical Policy Committee review
05/18/2016 Medical Policy Implementation Committee approval. Coverage eligibility unchanged.
11/03/2016 Medical Policy Committee review
11/16/2016 Medical Policy Implementation Committee approval. Added coverage statement for valve in valve for patient at high or prohibitive risk for open surgery.

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01/01/2017 Coding update: Removing ICD-9 Diagnosis Codes
05/04/2017 Medical Policy Committee review
05/17/2017 Medical Policy Implementation Committee approval. Added “native valve” to coverage statement.
Next Scheduled Review Date: 05/2018

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C. Not primarily for the personal comfort or convenience of the patient, physician or other health care provider, and 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.

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