APPENDIX to Transcatheter Aortic Valve Replacement for Aortic Stenosis Policy

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

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

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

Evidence Basis for the Policy

Rationale

Aortic Stenosis (AS). According to Freeman et al. (2005) AS is defined as narrowing of the aortic valve opening, resulting in obstruction of blood flow from the left ventricle into the ascending aorta. Progressive calcification of the aortic valve is the most common etiology in North America and Europe, while rheumatic fever is the most common etiology in developing countries. A congenital abnormality of the aortic valve, most commonly a bicuspid valve, increases the risk for AS, but AS can also occur in a normal aortic valve. Risk factors for calcification of a congenitally normal valve mirror those for atherosclerotic vascular disease including:

- Advanced age
- Male gender
- Smoking
- Hypertension
- Hyperlipidemia.

Thus, the pathogenesis of calcific AS is thought to be similar to that of atherosclerosis, which includes deposition of atherogenic lipids and infiltration of inflammatory cells, followed by progressive calcification.

The natural history of AS involves a long asymptomatic period, with slowly progressive narrowing of the valve until the stenosis reaches the severe stage. At this time, symptoms of shortness of breath, chest pain, and/or dizziness or syncope often occur and the disorder progresses rapidly. Treatment of AS 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 individuals older than 65 years of age have evidence of significant AS, increasing up to 8% of individuals by age 85 years (Freeman et al., 2005). In the Helsinki Aging Study, a population-based study of 501 patients aged 75 to 86 years, the prevalence of severe AS by echocardiography was estimated to be 2.9% (Lindross et al., 2003). In the United States, more than 50,000 aortic valve replacements are performed annually due to severe AS.

Aortic stenosis does not cause substantial morbidity or mortality when the disease is mild or moderate in severity. By the time it reaches the severe stage, there is an untreated mortality rate of approximately 50% within 2 years (Bonow et al., 2006). Open surgical repair is an effective treatment for reversing AS, and artificial valves have demonstrated good durability for periods of up to 20 years (Bonow et al., 2006). However, these benefits are accompanied by a perioperative mortality of approximately 3% to 4% and substantial morbidity (Bonow et al., 2006), both of which increase with advancing age.

Unmet needs. Many patients with severe, symptomatic AS are poor operative candidates. Approximately 30% of patients presenting with severe AS do not undergo open surgery due to factors such as advanced age, advanced left ventricular dysfunction, or multiple medical comorbidities (Lung et al., 2005). For patients who are not surgical candidates, medical therapy can partially alleviate the symptoms of AS but does not affect the underlying disease progression. Percutaneous balloon valvuloplasty can be performed, but this procedure has less than optimal outcomes (Lieberman et al., 1995). Balloon valvuloplasty can improve symptoms and increase flow across the stenotic valve but is associated with high rates of complications such as stroke, myocardial infarction (MI), and aortic regurgitation. In addition, restenosis can occur rapidly, and there is no improvement in mortality. As a result, there is a large unmet need for less invasive treatments for AS in patients who are at increased risk for open surgery.

Transcatheter aortic valve implantation. Transcatheter aortic valve implantation (TAVI) 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 in order to open up the stenotic area. This is followed by passage of a bioprosthetic artificial valve across the native aortic valve. The valve is initially compressed to allow passage across the native valve and is

then expanded and secured to the underlying aortic-valve annulus. The procedure is performed on the beating heart without the need for cardiopulmonary bypass.

There are at least two transcatheter aortic valve devices being used. The Edwards SAPIEN transcatheter heart-valve system™ (Edwards Lifesciences, Irvine, CA) is a tri-leaflet bioprosthetic porcine valve that is contained within a stainless steel frame. This device first received FDA approval in 2011, with expanded indications for approval granted in 2012 and 2013.

The Medtronic CoreValve ReValving System™ is a second transcatheter valve system under testing. This device is a porcine bioprosthetic valve that is sewn within a self-expanding nitinol frame. It is inserted via the transfemoral artery approach and has also been inserted via the subclavian artery approach. This device has also been approved for use in Europe since 2007 but has not yet received FDA approval in the United States.

Regulatory Status

The Sapien Transcatheter Heart Valve System™ (Edwards LifeSciences, Irvine, CA) received original FDA approval in November 2011 for patients with severe AS who are not eligible for open-heart procedures and have a calcified aortic annulus. In 2012, an additional FDA premarket approval (PMA) was granted for the Edwards SAPIEN™ transcatheter heart valve Model 9000TFX (Edwards LifeSciences, Irvine, CA) with expanded indications for use. Approval was granted for both the transfemoral and transapical approach. For the transfemoral approach, patient indications were broadened to include patients who are at high risk for open surgery. For the transapical approach, approval was granted for patients who are at high risk for open surgery. In September 2013, the FDA expanded the indications for the transapical approach to include both inoperable patients and patients who are at high risk for open surgery. As a result, as of September 2013, the Sapien Transcatheter Heart Valve System™ is approved for both high risk and inoperable patients when used by either the transapical or transfemoral approach.

Literature Review

The evidence on transcatheter aortic valve implantation (TAVI) consists of many uncontrolled case series and one pivotal randomized controlled trial (RCT)—the PARTNER trial. These studies report on two 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 two groups of patients will be discussed separately.

Does TAVI improve outcomes for patients with aortic stenosis who are not suitable candidates for open surgery?

Systematic Reviews. Systematic reviews on this question consist of studies that evaluate results from case series. An Agency for Healthcare Research and Quality (AHRQ)–sponsored systematic review in 2010 reviewed 84 publications enrolling 2375 patients (Coeytaux et al., 2010). Implantation was successful in 94% of patients overall, with higher success rates reported in more recent publications. The aggregate 30-day survival was 89% across all studies. Adverse event rates were reported in the larger case series, with an estimated 30-day rate of major cardiovascular adverse events and stroke of 8%.

A second systematic review was published in 2011 by Figulla et al. This review included studies that enrolled symptomatic patients with severe AS, 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 to a group of 11 studies that treated severe AS 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 to 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 U.S., Canada, and Germany, using the SAPIEN™ heart-valve system. Leon et al. (2010) reported results of patients from the PARTNER trial with AS who were not candidates for open surgery. In order to be classified as unsuitable for open surgery, patients had to have a predicted probability of 50% or higher for death or a serious irreversible condition at 30 days post-surgery. This probability was determined by two surgeon investigators using clinical judgment and the Society of Thoracic Surgery (STS) risk score. The executive committee of the PARTNER trial reviewed all patient selection decisions and approved the classification of patients as unsuitable for surgery. A total of 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. Transcatheter aortic valve replacement 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 not participating in the trial. The primary outcome was death from any cause over the course of the trial (median follow up 1.6 years). A co-primary endpoint was the composite of time to death from any cause or time to repeat hospitalization related to aortic or TAVI. Secondary endpoints were:

- Cardiovascular mortality
- New York Heart Association (NYHA) functional class
- Rate of hospitalizations due to AS or TAVI
- Six minute walk test
- Valve performance as measured by echocardiography
- Procedural complications (myocardial infarct, stroke, acute kidney injury, vascular complications, and 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 to the TAVI group (30.4±19.1 vs 26.4±17.2, p=0.04) and the STS score was numerically higher but did not reach statistical significance (12.1±6.1 vs 11.2±5.8, p=0.14). Significantly more patients in

the standard therapy group had chronic obstructive pulmonary disease (52.5% vs 41.3, p=0.04) and atrial fibrillation (48.8% vs 32.9%, p=0.04), and there was a nonsignificant trend for more patients in the standard therapy group having a lower ejection fraction (51.1 vs 53.9%) and frailty, as determined by prespecified criteria (28.0 vs 18.1%).

Death from any cause at 1 year following enrollment was lower for the TAVI group (30.7% vs 49.7%, p<0.001). This represents a 19% absolute risk reduction, a 38.2% relative risk reduction, and a number needed to treat of 5.3 to prevent one death over a 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. Quality of life outcomes were evaluated using the Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score, the Medical Outcomes Study 12-Item Short-Form (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 (Makkar et al.). Mortality at 2 years was 43.3% in the TAVI group compared to 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 to 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 to medical therapy (35.0% vs 72.5%, p<0.001).

Case Series. Many case series of TAVI have been published in the last 10 years, the majority of which have included patients who are not candidates for open surgery. However, the selection process for TAVI has largely been subjective, with the expert opinion of the surgeons and/or cardiologists as the main factor determining suitability for open surgery. As a result, there may

be some overlap in these series with patients who are surgical candidates, but the distinction cannot be easily made from the reported studies. Some of the larger case series are discussed below.

The two largest series included in the AHRQ review reported on 646 patients treated with the Medtronic CoreValve® (Piazza et al., 2008) and 339 patients treated with the Edwards SAPIEN® valve (Rodes-Cabau et al., 2010).The CoreValve study used more objective patient selection criteria than is common in this literature. Their criteria for eligibility included the following:

- Logistic EuroScore +/-15%
- Age +/- 75
- Age +/- 65 with concomitant:
    - 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
    - BMI +/- 18kg/m2

Procedural success was 97% and 30-day survival was 92%. The 30-day combined rate of death, myocardial infarct or stroke was 9.3%. The study by Rodes-Cabou et al. (2010) was performed in Canada and used Edwards SAPIEN valve. This study had subjective inclusion criteria relying on the judgment of the participating surgeons to determine eligibility for TAVR. 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.

Another larger case series was from Germany and reported on 697 patients treated with the CoreValve™ system (Zahn et al., 2011). Procedural success was 98.4%, and 30-day mortality was 12.4%. Another large case series from Italy (Tamburino et al., 2011) included 663 patients treated with the CoreValve™ device. Procedural success was 98% and mortality at 1 year was 15%. A notable study was published by Gurvitch et al. in 2011 that reported on durability and longer clinical outcomes up to 3 years. Seventy patients who underwent TAVI and survived for greater than 30 days were included. Survival at 1, 2, and 3 years was 81%, 74%, and 61%, respectively. One patient (1.5%) required reoperation during this time period. The valve area decreased from 1.7 cm^2 following the procedure to 1.4 (0.3) cm^2 at 3 years. Aortic incompetence was trivial or mild in 84% of patients and did not worsen over time.

Section Summary. Numerous case series have demonstrated feasibility and short-term efficacy for TAVI in patients who are not surgical candidates. In the PARTNER B trial, there was a large decrease in all-cause mortality and cardiovascular mortality at 1 year for TAVI compared to 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 an 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, since 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.

Does TAVI improve outcomes for high-risk patients with aortic stenosis as an alternative to open surgery?

Systematic Reviews. Several systematic reviews have been published on this question. The evidence in these studies is derived largely from nonrandomized comparative studies, as only 1 RCT has been published (the PARTNER trial). Panchal et al. (2013) reported results from a meta-analysis of 17 studies that included 4659 patients, 2267 treated with TAVI, and 2392 treated with open surgery. Patients in the TAVI group were more severely ill, as evidenced by a EuroSCORE for predicted 30-day mortality that was higher by a mean of 3.7 points compared to patients undergoing open surgery. On combined analysis, there were no differences between groups on 30-day mortality, mortality at longest follow-up, cardiovascular mortality, MI, stroke, or TIA. Patients in the open surgery group had a higher incidence of major bleeding complications (relative risk, 1.42; 95% CI, 1.20 to 1.67; $p<0.001$). In a similar meta-analysis 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) (Takagi et al., 2013).

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

A total of 699 patients were randomized to TAVI or usual care. The primary hypothesis was that TAVI was noninferior to open aortic valve replacement (AVR), using a 1-sided noninferiority boundary of 7.5% absolute difference in mortality at 1 year. TAVI was performed under general anesthesia using the transfemoral approach when possible (n=492). If the transfemoral approach was not possible, transapical approach was used (n=207). The comparison group underwent open AVR. Details of the open procedure were not provided in presentation slides.

The primary outcome was death from any cause at 1-year follow-up. A second powered end point was noninferiority at 1 year for the patients undergoing TAVI by the transfemoral approach. Secondary end points were cardiovascular mortality, NYHA functional class, rehospitalizations, the 6-minute walk test, valve performance as measured by echocardiography, and procedural complications (MI, stroke, AKI, vascular complications, and bleeding). The mean age of enrolled patients was 83.6 years in the TAVI group and 84.5 years in the open AVR group. Other baseline demographics and clinical characteristics were generally well-balanced, except for a trend toward an increased percent of patients in the TAVI group with a creatinine level 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 compared to 26.8% for the open AVR group (p=0.44 for difference between groups). The upper limit of the 95% CI for the difference between groups was a 3.0% excess mortality in the TAVI group, which was well within the 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 compared with 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) were not significantly different for the TAVI versus open AVR groups. The percent of patients in NYHA Class I or II at 1 year was similar between groups at 1 year, as was the improvement in the 6-minute walk test. On subgroup analysis, there was a significant effect for gender, 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% percent of patients undergoing TAVI, compared with 4.8% in the open AVR group (p=0.01), and major vascular complications were also higher in the TAVI group (11.3% vs 3.5%, p=0.01). On the other hand, major bleeding was more common in the open group compared to TAVI (25.7% vs 14.7%, p=0.01).

Reynolds et al. published QOL results from the PARTNER trial in 2012. Quality of life outcomes were evaluated using the KCCQ summary score, the SF-12, and the EQ-5D. Of 699 patients in the trial, 628 completed baseline QOL measures. Patients in both the TAVI group and the surgical AVR group demonstrated significant improvements in all QOL measures over the 12 months following treatment. The TAVI group had superior improvement at 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

Section Summary. 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 actuality, the reported mortality for the TAVI group was lower than for the open group, although not significantly different. QOL was also similar at 1 year between the TAVI and AVR groups. Stroke or TIA was significantly more

common for the TAVI group, occurring at a rate of almost two times that reported for open surgery. Other secondary outcomes were similar between groups, except for higher rates of vascular complications in the TAVI group and higher rates of major bleeding in the open surgery group. As in the first PARTNER cohort, there is concern for generalizability of results given that the patient selection process relied largely on the judgment of surgeons and cardiologists participating in the trial. In addition to this single RCT, several meta-analyses have compared outcomes between TAVI and open surgery using evidence that is primarily from nonrandomized comparative trials. These meta-analyses have concluded that there are no clear differences in mortality, or in secondary morbidity outcomes, between the two procedures

Does TAVI by alternative approaches (eg, transapical or transaxillary) achieve similar outcomes to those reported from the transfemoral approach?

The majority of all patients treated with TAVI, and all the patients enrolled in the PARTNER B trial, have been by the transfemoral approach. Other approaches, such as the transapical approach, have been used in patients with inadequate femoral access. There is a limited amount of evidence comparing outcomes from different approaches. In the PARTNER A trial, slightly less than one third of procedures were performed by the transapical approach (Leon et al., 2010) and there were no substantial differences in outcomes between the two approaches. The Edwards SAPIEN transcatheter heart-valve system™ has FDA approval for use by the transfemoral and transapical approach. There are no devices approved for use with other approaches such as the transiliac, transaxillary, or transaortic.

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

Nonrandomized comparative studies. Some nonrandomized, comparative studies have compared outcomes for the transfemoral approach compared to the transapical approach. In a retrospective, multicenter from 4 centers in Europe enrolling 882 patients, outcomes were compared between the transfemoral (n=793, 89.9% of total) and transapical (n=89, 10.1% of total) approaches (van der Boon et al., 2013). Patients treated by the transapical approach were more severely ill, as demonstrated by a higher median EuroSCORE (27.0 vs 20.0, $p<0.001$) and a higher median Society of Thoracic Surgeons Score (10.2 vs 6.7, $p<0.001$). Patients treated by the transapical approach had a higher 30-day mortality (OR=3.1, 95% CI, 1.4 to 6.8; p=0.004) and a higher overall mortality at a median follow-up of 365 days (HR=1.9; 95% CI, 1.2 to 2.9; p=0.004). The transapical approach was associated with a lower risk for major bleeding complications (OR=0.33; 95% CI, 0.12 to 0.90; p=0.03).

Ewe et al. (2011) included 107 consecutive patients undergoing TAVI, 47 by the transfemoral approach and 50 by the transapical approach. Mortality was not significantly different for the transfemoral approach versus the transapical approach at 30 days (11.1% vs 8.5%, respectively, p=0.74) or at 1 year (19.8% vs 14.3%, respectively). Vascular complications were more common

in the transfemoral group (18% vs 5%, respectively, p=0.05). Fluoroscopy time and total radiation exposure was more reduced for the transapical approach.

A nonrandomized, comparative study reported higher complication rates with the transapical approach. Thomas et al. (2011) used data from a European registry to compare patients undergoing TAVI by the transfemoral approach (n=463) with patients undergoing TAVI by the transapical approach (n=575). Complications were more frequent in the transapical group, but the transapical group also may have been more severely ill as judged by a higher EuroSCORE risk score. A publication from the UK TAVI registry (Moat et al., 2011) evaluated risk factors for adverse outcomes in 877 TAVI procedures. On univariate analysis, TAVI by the transapical approach was associated with lower survival, although this relationship did not persist after controlling for demographic and clinical factors.

Section Summary. The only approaches for TAVI that have FDA approval are the transfemoral and transapical. There is some evidence comparing different approaches for TAVI. The highest quality evidence is for the transapical approach. This evidence includes a subgroup analysis from the PARTNER RCT, and nonrandomized comparative studies. In the RCT, there was not a mortality difference between the two approaches. In the nonrandomized studies, mortality is higher for patients treated by the transapical approach. However, patients treated by the transapical approach were more severely ill, with a higher predicted mortality at baseline. It is not possible to determine whether this difference in mortality is due to noncomparability of groups or due to the specific approach. In addition, since the transapical approach is generally used in patients who are not suitable for the transfemoral approach due to advanced vascular disease, the transapical approach is usually done out of necessity, not by choice of the surgeon. There is very little evidence on other approaches such as the transaxillary, transaortic and transiliac.

In 2013, the FDA expanded approved TAVI by the transapical approach to include both patients who are not candidates for open surgery and patients who are at high risk for open surgery.

What is the complication rate following TAVI?

A systematic review of complications associated with TAVI was published by Khatri et al. in 2013. This study included all publications with at least 100 patients that had data on at least 1 type of complication. A total of 49 studies enrolling 16,063 patients were identified. The most common adverse event was heart block requiring a pacemaker insertion, which occurred in 13.1% of patients. Vascular complications occurred in 10.4% of patients. The third most common complication was acute renal failure requiring therapy in 4.9% of patients, and stroke was reported in 2.9% of patients. Other complications included moderate to severe aortic regurgitation in 4.5%, valve embolization in 1.3%, MI in 1.1% and coronary obstruction in 0.8%.

Some studies have specifically reported on one or more complications in large numbers of patients. Representative studies of this type will be reviewed here. The most common complications following TAVI are vascular complications related to the access site. Van Miegham et al. (2012) pooled results from prospective databases on 986 patients undergoing transfemoral TAVI from five clinical centers in Europe. The rate of major vascular complications was 14.2%. Major bleeding occurred at a rate of 17.8% and life-threatening/disabling bleeding occurred at a rate of 11%.

AKI is also relatively common following TAVI. In 218 patients treated at one academic medical center in the United States (Genereux et al., 2012) stage 2 or higher AKI occurred in 8.3% (18/218). Half of the patients with AKI (9/18) required dialysis. Mortality at 30 days (44.4% vs 3.0%, $p<0.001$) and 1 year (55.6% vs 16.0%, $p<0.001$) was much higher in patients with AKI compared to those without AKI. 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.

For patients with degenerated bioprosthetic valves or failed TAVI, does TAVI using the "valve-in-valve" approach improve outcomes?

The evidence on this question consists of case series, most of which are small. The largest case series published to date is from the Global Valve-in-Valve registry (Dvir et al., 2012). This study included 202 patients from 38 cardiac centers with a prior surgical bioprosthetic valve replacement that had failed. The procedure was successful in 93.1% of attempts, and 95% of patients had 1 degree or less of aortic regurgitation postprocedure. Early adverse events occurred in 15.3%, with the most common events being malposition of the device and ostial coronary obstruction. Overall mortality was 8.3% at 30 days and 16.3% at 1 year. At 30 days' follow-up, 83.7% of patients were in New York Heart Association functional Class I or II.

Other case series are smaller and generally from a single-center. A case series from Europe using the Medtronic CoreValve enrolled 27 patients from 1 cardiology center (Linke et al., 2012). There were two deaths within 30 days. Improvements in the aortic valve gradient and the degree of regurgitation were noted. Adverse events included stroke (7.4%), kidney failure (7.4%), life-threatening bleeding (7.4%), and access site complications (11.1%). Another case series from Europe treated 18 patients with a degenerated bio-prosthetic valve and symptoms due to valve dysfunction (Latib et al., 2012). Implantation was successful in 17/18 patients. Complications included AKI in 3/18 patients, major bleeding in 4/18 patients, and major access site complications in 1/18 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.

Smaller case series have reported on valve-in-valve implantation for patients with failed TAVI. For example, a publication from Canada reported on 21 patients with transcatheter valve failure due to aortic regurgitation (Toggweiler et al., 2012). The procedure was successful in 19/21 patients; the remaining 2 patients required conversion to open surgery. Mortality at 30 days was 14.3% and at 1 year was 24%. Aortic regurgitation was absent in 4 patients, mild in 13 patients, and moderate in 2 patients.

Clinical Input Received through Physician Specialty Societies and Academic Medical Centers

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

Clinical input was received by Blue Cross Blue Shield Association from six academic medical centers and one specialty society in 2011. At the time of vetting, FDA approval had not yet been granted for any TAVI device. Reviewers were mixed in support for a medically necessary indication for patients who are not surgical candidates. However, all reviewers indicated that they would consider this procedure medically necessary if FDA approval was granted. None of the reviewers expressed support for medical necessity in other patient populations, including patients who were at high risk for surgery, but were surgical candidates. Concerning patient selection criteria, most reviewers referred to the study selection criteria in the PARTNER trial and did not offer further options for objective patient selection.

Ongoing Clinical Trials

A search of online site ClinicalTrials.gov returned numerous ongoing trials of TAVI in various stages of evolution. The majority of these are single-arm trials evaluating the safety and efficacy of TAVI, using various types of valves, delivery systems, ancillary treatments, and outcomes. The following RCTs were identified that compared TAVI to alternative treatments, or compared outcomes of different types of valves:

- NCT01057173. Transcatheter compared to surgical valve implantation in patients with severe aortic stenosis. This is an RCT underway in Europe that is comparing TAVI with open surgical valve replacement using the Medtronic CoreValve. Estimated completion date is December 2018.
- NCT01314313. The PARTNER II Trial: Placement of Aortic Transcatheter Valves. This is an RCT underway in the U.S. that is comparing 2 types of the Edwards SAPIEN Valve system, the SAPIEN valve with RetroFlex3 and the SAPIEN XT with NovaFlex. Estimated completion date is March 2018.
- NCT01240902. Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Symptomatic Severe Aortic Stenosis in High Risk and Very High Risk Subjects Who Need Aortic Valve Replacement. This is an RCT underway in the U.S. that is comparing TAVI with open surgical valve repair using the Medtronic CoreValve in patients who are at high risk for open surgery. Estimated completion date November 2017.
- NCT01586910. Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement (SURTAVI). This is an RCT of 2,500 patients at intermediate risk for surgery comparing TAVI with open AVR. The study is listed as recruiting, but no estimated completion date was provided.
- NCT01645202. A Comparison of Transcatheter Heart Valves in High Risk Patients with Severe Aortic Stenosis: The CHOICE trial. This is an RCT of 240 patients that compares TAVI using the Edwards SAPIEN™ valve to TAVI using the Medtronic CoreValve® system. Estimated completion date for the primary outcomes is estimated to be March 2014.

Clinical Practice Guidelines and Position Statements

A "Professional Society Overview" on transcatheter valve therapy was published July 2011 by the American College of Cardiology Foundation and the Society of Thoracic Surgeons (Holmes & Mack, 2011). The purpose of this document was to enumerate the core issues that will be anticipated in integrating TAVI into general clinical care. As part of this document, a list of necessary components for the successful introduction of Transcatheter Heart Valve Therapies was developed:

- Specialized heart centers with experienced multidisciplinary physicians and paramedical personnel
- Professional multidisciplinary heart team:
    - Primary cardiologists
    - Cardiac surgeons
    - Interventional cardiologists
    - Echocardiographers and imaging specialists
    - Heart failure specialists
- Proper procedure and facilities
    - Modified conventional cardiac laboratory
    - Hybrid operating room
- Development of and participation in clinical database and registries
- Knowledge of, and evaluation of, evidence-based medical literature concerning patient selection, procedural performance, and complication management
- Specific standardized protocols for management strategies, procedural performance, problem-solving, and complication management

The National Institute for Health and Clinical Excellence (NICE) published interventional procedure guidance entitled Transcatheter Aortic Valve Implantation for Aortic Stenosis (266; 2008). The NICE guidance noted that the evidence on TAVI for AS is limited to small numbers of patients who were considered to be at high risk for conventional cardiac surgery. It shows good short-term efficacy, but there is little evidence on long-term outcomes. There is a potential for serious complications; however, the patients on whom this procedure has been used have a poor prognosis without treatment and are at high risk if treated by open heart surgery. Clinicians wishing to use this procedure should do so only with special arrangements for clinical governance, consent and for audit or research.

Other guidelines include:

- The AHRQ Technical brief: Percutaneous heart valve replacement (August 2010; Project ID EHC056-EF).
- European Society of Cardiology (ESC). ESC guidelines for the management of grown-up congenital heart disease (new version 2010). The Task Force on the Management of Grown-up Congenital Heart Disease of the European Society of Cardiology (ESC) (Baumgartner H et al., 2010).

- Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): developed in collaboration with the Society of Cardiovascular Anesthesiologists: endorsed by the Society for Cardiovascular Angiography and Interventions and the Society of Thoracic Surgeons (Bonow et al., 2008).

Summary

Transcatheter aortic valve implantation is a treatment for patients with severe AS who require intervention, but who are a high or prohibitive risk for open surgery. There is currently one transcatheter aortic valve that is FDA-approved, the Edwards SAPIEN™ valve (Edwards LifeSciences, Irvine, CA).

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 to medical care. This trial also reported improvements on other relevant clinical outcomes for the TAVI group. There was an increased risk of stroke and vascular complications in the TAVI group. Despite these concerns, the overall balance of benefits and risks from this trial indicate that health outcomes are improved. For patients who are high risk for open surgery, but are operable candidates, the PARTNER A trial reported noninferiority for survival at 1 year compared to open surgery. In this trial, TAVI patients also had higher risks for stroke and vascular complications. Nonrandomized comparative studies of TAVI versus open surgery in high-risk patients have reported no major differences in mortality or in rates of stroke between the two procedures.

The PARTNER A trial also included a subgroup analysis comparing the transfemoral and transapical approaches and reported no outcome differences between the two approaches. Some nonrandomized comparative studies have reported higher mortality in patients treated by the transapical approach, but these comparisons are inconclusive because patients treated by the transapical route had a higher baseline risk for mortality. In 2013, the FDA expanded approved of TAVI by the transapical approach to include both patients who not candidates for open surgery and patients who are at high risk for open surgery. Based on the available evidence and the 2013 FDA approval, TAVI performed by either the transfemoral or transapical approach may be considered medically necessary in patients who are not suitable candidates for open surgery, and in patients who are operable candidates but at high risk for open surgery.

TAVI has also been used as a “valve-in-valve” treatment for degenerated bio-prosthetic valves and for failed transcatheter valves. The evidence on this indication consists only of case series and is insufficient to determine whether outcomes are improved compared to alternatives. As a result, TAVI used for a “valve-in-valve” approach is considered investigational.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

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

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

Type	Number	Description
CPT	33361	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach
	33362	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open femoral artery approach
	33363	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open axillary artery approach
	33364	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open iliac artery approach
	33365	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transaortic approach (eg, median sternotomy, mediastinotomy)
	33366	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transapical exposure (eg, left thoracotomy)
	33367	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with percutaneous peripheral arterial and venous cannulation (eg, femoral vessels) (List separately in addition to code for primary procedure)

Type	Number	Description
	33368	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with open peripheral arterial and venous cannulation (eg, femoral, iliac, axillary vessels) (List separately in addition to code for primary procedure)
	33369	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with central arterial and venous cannulation (eg, aorta, right atrium, pulmonary artery) (List separately in addition to code for primary procedure)
	33999	Unlisted procedure, cardiac surgery
HCPC	None	
ICD9 Procedure	35.05	Endovascular replacement of aortic valve
	35.06	Transapical replacement of aortic valve
	35.09	Endovascular replacement of unspecified heart valve
ICD9 Diagnosis	All Diagnoses	
Place of Service	All Places of Service	

Tables

N/A

Definitions

New York Heart Association (NYHA) Functional Classification - A standard by which the extent of cardiac failure is measured. The classification definitions are:

- I: No symptoms and no limitation in ordinary physical activity
- II: Mild symptoms, including mild shortness of breath and/or angina, and slight limitation during ordinary activity
- III: Marked limitation in activity due to symptoms, even during less than ordinary activity; for example, walking short distances

- IV: Severe limitation. Experiences symptoms even while at rest. Mostly bedbound patients

Society of Thoracic Surgeons (STS) Risk Score Calculator - Used to calculate a patient's risk for mortality and other morbidities, such as long length of stay and renal failure. The risk calculator incorporates the STS risk models that are designed to serve as statistical tools to account for the impact of patient risk factors on operative mortality and morbidity.

Index / Cross Reference of Related BSC Medical Policies

The following Medical Policies share diagnoses and/or are equivalent BSC Medical Policies:

- Transcatheter Pulmonary Valve Implantation

Key / Related Searchable Words

- Aortic stenosis
- Aortic valve replacement, transcatheter
- Catheter-delivered prosthetic aortic heart valve
- Edwards SAPIEN Transcatheter aortic valve
- Edwards SAPIEN XT valve system
- Medtronic CoreValve system
- TAVI
- TAVR
- Transcatheter aortic valve implantation
- Transcatheter aortic valve replacement

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Policy History

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

Effective Date	Action	Reason
3/30/2012	BCBSA Medical Policy adoption	Medical Policy Committee
2/22/2013	Coding Update	Administrative Review

Effective Date	Action	Reason
3/29/2013	Policy revision with position change	Medical Policy Committee
3/7/2014	Coding and Administrative Update	Administrative Review

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.

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