Clinical Policy Bulletin: Transcatheter Aortic Valve Implantation

Number: 0826

Policy

I. Aetna considers transcatheter aortic valve implantation (TAVI) by means of an FDA-approved aortic valve (e.g., the Edwards Sapien transcatheter heart valve, Medtronic CoreValve System) medically necessary for without severe aortic insufficiency and with an ejection fraction greater than 20% who are inoperable for open aortic valve replacement and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis.

II. Aetna considers TAVI by means of an FDA-approved aortic valve (e.g., the Edwards Sapien transcatheter heart valve, Medtronic CoreValve System) medically necessary for persons with severe symptomatic calcified native aortic valve stenosis without severe aortic insufficiency and with an ejection fraction greater than 20% who are operative candidates for aortic valve replacement but who have a Society of Thoracic Surgeons operative risk score (see Appendix) greater than or equal to 8% or are judged to be at 15% or greater risk of mortality for surgical aortic valve replacement.

III. Aetna considers TAVI experimental and investigational for persons with aortic stenosis that can be treated by open-heart surgery and for all other indications (e.g., as an alternative to valve-in-valve implantation for failed aortic bioprostheses; native aortic valve regurgitation; not an all-inclusive list) because its effectiveness for indications other than the one listed above has not been established.

Background

Aortic stenosis is the most commonly acquired valvular heart disease in the Western countries. Without surgery, the prognosis is extremely poor; with a 3-year survival rate of less than 30%. For symptomatic patients with severe aortic valve stenosis, the open heart approach for surgical aortic valve replacement (SAVR) is currently the gold standard treatment. Cumulative surgical experience and technical advent have led to excellent peri-operative results with low morbidity and mortality. Long-term results are convincing,
and even in octogenarians, SAVR is feasible with acceptable results. However, in very old patients with many co-morbidities, the outcome is less favorable, and many of these patients may be inoperable or carry an unacceptably high peri-operative risk.

Transcatheter aortic valve implantation (TAVI), first introduced in 2002, represents an alternative to SAVR in elderly patients who are at high-risk for conventional surgery. Transcatheter aortic valve is usually delivered in 2 manners: (i) the retrograde trans-femoral (TF) approach via the femoral artery that is associated with a relatively high incidence of vascular complications to the down-stream aorta, iliac and femoral arteries, and (ii) the antegrade trans-apical (TA) approach that requires intubation and thoracotomy, with the risk of bleeding from the fragile apex of the heart. Transcatheter aortic valve implantation is available in Europe as an alternative to conventional SAVR for patients with severe symptomatic aortic stenosis who are deemed to be at very high surgical risk for open-heart surgery (Kallenbach and Karck, 2009; Sambu and Curzen, 2010).

Bleiziffer et al (2009) noted that suspicion had been expressed that survival might be impaired after antegrade TA as opposed to retrograde TF valve implantation in high-risk patients with aortic stenosis. These researchers analyzed survival in patients undergoing TAVI with special emphasis on the access site for valvular implantation. A total of 203 high-risk patients (European system for cardiac operative risk [EuroSCORE] of 22 % +/- 14 %; mean age of 81 +/- 7 years) underwent TAVI via a TA (n = 50) or TF (n = 153) access. The TA implantation technique was chosen only in patients who had no access through diseased femoral arteries. Thirty-day survival was 88.8 % after TF versus 91.7 % after TA implantation (p = 0.918). The TA group had a significantly higher pre-operative brain natriuretic peptide value and a significantly higher incidence of peripheral vessel, cerebrovascular, and coronary heart disease. Death within 30 days was valve-related in 25 % (TA) and 31 % (TF), cardiac in 25 % and 13 %, and non-cardiac in 50 % and 56 %, respectively (no significant differences). Complications specific to the access site (peripheral vessel injury or apex complications) occurred in both groups, whereas neurological events did not occur in the TA group (p = 0.041). The authors concluded that their patient and access site selection process, with the TF technique considered the access site of first choice, results in comparable morbidity and survival for either TF or TA TAVI. Both techniques are associated with certain access site-specific complications that require highly qualified management.

Rodés-Cabau et al (2010) (i) evaluated the acute and late outcomes of a TAVI program including both the TF and TA approaches; and (ii) determined the results of TAVI in patients deemed inoperable because of either porcelain aorta or frailty. Consecutive patients who underwent TAVI with the Sapien valve (Edwards Lifesciences, Inc., Irvine, CA) were included. A total of 345 procedures (TF: n = 168; TA: n = 177) were carried out in 339 patients. The predicted surgical mortality (Society of Thoracic Surgeons [STS] risk score) was 9.8 % +/- 6.4 %. The procedural success rate was 93.3 %, and 30-day mortality was 10.4 % (TF = 9.5 %, TA = 11.3 %). After a median follow-up of 8 months (25th to 75th inter-quartile range: 3 to 14 months) the mortality rate was 22.1 %. The predictors of cumulative late mortality were peri-procedural sepsis (hazard ratio [HR]: 3.49, 95 % confidence interval [CI]: 1.48 to 8.28) or need for hemodynamic support (HR: 2.58, 95 % CI: 1.11 to 6), pulmonary hypertension (PH) (HR: 1.88, 95 % CI: 1.17 to 3), chronic kidney disease (CKD) (HR: 2.30, 95 % CI: 1.38 to 3.84), and chronic obstructive pulmonary disease (COPD) (HR: 1.75, 95 % CI: 1.09 to 2.83). Patients with either porcelain aorta (18 %) or frailty (25 %) exhibited acute outcomes similar to the rest of the study population, and porcelain aorta patients tended to have a better survival rate at 1-
year follow-up. The authors concluded that a TAVI program including both TF and TA approaches was associated with comparable mortality as predicted by surgical risk calculators for the treatment of patients at very high or prohibitive surgical risk, including porcelain aorta and frail patients. Baseline (PH, COPD, CKD) and peri-procedural (hemodynamic support, sepsis) factors but not the approach determined worse outcomes.

Ye and colleagues (2010) reported clinical and echocardiographical outcomes of TA-TAVI in 71 patients (27 males and 44 females) who underwent TAVI with either 23- or 26-mm Edwards Lifesciences transcatheter valve. All patients with symptomatic aortic stenosis were declined for conventional SAVR as a consequence of unacceptable operative risks and were not candidates for TF-TAVI because of poor arterial access. Clinical and echocardiographical follow-ups were performed before discharge, at 1 and 6 months, and then yearly. The mean follow-up was 12.9 +/- 11.5 months with a total of 917.3 months of follow-up. Mean age was 80.0 +/- 8.1 years and predicted operative mortality was 34.5% +/- 20.4 % by EuroSCORE and 12.1 % +/- 7.7 % by the STS risk score. Valves were successfully implanted in all patients. Twelve patients died within 30 days (30-day mortality: 16.9 % in all patients, 33 % in the first 15 patients, and 12.5 % in the remainder), and 10 patients died subsequently. Overall survivals at 24 and 36 months were 66.3 % +/- 6.4 % and 58.0 % +/- 9.5 %, respectively. Among 59 patients who survived at least 30 days, 24- and 36-month survivals were 79.8 % +/- 6.4 % and 69.8 % +/- 10.9 %, respectively. Late valve-related complications were rare. New York Heart Association (NYHA) functional class improved significantly from pre-operative 3.3 +/- 0.8 to 1.8 +/- 0.8 at 24 months. The aortic valve area and trans-aortic mean gradient remained stable at 24 months (1.6 +/- 0.3 cm(2) and 10.3 +/- 5.9 mm Hg, respectively). The authors concluded that these findings suggest that TA-TAVI provides sustained clinical and hemodynamic benefits for up to 36 months in selected high-risk patients with symptomatic severe aortic stenosis.

Attias and associates (2010) described the results of TF-TAVI using either the Sapien prosthesis (Edwards Lifesciences, Irvine, CA) or the CoreValve ReValving system (CoreValve ReValving Technology Medtronic, Minneapolis, MN). Of 236 patients at high-risk or with contraindications to surgery, 83 were treated with TF-TAVI. The Sapien was the only prosthesis available until May 2008 and, since then, was used as the first option, while the CoreValve system was used when contraindications to the Sapien prosthesis were present. Patients were aged 81 +/- 9 years, 98 % in NYHA classes III/IV, with predicted surgical mortalities of 26 % +/- 14 % using the EuroSCORE and 15 % +/- 8 % using the STS risk score. Seventy-two patients were treated with the Sapien prosthesis and 11 with the CoreValve system. The valve was implanted in 94 % of the cases. Thirty-day mortality was 7 %. Overall, 1- and 2-year survival rates were 78 % +/- 5 % and 71 % +/- 7 %, respectively. Among patients treated with the Sapien, the 1-year survival rate was 67 % +/- 12 % in the first 20 % of patients versus 86 % +/- 5 % in the last 80 % of patients (p = 0.02). In uni-variate analysis, early experience was the only significant predictor of 1-year mortality. The authors concluded that combining the use of the Sapien and the CoreValve prostheses increases the number of patients who can be treated by TF-TAVI and provides satisfactory results at 2 years in this high-risk population.

Rajani et al (2010) compared survival in patients with inoperable aortic stenosis who undergo TAVI against those managed medically. Survival rates were compared in consecutive patients with severe symptomatic aortic stenosis who either underwent TAVI or continued on medical management following multi-disciplinary team assessment. All patients had been turned down, or considered at unacceptably high risk, for SAVR.
Patients were reviewed in clinic or by telephone every 6 months. Mortality data was obtained from the United Kingdom Office of National Statistics. The study group included 85 patients aged 81 +/- 7 years (range of 62 to 94), of whom 48 were males. A total of 38 patients underwent TAVI while 47 patients were deemed unsuitable based on echocardiographical, angiographical, or clinical criteria and remained on medical therapy. The calculated EuroSCORE for the TAVI group was 11 +/- 2 and for the medical group 9 +/- 2 (p < 0.001). TAVI-related procedural mortality was 2.6 %, and 30-day mortality was 5.2 %. Among the medically-treated patients, 14 (30 %) underwent palliative balloon aortic valvuloplasty, with a trend toward improved survival (p = 0.06). During overall follow-up of 215 +/- 115 days, there were a total of 18 deaths; TAVI, n = 5 (13 %); Medical, n = 13 (28 %) (p = 0.04). The authors concluded that patients with severe aortic valve disease who are not suitable for SAVR have an improved prognosis if treated with TAVI rather than continuing on medical management alone.

Avanzas et al (2010) described early experience and medium-term follow-up with the CoreValve prosthesis at 3 Spanish hospitals. The study included patients with severe symptomatic aortic stenosis. Other inclusion criteria were: aortic valve annulus diameter in the range 20 to 27 mm; diameter of the ascending aorta at the level of the sino-tubular junction less than or equal to 40 mm (small prosthesis) or less than or equal to 43 mm (large prosthesis), and femoral artery diameter greater than 6 mm. The study included 108 patients with a mean age of 78.6 +/- 6.7 years, a mean aortic valve area of 0.63 +/- 0.2 cm$^2$, and a mean EuroSCORE of 16 % +/- 13.9 % (range of 2.27 % to 86.4 %). After valve implantation, the maximum echocardiographical trans-aortic valve gradient decreased from 83.8 +/- 23 to 12.6 +/- 6 mmHg. No patient presented with greater than grade-2 residual aortic regurgitation on angiography. The procedural success rate was 98.1 %. No patient died during the procedure. Definitive pace-maker implantation was carried out for atrio-ventricular block in 38 patients (35.2 %). At 30 days, all-cause mortality and the rate of the combined end point of death, stroke, myocardial infarction or referral for surgery were 7.4 % and 8.3 %, respectively. The estimated 1-year survival rate calculated using the Kaplan-Meier method was 82.3 % (for a median follow-up period of 7.6 months). The authors concluded that their early experience indicates that percutaneous aortic valve replacement is a safe and practical therapeutic option for patients with severe aortic stenosis who are at a high surgical risk.

In the PARTNER trial, Leon and colleagues (2010) randomly assigned patients with severe aortic stenosis, whom surgeons considered not to be suitable candidates for surgery, to standard therapy (including balloon aortic valvuloplasty) or TF-TAVI of a balloon-expandable bovine pericardial valve. The primary end point was the rate of death from any cause. A total of 358 patients with aortic stenosis who were not considered to be suitable candidates for surgery underwent randomization at 21 centers (17 in the United States). At 1 year, the rate of death from any cause (Kaplan–Meier analysis) was 30.7 % with TAVI, as compared to 50.7 % with standard therapy (HR with TAVI, 0.55; 95 % CI: 0.40 to 0.74; p < 0.001). The rate of the composite end point of death from any cause or repeat hospitalization was 42.5 % with TAVI as compared to 71.6 % with standard therapy (HR, 0.46; 95 % CI: 0.35 to 0.59; p < 0.001). Among survivors at 1 year, the rate of cardiac symptoms (NYHA class III or IV) was lower among patients who had undergone TAVI than among those who had received standard therapy (25.2 % versus 58.0 %, p < 0.001). At 30 days, TAVI, as compared with standard therapy, was associated with a higher incidence of major strokes (5.0 % versus 1.1 %, p = 0.06) and major vascular complications (16.2 % versus 1.1 %, p < 0.001). In the year after TAVI, there was no deterioration in the functioning of the bioprosthetic valve, as assessed by evidence of
stenosis or regurgitation on an echocardiogram. The authors concluded that in patients with severe aortic stenosis who were not suitable candidates for surgery, TAVI, as compared with standard therapy, significantly reduced the rates of death from any cause, the composite end point of death from any cause or repeat hospitalization, and cardiac symptoms, despite the higher incidence of major strokes and major vascular events. Moreover, the authors stated that these findings cannot be extrapolated to other patients with aortic stenosis. Additional randomized trials are needed to compare TAVI with aortic valve replacement among high risk patients with aortic stenosis for whom surgery is a viable option and among low risk patients with aortic stenosis.

In an editorial that accompanied that afore-mentioned study, Lazar (2010) stated that "[d]espite the promising results of the PARTNER trial, surgical aortic-valve replacement remains the standard for the treatment of aortic stenosis. TAVI should be reserved for patients at inordinately high risk who are not suitable candidates for surgery and who have decreased life expectancy. Given the unknown durability of these prostheses and the high incidence of regurgitation, TAVI should not be performed in patients with long life expectancies".

The editorialist noted that advanced age alone is not a reason to perform TAVI over an open aortic valve implantation; there needs to be other risk factors for open surgery. It is important to define the criteria for high risk or inoperable aortic stenosis, since there are discrepancies among various risk-scoring systems in the prediction of the risk of death. The EuroSCORE has been shown to consistently over-estimate the risk of death, whereas most people consider the STS risk score to be more accurate. An analysis of data from the STS National Database on 108,687 isolated aortic-valve replacements shows that overall mortality is now 2.6 %, and the incidence of stroke is 1.3 %. Among patients 80 to 85 years of age, 30-day mortality is less than 5 % and the rate of stroke is less than 2.5 %. These values should be the yardstick by which other strategies to treat aortic stenosis should be measured.

Clavel et al (2010) stated that patients with severe aortic stenosis and reduced left ventricular ejection fraction (LVEF) have a poor prognosis with conservative therapy but a high operative mortality when treated surgically. Recently, TAVI has emerged as an alternative to SAVR for patients considered at high or prohibitive operative risk. The objective of this study was to compare TAVI and SAVR with respect to post-operative recovery of LVEF in patients with severe aortic stenosis and reduced LV systolic function. Echocardiographical data were prospectively collected before and after the procedure in 200 patients undergoing SAVR and 83 patients undergoing TAVI for severe aortic stenosis (aortic valve area less than or equal to 1 cm²) with reduced LV systolic function (LVEF less than or equal to 50 %). Patients who underwent TAVI were significantly older (81 +/- 8 versus 70 +/- 10 years; p < 0.0001) and had more co-morbidities compared with patients who underwent SAVR. Despite similar baseline LVEF (34 +/- 11 % versus 34 +/- 10 %), TAVI patients had better recovery of LVEF compared with SAVR patients (change in LVEF, 14 +/- 15 % versus 7 +/- 11 %; p = 0.005). At the 1-year follow-up, 58 % of TAVI patients had a normalization of LVEF (greater than 50 %) as opposed to 20 % in the SAVR group. On multi-variable analysis, female gender (p = 0.004), lower LVEF at baseline (p = 0.005), absence of atrial fibrillation (p = 0.01), TAVI (p = 0.007), and larger increase in aortic valve area after the procedure (p = 0.01) were independently associated with better recovery of LVEF. The authors concluded that in patients with severe aortic stenosis and depressed LV systolic function, TAVI is associated with better LVEF recovery compared
with SAVR; and TAVI may provide an interesting alternative to SAVR in patients with depressed LV systolic function considered at high surgical risk.

Dworakowski et al (2010) stated that TAVI is an alternative treatment option for patients with aortic stenosis deemed high-risk or unsuitable for aortic valve replacement. The aim of this study was to assess the feasibility of TAVI in elderly patients, the delivery of this technology with a multi-disciplinary approach, and the use of traditional surgical scoring systems. A total of 151 consecutive patients (mean age of 82.6 +/- 7.3 years) with severe aortic stenosis underwent TAVI with the Edwards Lifesciences Sapien bioprosthesis using the TA (n = 84; 56 %) or TF (n = 67; 44 %) approach. These investigators analyzed procedural outcome, complications, functional status, and mid-term outcome of patients. The multi-disciplinary team comprised interventional cardiologists, cardiothoracic surgeons, imaging specialists, cardiac anesthetists, and specialist nurses. A total of 70 % of patients were in NYHA class III/IV, and EuroSCORE was 21.6 +/- 11.9. Procedural success was achieved in 98 %. Post-operative complications included stroke (6 %), complete atrio-ventricular block (5.3 %), renal failure requiring hemo-filtration (9.3 %), and vascular injury (8.6 %). Overall 30-day mortality was 9.9 % (n = 15). The EuroSCORE was a predictor of short-term mortality (logistic regression model, p < 0.05). Thirty-day mortality post-TAVI for patients with EuroSCORE less than 20, 20 to 40, and greater than 40 was 5.4 %, 13.2 %, and 22.2 %, respectively. The authors concluded that TAVI is a feasible treatment option in this patient group with promising short- to medium-term results. Renal failure is the commonest short-term complication, and the incidence of vascular complications remains high.

Bollati et al (2010) noted that aortic valve disease is a growing cause of mortality and morbidity, especially in developed countries. Whereas medical therapy is associated with an ominous prognosis, since the 1970s, SAVR has represented a standard therapy for fit patients. Indeed, this approach is safe and feasible in younger patients without co-morbidities. However, in unfit patients, surgery may be associated with a very high risk. The advent of transcatheter valve replacement techniques, by means of percutaneous or TA approaches, has been recently introduced into mainstream clinical practice and is likely to radically change the treatment of aortic valve disease. At present, further data are needed to thoroughly appraise the long-term risk-benefit balance of transcatheter valve replacement techniques. For this reason, it can only be considered for high surgical risk patients, but early results are so promising that in the future, TAVI could become the first therapeutic choice, even for low risk patients.

Zahn et al (2011) reported the first results of the prospective multi-center German TAVI-Registry. Between January 2009 and December 2009, a total of 697 patients (81.4 +/- 6.3 years, 44.2 % males, and logistic EuroScore 20.5 +/- 13.2 %) underwent TAVI. Pre-operative aortic valve area was 0.6 +/- 0.2 cm(2) with a mean trans-valvular gradient of 48.7 +/- 17.2 mm Hg. Transcatheter aortic valve implantation was performed percutaneously in the majority of patients [666 (95.6 %)]. Only 31 (4.4 %) procedures were done surgically: 26 (3.7 %) transapically and 5 (0.7 %) transaortically. The Medtronic CoreValve prosthesis was used in 84.4 %, whereas the Sapien Edwards prosthesis was used in the remaining cases. Technical success was achieved in 98.4 % with a post-operative mean trans-aortic pressure gradient of 5.4 +/- 6.2 mm Hg. Any residual aortic regurgitation was observed in 72.4 % of patients, with a significant aortic insufficiency (greater than or equal to grade III) in 16 patients (2.3 %). Complications included pericardial tamponade in 1.8 % and stroke in 2.8 % of patients. Permanent pacemaker implantation after TAVI became necessary in 39.3 % of patients. In-hospital death rate
was 8.2 %, and the 30-day death rate 12.4 %. The authors concluded that in this real-world registry of high-risk patients with aortic stenosis, TAVI had a high success rate and was associated with moderate in-hospital complications. However, careful patient selection and continued hospital selection seem crucial to maintain these results.

In a prospective, multi-center, single-arm study, Buellesfeld et al (2011) evaluated the safety, device performance, and clinical outcome up to 2 years for patients undergoing TAVI. This trial was conducted with symptomatic patients undergoing TAVI for the treatment of severe aortic valve stenosis using the 18-F Medtronic CoreValve prosthesis. In all, 126 patients (mean age of 82 years, 42.9 % male, mean logistic European System for Cardiac Operative Risk Evaluation score 23.4 %) with severe aortic valve stenosis (mean gradient of 46.8 mm Hg) underwent the TAVI procedure. Access was TF in all but 2 cases with subclavian access. Retrospective risk stratification classified 54 patients as moderate surgical risk, 51 patients as high-risk operable, and 21 patients as high-risk inoperable. The overall technical success rate was 83.1 %. Thirty-day all-cause mortality was 15.2 %, without significant differences in the subgroups. At 2 years, all-cause mortality was 38.1 %, with a significant difference between the moderate-risk group and the combined high-risk groups (27.8 % versus 45.8 %, p = 0.04). This difference was mainly attributable to an increased risk of non-cardiac mortality among patients constituting the high-risk groups. Hemodynamic results remained unchanged during follow-up (mean gradient of 8.5 +/- 2.5 mm Hg at 30 days and 9.0 +/- 3.4 mm Hg at 2 years). Functional class improved in 80 % of patients and remained stable over time. There was no incidence of structural valve deterioration. The authors concluded that the TAVI procedure provides sustained clinical and hemodynamic benefits for as long as 2 years for patients with symptomatic severe aortic stenosis at increased risk for surgery.

Smith et al (2011) compared transcatheter versus surgical aortic-valve replacement in high-risk patients. At 25 centers, these investigators randomly assigned 699 high-risk patients with severe aortic stenosis to undergo either TAVI with a balloon-expandable bovine pericardial valve (either a TF or a TA approach) or surgical replacement. The primary end point was death from any cause at 1 year. The primary hypothesis was that TAVI is not inferior to surgical replacement. The rates of death from any cause were 3.4 % in the TAVI group and 6.5 % in the surgical group at 30 days (p = 0.07) and 24.2 % and 26.8 %, respectively, at 1 year (p = 0.44), a reduction of 2.6 percentage points in the TAVI group (upper limit of the 95 % CI: 3.0 percentage points; pre-defined margin, 7.5 percentage points; p = 0.001 for non-inferiority). The rates of major stroke were 3.8 % in the TAVI group and 2.1 % in the surgical group at 30 days (p = 0.20) and 5.1 % and 2.4 %, respectively, at 1 year (p = 0.07). At 30 days, major vascular complications were significantly more frequent with TAVI (11.0 % versus 3.2 %, p < 0.001); adverse events that were more frequent after surgical replacement included major bleeding (9.3 % versus 19.5 %, p < 0.001) and new-onset atrial fibrillation (8.6 % versus 16.0 %, p = 0.006). More patients undergoing TAVI had an improvement in symptoms at 30 days, but by 1 year, there was not a significant between-group difference. The authors concluded that in high-risk patients with severe aortic stenosis, transcatheter and surgical procedures for aortic-valve replacement were associated with similar rates of survival at 1 year, although there were important differences in peri-procedural risks.

Thomas et al (2011) stated that the Edwards SAPIEN aortic bioprosthesis European outcome (SOURCE) registry was designed to assess initial post-commercial clinical TAVI results of the Edwards SAPIEN valve in consecutive patients in Europe. Cohort 1 consists of 1,038 patients enrolled at 32 centers. One-year outcomes were presented. Patients
with the TA approach \( (n = 575) \) suffered more co-morbidities than TF patients \( (n = 463) \) with a significantly higher logistic EuroSCORE \( (29 \% \text{ versus } 25.8 \%; \ p = 0.007) \). These groups are different; therefore, outcomes can not be directly compared. Total Kaplan Meier 1-year survival was 76.1 \% overall, 72.1 \% for TA and 81.1 \% for TF patients, and 73.5 \% of surviving patients were in NYHA class I or II at 1 year. Combined TA and TF causes of death were cardiac in 25.1 \%, non-cardiac in 49.2 \%, and unknown in 25.7 \%. Pulmonary complications \( (23.9 \%) \), renal failure \( (12.5 \%) \), cancer \( (11.4 \%) \), and stroke \( (10.2 \%) \) were the most frequent non-cardiac causes of death. Multi-variable analysis identified logistic EuroSCORE, renal disease, liver disease, and smoking as variables with the highest HRs for 1-year mortality whereas carotid artery stenosis, hyperlipidemia, and hypertension were associated with lower mortality. The authors concluded that the SOURCE Registry is the largest consecutively enrolled registry for TAVI procedures. It demonstrated that with new transcatheter aortic techniques excellent 1-year survival in high-risk and inoperable patients is achievable and provides a benchmark against which future TAVI cohorts and devices can be measured.

Kalavrouziotis et al (2011) examined valve hemodynamics and clinical outcomes among patients with a small aortic annulus who underwent TAVI. Between 2007 and 2010, a total of 35 patients \( \text{(mean age of } 79.2 +/- 9.4 \text{ years)} \) with severe aortic stenosis and an aortic annulus diameter less than 20 mm \( \text{(mean of } 18.5 +/- 0.9 \text{ mm)} \) underwent TAVI with a 23-mm Edwards SAPIEN bioprosthesis. Echocardiographical parameters and clinical outcomes were assessed prior to discharge and at 6, 12, and 24 months. Procedural success was achieved in 34 patients \( (97.1 \%) \). There was 1 in-hospital death. Peak and mean transaortic gradients decreased from 76.3 +/- 33.0 mm Hg and 45.2 +/- 20.6 mm Hg at baseline to 21.8 +/- 8.4 mm Hg and 11.7 +/- 4.8 mm Hg post-procedure, respectively \( \text{(both } p < 0.0001) \). Mean indexed effective orifice area \( \text{(IEOA)} \) increased from 0.35 +/- 0.10 cm\(^{2}\)/m\(^{2}\) at baseline to 0.90 +/- 0.18 cm\(^{2}\)/m\(^{2}\) post-procedure \( \text{(p < 0.0001)} \). Severe prosthesis-patient mis-match \( \text{(IEOA less than 0.65 cm}^{2}\)/m\(^{2}\)) \) occurred in 2 patients \( (5.9 \%) \). At a mean follow-up of 14 +/- 11 months, gradients remained low and 30 of the 31 remaining survivors were in NYHA functional class I or II. The authors concluded that in high-risk patients with severe aortic stenosis and a small aortic annulus, TAVI is associated with good post-procedural valve hemodynamics and clinical outcomes. They stated that TAVI may provide a reasonable alternative to conventional AVR in elderly patients with a small aortic annulus.

Quality-of-life (QOL) is a critical measure of effectiveness of TAVI in patients with severe aortic stenosis. There are studies that showed a marked improvement in QOL in patients who underwent TAVI. Ussia et al (2011) evaluated 1 year changes in QOL in patients who underwent TAVI. A total of 149 consecutive patients underwent TAVI using the 18 Fr CoreValve \( \text{(Medtronic Inc, Minneapolis, MN)} \) or the Edwards Sapien XT heart valve \( \text{(Edwards Lifescience, Irvine, CA)} \). Of these, 143 patients with successful prosthesis implantation comprised the study population. The shorter SF-12 version 2 \( \text{(SF-12v2)} \) Health-Survey questionnaire provides scales for physical \( \text{(physical component summary [PCS])} \) and mental \( \text{(mental component summary [MCS])} \) health. Among patients included in the present analysis, device success was obtained in 138 patients \( (96.5 \%) \). Mean pre-procedural SF-12v2 scores showed an important upgrading after TAVI: PCS improved from 28.3 to 44.0 at 5 months and 42.4 at 12 months \( \text{(p < 0.001)} \); MCS increased from 38.0 to 47.3 at 5 months and 48.2 at 12 months \( \text{(p < 0.001)} \). Both the physical and mental score summaries at follow-up of these post-TAVI patients were not significantly different from the anticipated thresholds of the general Italian population over the age of 75 years. New York Heart Association functional class improvement was reported in all patients.
The authors concluded that these findings showed a marked mid-term improvement in functional status as well as physical and mental health in patients who underwent TAVI.

Georgiadou et al (2011) assessed changes in QOL along with functional status and late survival after TAVI. A total of 36 consecutive patients (80.5 +/- 5.9 years, 21 men and 15 women) with a logistic Euroscore of 29.7 +/- 13.7 underwent TAVI using the 18-Fr CoreValve prosthesis. Aortic valve prosthesis was inserted retrograde using a femoral or a subclavian arterial approach. QOL was evaluated by administering the Short Form 36 (SF-36) tool and SF-12v2 questionnaires before and 1 year after TAVI. Transcatheter aortic valve implantation was successfully performed in all patients. The estimated 1-year overall survival rate using Kaplan-Meier method was 68 %. One-year follow-up also showed a marked improvement in echocardiographic parameters (peak gradient 76.2 +/- 26.1 versus 15.4 +/- 7.8 mm Hg, p < 0.001; aortic valve area 0.7 +/- 0.1 versus 2.6 +/- 2.7 cm(2), p < 0.001) with a significant change in NYHA functional class (3 +/- 0.7 versus 1.2 +/- 0.4, p < 0.001). Both pre-procedural summary SF-36 and SF-12v12 physical and mental scores showed a significant improvement 1 year after TAVI (21.6 versus 46.7, p < 0.001; 42.9 versus 55.2, p < 0.001; 22 versus 48.9, p < 0.001; 43.3 versus 52.2, p < 0.001, respectively). The authors concluded that these findings showed a marked 1-year clinical benefit in functional status as well as physical and mental health in patients who underwent TAVI.

On November 2, 2011, the Food and Drug Administration (FDA) approved the Sapien transcatheter heart valve (THV) as a replacement of an aortic heart valve damaged by senile aortic valve stenosis without open-heart surgery. The Sapien THV is made of bovine tissue and polyester supported with a stainless steel mesh frame. To replace the diseased valve, the Sapien THV is compressed into the end of a long, thin, tube-like device called a delivery catheter. The delivery catheter, which is slightly wider than a pencil, and the Sapien THV are inserted into the femoral artery and threaded to the site of the diseased valve. The heart valve is then released from the delivery catheter and expanded with a balloon and is immediately functional. The RetroFlex 3 delivery system is used for the trans-femoral delivery of the Edwards Sapien transcatheter heart valve.

The FDA's approval of the Sapien THV is based on a study in 365 patients who were not eligible for open-heart surgery. Half of the patients received the Sapien valve; remaining patients received another treatment that did not require open-heart surgery. One alternative procedure involved enlarging the aortic valve opening by stretching it with a balloon (balloon valvuloplasty). Patients receiving the Sapien valve experienced 2.5 times more strokes and 8 times as many vascular and bleeding complications than patients who did not receive the implant; however, they were more likely to survive 1 year after surgery. After 1 year, 69 % of the Sapien patients were alive compared with 50 % of those who received an alternative treatment. The most common serious and potentially life-threatening side effects in patients receiving the Sapien valve and the procedure to implant the valve include death, stroke, perforation of the blood vessels, ventricle or valvular structures, damage to the conduction system in the heart, significant bleeding, and leaks around the new valve.

The Sapien THV is approved for patients who are not eligible for open-heart surgery for replacement of their aortic valve and have a calcified aortic annulus (calcium build-up in the fibrous ring of the aortic heart valve). The Sapien THV is not indicated for patients who can be treated by open-heart surgery. Patients who have congenital heart valve
anomalies, have masses or an infection in their hearts, or can not tolerate anti-coagulation/anti-platelet therapy should not receive the Sapien THV.

According to the FDA-approved product labeling, transcatheter aortic valve implantation is not indicated for individuals who can be treated by open-heart surgery. It is also contraindicated in persons who can not tolerate anti-coagulation/anti-platelet therapy, or who have active bacterial endocarditis, or other active infections.

In 2014, the U.S. Food and Drug Administration (FDA) approved the self-expanding transcatheter Medtronic CoreValve System for patients with severe aortic stenosis who are at high risk for surgery (Medtronic, 2014). This approval is based on the Hith Risk Study of the CoreValve U.S. Pivotal Trial that showed clinical outcomes at one year with the CoreValve System were superior to open-heart surgery. The head-to-head study, comparing transcatheter aortic valve replacement (TAVR) with the CoreValve System to traditional surgical aortic valve replacement, met its primary endpoint with survival at one year for patients receiving the CoreValve System (85.8 percent), which was statistically superior to patients receiving a surgical valve (80.9 percent).

For patients treated with the CoreValve System in the High Risk Study, rates of stroke were not statistically different than rates experienced by surgery patients (Medtronic, 2014). The rate of MACCE (major adverse cardiovascular or cerebral events) was significantly lower for CoreValve patients at one year, and overall hemodynamic performance was better in CoreValve patients than in surgical patients across all time points.

According to the manufacturer, the CoreValve System's self-expanding frame provides controlled deployment, enabling physicians to accurately place the valve inside a patient's original valve, while conforming to the native annulus to provide a seal (Medtronic, 2014). The FDA approved the CoreValve platform, including the 23mm, 26mm, 29mm and 31mm size valves, all of which are delivered through an 18 Fr TAVR delivery system.

Gurvitch and colleagues (2011) stated that when bioprosthetic cardiac valves fail, re-operative valve replacement carries a higher risk of morbidity and mortality compared with initial valve replacement. Transcatheter heart valve implantation may be a viable alternative to surgical aortic valve replacement for high-risk patients with native aortic stenosis, and valve-in-valve (V-in-V) implantation has been successfully performed for failed surgical bioprostheses in the aortic, mitral, pulmonic, and tricuspid positions. Despite some core similarities to transcatheter therapy of native valve disease, V-in-V therapy poses unique clinical and anatomic challenges. The authors noted that initial results with V-in-V therapy are very encouraging. However, in the absence of vigorous evaluation and long-term follow-up, V-in-V therapy is probably best considered only for patients who present with a prohibitive re-operative risk. Therapy of small (e.g., less than or equal to 2 mm aortic valves) should be approached with caution as significant residual gradients may remain with currently available valves. Operators should be encouraged to share their experience, whether favorable or unfavorable. They stated that future technologic advances may continue to improve both hemodynamic and clinical outcomes.

Piazza and colleagues (2012) reviewed the acute procedural outcomes of patients who underwent transcatheter aortic valve (TAV)-in-surgical aortic valve (SAV) implantation at the German Heart Center, Munich, and summarized the existing literature on TAV-in-SAV implantation (n = 47). From January 2007 to March 2011, 20 out of 556 patients underwent a TAV-in-SAV implantation at the German Heart Center Munich. Baseline
characteristics and clinical outcome data were prospectively entered into a dedicated database. The mean patient age was 75 +/- 13 years, and the mean logistic European System for Cardiac Operative Risk Evaluation and Society of Thoracic Surgeons' Risk Model scores were 27 +/- 13 % and 7 +/- 4 %, respectively. Of the 20 patients, 14 had stented and 6 had stentless surgical bioprostheses. Most cases (12 of 20) were performed via the TA route using a 23-mm Edwards Sapien prosthesis. Successful implantation of a TAV in a SAV with the patient leaving the catheterization laboratory alive was achieved in 18 of 20 patients. The mean trans-aortic valve gradient was 20.0 +/- 7.5 mm Hg. None-to-trivial, mild, and mild-to-moderate para-valvular aortic regurgitation was observed in 10, 6, and 2 patients, respectively. These investigators experienced 1 intra-procedural death following pre-implant balloon aortic valvuloplasty ("stone heart") and 2 further in-hospital deaths due to myocardial infarction. The authors concluded that TAV-in-SAV implantation is a safe and feasible treatment for high-risk patients with failing aortic bioprosthetic valves and should be considered as part of the armamentarium in the treatment of aortic bioprosthetic valve failure. The findings of this small study need to be validated by well-designed studies with long-term follow-up.

Ferrari (2012) stated that the advent of TAVI has opened new horizons in cardiac surgery and, in particular, the possibility of implanting stented valves within the degenerated stented bioprosthesis, the so-called "V-in-V" concept, has become a clinical practice in experienced cardiac centers. The V-in-V procedure represents a minimally invasive approach dedicated to high-risk redo patients, and published preliminary reports have shown a success rate of 100 % with absence of significant valvular leaks, acceptable trans-valvular gradients and low complication rate. However, this procedure is not riskless and the most important concerns are about the size mis-match and the right positioning within the degenerated bioprosthesis.

A review on "Indication and structures and management of transcatheter aortic valve implantation" (Doebler et al, 2012) states that TAVI should be restricted to patients with severe symptomatic aortic valve stenosis and contraindications against open heart surgery or maximum peri-operative risk. Aortic bioprosthetic valve failure is not mentioned as indication. Furthermore, the National Institute for Health and Clinical Excellence's clinical practice guideline on "Transcatheter aortic valve implantation for aortic stenosis" (NICE, 2012) does not list valve-in-valve implantation for failed aortic bioprostheses as an indication.

On October 19, 2012, the FDA expanded the approved indication for the Sapien THV to include patients with aortic valve stenosis who are eligible for surgery, but who are at high risk for serious surgical complications or death. The manufacturer submitted a Premarket Application (PMA) in April 2011 based on data from the high-risk cohort (Cohort A) of The PARTNER Trial. Cohort A compared the outcomes of patients at high risk for traditional open-heart surgery randomized to receive either surgical aortic valve replacement or the SAPIEN valve via transfemoral or transapical delivery. The trial was successful in meeting its primary endpoint at one year, concluding that survival of high-risk patients treated with the SAPIEN valve was equivalent to those treated with traditional open-heart surgery. The high risk cohort of the PARTNER trial supporting the expanded approval included 348 surgical patients who received the Sapien THV and 351 similar patients who received AVR through open-heart surgery. Both groups had similar death rates at 1 month, 1 year, and 2 years after the procedures. Those who received the THV showed an increased risk for major vascular complications, such as artery dissection or perforation, and for stroke
during the first month following the procedure. Patients who received the AVR were more likely than the THV recipients to experience major vascular bleeding during the procedure.

Chao and associates (2013) stated that TAVI has emerged as an acceptable treatment modality for patients with severe aortic stenosis who are deemed inoperable by conventional SAVR. However, the role of TAVI in patients who are potential surgical candidates remains controversial. These investigators performed a systematic review using 5 electronic databases, identifying all relevant studies with comparative data on TAVI versus conventional SAVR. The primary end-point was all-cause mortality. A number of peri-procedural outcomes were also assessed according to the Valve Academic Research Consortium end-point definitions. A total of 14 studies were quantitatively assessed and included for meta-analysis, including 2 randomized controlled trials (RCTs) and 11 observational studies. Results indicated no significant differences between TAVI and conventional SAVR in terms of all-cause and cardiovascular related mortality, stroke, myocardial infarction or acute renal failure. A subgroup analysis of RCTs identified a higher combined incidence of stroke or transient ischemic attacks in the TAVI group compared to the conventional SAVR group. Transcatheter aortic valve implantation was also found to be associated with a significantly higher incidence of vascular complications, permanent pacemaker requirement and moderate or severe aortic regurgitation. However, patients who underwent conventional SAVR were more likely to experience major bleeding. Both treatment modalities appeared to effectively reduce the trans-valvular mean pressure gradient. The authors concluded that the available data on TAVI versus conventional SAVR for patients at a higher surgical risk showed that major adverse outcomes such as mortality and stroke appeared to be similar between the 2 treatment modalities. Evidence on the outcomes of TAVI compared with conventional SAVR in the current literature is limited by inconsistent patient selection criteria, heterogeneous definitions of clinical end-points and relatively short follow-up periods. The indications for TAVI should therefore be limited to inoperable surgical candidates until long-term data become available.

Dubois and colleagues (2013) noted that TAVI has been proposed as a treatment alternative for patients with aortic valve stenosis at high or prohibitive risk for SAVR. These researchers evaluated outcomes after treatment according to the decisions of the multi-disciplinary heart team. At a tertiary center, all high-risk patients referred between March 1, 2008 and October 31, 2011 for symptomatic aortic stenosis were screened and planned to undergo SAVR, TAVI or medical treatment. These investigators reported clinical outcomes as defined by the Valve Academic Research Consortium. Of 163 high-risk patients, those selected for SAVR had lower logistic EuroSCORE and STS scores when compared with TAVI or medical treatment (median [interquartile range] 18 [12 to 26]; 26 [17 to 36]; 21 [14 to 32] % (p = 0.015) and 6.5 [5.1 to 10.7]; 7.6 [5.8 to 10.5]; 7.6 [6.1 to 15.7] % (p = 0.056)). All-cause mortalities at 1 year in 35, 73 and 55 patients effectively undergoing SAVR, TAVI and medical treatment were 20, 21 and 38 %, respectively (p = 0.051). Cardiovascular death and major stroke occurred in 9, 8 and 33 % (p < 0.001) and 6, 4 and 2 % (p = 0.62), respectively. For patients undergoing valve implantation, device success was 91 and 92 % for SAVR and TAVI, respectively. The combined safety end-point at 30 days was in favor of TAVI (29 %) versus SAVR (63 %) (p = 0.001). In contrast, the combined efficacy end-point at 1 year tended to be more favorable for SAVR (10 versus 24% for TAVI, p = 0.12). The authors concluded that patients who are less suitable for SAVR can be treated safely and effectively with TAVI with similar outcomes when compared with patients with a lower-risk profile undergoing SAVR. Patients with TAVI or SAVR have better survival than those undergoing medical treatment only.
Chieffo et al (2013) compared outcomes after TF-TAVI with the Medtronic CoreValve (MCV) versus the Edwards SAPIEN/SAPIEN XT transcatheter heart valve (ESV) for severe aortic stenosis. The data from databases of 4 experienced European centers were pooled and analyzed. Due to differences in baseline clinical characteristics, propensity score matching was performed. Study objectives were Valve Academic Research Consortium outcomes at 30 days and 1 year. In total, 793 patients were included: 453 (57.1 %) treated with the MCV and 340 (42.9 %) with the ESV. After propensity matching, 204 patients were identified in each group. At 30 days, there were no differences in all-cause mortality (MCV, 8.8 % versus ESV, 6.4 %; HR: 1.422; 95 % CI: 0.677 to 2.984; p = 0.352), cardiovascular mortality (MCV, 6.9 % versus ESV, 6.4 %; HR: 1.083; 95 % CI: 0.496 to 2.364; p = 0.842), myocardial infarction (MCV, 0.5 % versus ESV, 1.5 %; HR: 0.330; 95 % CI: 0.034 to 3.200; p = 0.339), stroke (MCV, 2.9 % versus ESV, 1.0 %; HR: 3.061; 95 % CI: 0.610 to 15.346; p = 0.174), or device success (MCV, 95.6 % versus ESV, 96.6 %; HR: 0.770; 95 % CI: 0.281 to 2.108; p = 0.611). Additionally, there were no differences in major vascular complications (MCV, 9.3 % versus ESV, 12.3 %; HR: 0.735; 95 % CI: 0.391 to 1.382; p = 0.340) or life-threatening bleeding (MCV, 13.7 % versus ESV, 8.8 %; HR: 1.644; 95 % CI: 0.878 to 3.077; p = 0.120). Medtronic CoreValve was associated with more permanent pacemakers (22.5 % versus 5.9 %; HR: 4.634; 95 % CI: 2.373 to 9.050; p < 0.001). At 1 year, there were no differences in all-cause (MCV, 16.2 % versus ESV, 12.3 %; HR: 1.374; 95 % CI: 0.785 to 2.407; p = 0.266) or cardiovascular mortality. The authors concluded that no differences between the 2 commercially available TF-TAVI devices were observed at the adjusted analysis in Valve Academic Research Consortium outcomes except for the need for permanent pacemakers with the MCV.

Roy and colleagues (2013) evaluated the anecdotal use of TAVI in pure native aortic valve regurgitation (NAVR) for patients who were deemed surgically inoperable. Data on baseline patient characteristics, device and procedure parameters, echocardiographic parameters, and outcomes up to July 2012 were collected retrospectively from 14 centers that have performed TAVI for NAVR. A total of 43 patients underwent TAVI with the CoreValve prosthesis (Medtronic, Minneapolis, MN) at 14 centers (mean age of 75.3 ± 8.8 years; 53 % female; mean logistic EuroSCORE, 26.9 ± 17.9 %; and mean Society of Thoracic Surgeons score, 10.2 ± 5.3 %). All patients had severe NAVR on echocardiography without aortic stenosis and 17 patients (39.5 %) had the degree of aortic valvular calcification documented on CT or echocardiography. Vascular access was TF (n = 35), subclavian (n = 4), direct aortic (n = 3), and carotid (n = 1). Implantation of a TAVI was performed in 42 patients (97.7 %), and 8 patients (18.6 %) required a second valve during the index procedure for residual aortic regurgitation. In all patients requiring 2nd valves, valvular calcification was absent (p = 0.014). Post-procedure aortic regurgitation grade I or lower was present in 34 patients (79.1 %). At 30 days, the major stroke incidence was 4.7 %, and the all-cause mortality rate was 9.3 %. At 12 months, the all-cause mortality rate was 21.4 % (6 of 28 patients). The authors concluded that this registry analysis demonstrated the feasibility and potential procedure difficulties when using TAVI for severe NAVR. They stated that acceptable results may be achieved in carefully selected patients who are deemed too high risk for conventional surgery, but the possibility of requiring 2 valves and leaving residual aortic regurgitation remain important considerations. The findings of this small, predominantly retrospective voluntary registry of a novel indication for transcatheter valve therapy need to be validated in well-designed studies.
Appendix


The European Association for Cardio-Thoracic Surgery's Joint Task Force on the "Management of Valvular Heart Disease" (Vahanian et al, 2012) listed contraindications for TAVI:

**Absolute contraindications:**

- Absence of a “heart team” and no cardiac surgery on the site
- Active endocarditis
- Appropriateness of TAVI, as an alternative to aortic valve replacement (AVR), not confirmed by a “heart team”
- Elevated risk of coronary ostium obstruction (asymmetric valve calcification, short distance between annulus and coronary ostium, small aortic sinuses)
- Estimated life expectancy less than 1 year
- For trans-femoral/subclavian approach: Inadequate vascular access (calcification, tortuosity, vessel size)
- Improvement of quality of life by TAVI unlikely because of co-morbidities
- Inadequate annulus size (less than 18 mm, greater than 29 mm) (contraindication when using the current devices)
- Plaques with mobile thrombi in the ascending aorta, or arch
- Severe primary associated disease of other valves with major contribution to the patient's symptoms that can be treated only by surgery
- Thrombus in the left ventricle

**Relative contraindications:**

- Bicuspid or non-calcified valves
- For trans-apical approach: Severe pulmonary disease, left ventricular apex not accessible
- Hemodynamic instability
- Left ventricular ejection fraction less than 20 %
- Untreated coronary artery disease requiring revascularization

**CPT Codes / HCPCS Codes / ICD-9 Codes**

**CPT codes covered for indications listed in the CPB:**

- 33361
- 33362
- 33363
- 33364
- 33365
ICD-9 codes covered if selection criteria are met:

- 395.0  Rheumatic aortic stenosis
- 396.0  Mitral valve stenosis and aortic valve stenosis
- 396.2  Mitral valve insufficiency and aortic valve stenosis
- 424.1  Aortic valve disorders [stenosis]
- 746.3  Congenital stenosis of aortic valve

ICD-9 codes not covered for indications listed in the CPB (not all-inclusive):

- 996.71  Other complications due to heart valve prosthesis [not covered as an alternative to valve-in-valve implantation for failed aortic bioprostheses]

The above policy is based on the following references:


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