**Clinical Review Criteria**

**Transcatheter Aortic Valve Replacement (TAVR)**
- Valve-in Valve Transcatheter Aortic Valve Implantation (VI-TAVI) in Failed Bioprosthetic Aortic Valves
- Transcatheter Valve-in Valve Implantation (TAVIV)
- Transcatheter aortic valve in surgical aortic valve (TAV-in-SAV)

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### Criteria

**For Medicare Members**

<table>
<thead>
<tr>
<th>Source</th>
<th>Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMS Coverage Manuals</td>
<td>None</td>
</tr>
<tr>
<td>National Coverage Determinations (NCD)</td>
<td>Transcatheter Aortic Valve Replacement (TAVR) (20.32)**</td>
</tr>
<tr>
<td>Local Coverage Determinations (LCD)</td>
<td>None</td>
</tr>
<tr>
<td>Local Coverage Article</td>
<td>None</td>
</tr>
</tbody>
</table>

**Medicare requires that TAVR only be used for FDA approves conditions. The FDA has approved all valves used for the TAVR procedure only for use in members who cannot undergo, or are at intermediate or high risk for open heart surgery as determined by their heart team (a cardiologist and surgeon). TAVR is not approved for use in members that have a low risk as determined by their heart team.**

- For Medicare members requesting Valve in Valve replacement Kaiser Permanente Washington has chosen to use the criteria below.

**For Non-Medicare Members**

I. Transcatheter Aortic Valve Replacement (TAVR)
   A. Transcatheter aortic valve replacement is medically necessary when **ALL of the following** are met:
      1. Use of an FDA approved device
      2. Documentation of severe, symptomatic aortic valve stenosis
      3. Ejection fraction >20%
      4. Documentation that the patient has **ONE of the** following:
         a. The patient has least moderate risk for SAVR as judged by at least two cardio surgeons in a face to face evaluation
         b. Documentation should be supported by a Mortality Risk of >= 3% as defined by the Society of Thoracic Surgeons operative risk scoring (http://riskcalc.sts.org ) but the opinion of the 2 cardio surgeons can override the actual % if below 3%.
         c. Judgment of the heart team that there is >=15% risk of mortality for surgical aortic valve replacement and there is documentation in the medical record to support this mortality risk scoring.

II. Valve-in Valve Transcatheter Aortic Valve Implantation
   A. Valve in Valve TAVR is medically necessary when **ALL of the following** are met:
      1. Use of an FDA approved device
      2. The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multi-disciplinary, team of medical professionals.
      3. Documentation of a failed aortic tissue prosthesis resulting in symptomatic stenosis or regurgitation.
      4. Ejection fraction >20%.
      5. Documentation that the patient has **ONE of the following**:
         a. The patient is either high risk or not a candidate for repeat surgical aortic valve replacement, as judged by at least two cardiovascular specialists (cardiologist and/or cardiac surgeon) in a face to face evaluation.
b. Risk of $\geq 8\%$ as defined by the Society of Thoracic Surgeons operative risk scoring (http://riskcalc.sts.org) and there is documentation in the medical record to support this risk score.

c. Judgment of the heart team that there is $\geq 15\%$ risk of mortality for repeat surgical aortic valve replacement and there is documentation in the medical record to support this mortality risk scoring.

All other indications are not covered as there is insufficient evidence to support effectiveness.

The following information was used in the development of this document and is provided as background only. It is not to be used as coverage criteria. Please only refer to the criteria listed above for coverage determinations.

**Background**

Aortic stenosis (AS) is one of the most frequent degenerative valve diseases in developed countries with a prevalence of approximately $5\%$ in individuals over the age of $75$ years. The absolute numbers continue to increase with the increase in life expectancy. Aortic stenosis has a long latency period followed by a rapid progression after the appearance of symptoms. It is estimated that up to $2.9\%$ of adults between the ages of $75$ and $86$ years have severe aortic stenosis, and that the two year mortality among adults with severe symptoms is as high as $50\%$ (Leon 2010, Rajani 2011, Amonn 2012).

Currently, surgical aortic valve replacement (SAVR) is the treatment of choice in patients with symptomatic severe aortic stenosis in the absence of severe co-morbid conditions. It is the only treatment that has been shown to reduce symptoms and improve functional status and survival in patients with severe aortic stenosis. The conventional surgical aortic valve replacement is performed via sternotomy using cardiopulmonary bypass. The procedure is associated with low operative mortality; however, at least $30\%$ of the patients with severe symptomatic aortic valve stenosis are not suitable candidates for open SAVR due to advanced age, left ventricular dysfunction, concomitant coronary artery disease, and/or other pre-existing conditions. Historically these high surgical risk patients were treated with palliative medical therapy or aortic valve balloon valvuloplasty (BAV) (Leon 2010, Rajani 2011, Amonn 2012, Staubach 2012).

Transcatheter aortic valve replacement (TAVR) has emerged as an alternative minimally invasive treatment option for elderly patients with aortic stenosis who are at high surgical risk. The first transcatheter aortic valve implantation in humans was performed by Alain Cribier in France ten years ago, and has developed rapidly and tremendously since then. Over $50,000$ patients in $500$ European centers have undergone the procedure after two prosthetic valves (Edwards SAPIEN and Medtronic CoreValve) was approved by the Conformité Européenne (CE) in 2007. TAVR involves the insertion of a bioprosthetic aortic valve through a catheter and implanting it within the diseased native aortic valve. Patients are treated off-pump i.e. on a beating heart, and the new prosthesis is implanted within the calcified native valve leaflets that remain in place while being squeezed aside. In most patients the prosthetic valve is inserted through the groin and advanced to the heart using X-ray guidance (retrograde approach). In patients who cannot undergo catheterization of the femoral artery due to vessel disease, the valve can be delivered from the left ventricular apex (antegrade approach) through a small chest incision between the ribs (Amonn 2012, Walther 2012).

Currently, TAVR is indicated for the management of high-risk patients with severe aortic stenosis who are not candidates for open surgical valve replacement. However, some patients are at too high risk even for TAVR, and patient selection plays a crucial role in the success of the procedure. Patients have to be evaluated thoroughly for their risk and anatomical suitability for the procedure. A heart team comprised of clinical cardiologists, cardiac surgeons, interventionists, anesthesiologists, geriatricians, and imaging specialists, is essential for the patient selection and performance of the procedure. The collaboration of such a multidisciplinary team is reported to be a key to the success of the procedure and achievement of optimal clinical outcomes (Piazza 2012, Vahanian 2012).

TAVR is not without complications; the increased risk of stroke is a significant safety concern of the procedure. Other major vascular complications, valve embolization, complete heart block, and moderate to severe paravalvular aortic regurgitation have also been reported. In addition, once the transcatheter aortic valve is implanted, it cannot be removed, and may lead to performing other risky procedures. Researchers are investigating different approaches to reduce the occurrence of these TAVR-related complications e.g. through better screening of the candidates for the intervention; refinement of the implantable devices and their delivery systems; improving the techniques in valve sizing and positioning; use of embolic protection devices as cerebral filters, carotid filters, or membrane covering of the carotid ostia; modification of periprocedure and postoperative antiplatelet strategies; use of antiarrhythmic treatment, and others (Vahanian 2012, Cribier 2012).

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Over the years, different prostheses have become available for performing TAVR. The Edward SAPIEN (Edwards Lifesciences, Irvine, CA, USA) prosthesis consists of bovine pericardial leaflets mounted on a balloon-expandable cobalt-chromium stent. It is available in 2 sizes (23 mm and 26 mm) and can be inserted by either the retrograde or antegrade approach. The prosthesis was approved by the US Food and Drug Administration in 2011 based on data from the inoperable cohort of PARTNER study, for its use patients with severe aortic stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement, and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis (FDA website). The FDA requested two post-approval studies to assess the long-term safety and effectiveness of the TAVR, as well as adherence to the indication of SAPIEN utilization. Other devices including the COREValve ® (Medtronic, Minneapolis, MN, USA), ACURATE TATM valve, and JenaValveTM, have received CE approval, but have not been approved by the USA FDA to date.

Medical Technology Assessment Committee (MTAC)

Transcatheter Aortic Valve Replacement (TAVR)

6/18/2012: MTAC REVIEW

Evidence Conclusion: The PARTNER (Placement of AoRTic traNcathetER valves) trial is the first prospective, multicenter, randomized, controlled trial that compared TAVR in inoperable and high-risk operable patients with severe symptomatic aortic stenosis to surgical or non-surgical treatments. PARTNER consisted of two trials individually powered and with all-cause mortality at one year, as the primary endpoint in each: PARTNER Cohort A trial had a non-inferiority design and involved a high-risk operable population in whom both the transcatheter and surgical aortic valve replacement were clinically acceptable. PARTNER Cohort B was designed as a superiority trial and was conducted upon a very high-risk patient population considered unsuitable for open surgery. The trial had valid methodology; it was randomized, controlled, multicenter, had sufficient power to detect significant differences for the mortality endpoint, and the analysis was based on intention to treat. However, it was conducted among a highly selected group of patients, in highly selected centers, and performed by physicians with high expertise in the implantation technique, all of which may limit generalization of the results. In addition, it was sponsored by the aortic valve manufacturer (Edwards Lifesciences) who funded the study, participated in the selection and management of the sites, as well as the collection and monitoring of the data. Transcatheter aortic valve replacement has a learning curve, and the aortic valve prosthesis used in the PARTNER trial was the first generation device, both of which may not reflect the outcomes of the procedure with the current generations of the device and the gained operator experience in their implantation. PARTNER Cohort B Evidence Table Inoperable Cohort B patients (N=358) were randomized to receive standard medical therapy including balloon aortic valvuloplasty or to undergo TAVR using Edward SAPIEN heart valve system. The primary endpoint was the rate of death from any cause at one year. The results of the trial showed a 19% absolute mortality reduction at one year after TAVR with a number needed to treat of 5. Cardiac symptoms also improved significantly in the TAVR group. TAVR however, was associated with higher rates of stroke/TIA, vascular events, and bleeding (NNH with TAVR was 20 for stroke or TIA, 7 for major vascular complications, and 8 for major bleeding).

2-year outcomes of the trial (Makkar et al, 2012) showed that the rate of death from any cause, death from cardiovascular causes, and rate of hospitalization for cardiac reasons were all significantly lower in the TAVR group vs. standard therapy group. The death from any cause at 2 years was 68.0% in the standard therapy group and 43.3% in the TAVR group. The calculated NNT with TAVR was 4 to prevent one death and 3 to prevent one cardiac death in 2 years. As regards the adverse events, the rate of stroke was higher at 2 years in the TAVR vs. standard therapy (13.8% vs. 5.5%, p=0.01). The authors explained that the excess of stroke in the TAVR in the first 30 days was attributed to greater number of ischemic strokes in that group. Beyond 30 days and up to 2 years, the higher rate of stroke was attributable to hemorrhagic events. Echocardiographic analyses showed that the early hemodynamic benefits of TAVR were sustained at 2 years (sustained increase in aortic valve area, and a decrease in aortic valve gradient withy no worsening in paravalvular regurgitation). PARTNER Cohort B Evidence Table High-risk operable patients (N=699) were randomized to undergo either TAVR using Edward SAPIEN valve or traditional surgical aortic replacement (SAVR). The results of the trial showed no significant difference in survival between the two procedures. The primary endpoint was rate of death from any cause at one year. Cohort A study was designed as a noninferiority trial to determine whether transcatheter replacement of the aortic valve is not inferior to surgical replacement of the valve. It was not designed to demonstrate that the two interventions are equivalent. The results of the trial showed that TAVR was non-inferior to SAVR for all-cause mortality in one year. Patients in TAVR had a lower risk of major bleeding (NNT 5 in one year), and better improvement than surgical replacement group in cardiac symptoms and 6-minute walk distance at 30 days. These differences were insignificant by the end of the year. On the other hand, the TAVR patients had an increased risk of stroke or TIA (NNH=13) and more major vascular events (NNH=13) than those in the SAVR group. The authors explained that the differences in stroke appeared in the first few days or weeks after TAVR most likely due to the increased liberation atherothrombotic debris from the aorta or the valve causing embolic ischemic strokes. 2-year outcomes...
of Cohort A (Kodali et al, 2012) showed that between year one and year two there were 32 additional deaths in the TAVR group and 25 in the SAVR group (statistically insignificant difference at 2 years, p=0.78). It also showed that by the end of 2 years the overall incidence of neurological events (stroke and TIA) was higher in the TAVR group (11.2%, vs. 6.5% in the SAVR group, but the difference did not reach a statistically insignificant level (p=0.05). After the first year, the major vascular complications and major bleeding were uncommon in the two groups, maintaining the difference observed at 1 year. Electrocardiographic analysis at 2 years showed no significant changes in the valve areas or mean gradients. Moderate or severe paravalvular aortic regurgitation was more frequent after TAVR than SAVR at both one and 2 years (p<0.001 for both comparisons). The presence of aortic regurgitation (mild, moderate, or severe vs., none or trace) was associated with an increases late mortality (hazard ration 2.11; 95% CI 1.43-3.10, p<0.001). Conclusion: PARTNER Cohort A showed that transcatheter aortic valve replacement was non-inferior to open heart surgical aortic valve replacement for all-cause mortality at one year in patients with severe aortic stenosis at high-risk of operation. PARTNER Cohort B showed a 19% absolute mortality reduction at one year after transcatheter aortic valve replacement (number needed to treat of 5) when compared to standard medical therapy in patients with severe aortic stenosis and symptoms who are not suitable candidates for surgery. In the two cohorts TAVR was associated with a higher risk of neurological and cardiovascular events. The follow-up duration in the two cohorts of PARTNER may be insufficient to determine long-term safety and durability of the prosthesis, and whether the benefits observed with TAVR will be sustained over time.

**Articles:** The literature search revealed several publications on the PARTNER trial; another small trial (STACCATO trial); a meta-analysis that pooled the results of 16 heterogeneous studies; and a large number of case series, feasibility studies, and registry data. The pivotal PARTNER trial was selected for critical appraisal. The STACCATO study, a randomized controlled trial conducted on operable elderly patients with aortic stenosis, was not selected for critical appraisal due to its small size and premature termination. The meta-analysis was not reviewed further due to the heterogeneity of studies it included. The following studies were critically appraised: Leon MB, Smith CR, Mack M, for the PARTNER Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010 ;363:1597-607. See Evidence Table Smith CR, Leon MB, Mark MJ, for the PARTNER trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med .2011;364:2187-2198. See Evidence Table

The use of TAVR does meet the Kaiser Permanente Medical Technology Assessment Criteria.

**Valve-in Valve Transcatheter Aortic Valve Implantation (VI-TAVI) in Failed Bioprosthetic Aortic Valves [Transcatheter Valve-in Valve Implantation (TAVIV), transcatheter aortic valve in surgical aortic valve (TAV-in-SAV)]**

**BACKGROUND**

Degenerative aortic stenosis is one of the most common and most serious acquired valvular heart diseases among adults. Surgical aortic valve replacement (SAVR) has been the standard treatment for symptomatic severe aortic stenosis for over forty years. SAVR is an open heart procedure that involves removing the diseased aortic valve and replacing it with either a man-made mechanical valve or a biological valve. Mechanical valves are strong and long-lasting, but patients receiving them will need to use a blood thinning medication for the rest of their lives. In the last two decades, there has been a shift toward the use of biological (bioprosthetic) valve implants rather than mechanical valves. These are tissue valves made from human aortic valves (homografts) or more commonly from animal tissue (xenografts). The latter are made from porcine valve leaflets, bovine pericardium, or less frequently from porcine pericardium. Surgical bioprosthesis are commonly stratified into stented and stentless valves. Compared with mechanical valves, bioprosthetic valves are associated with a lower risk of thromboembolic events and do not require long-term anticoagulation. However, these tissue valves have a limited durability, and the majority deteriorates within 10-20 years leading to structural dysfunction. Valve failure may present as stenosis due to calcification, pannus or thrombosis; regurgitation secondary to wear and tear or infection; or as a combination of both stenosis and regurgitation (Seiffert 2010, Bapat 2012, Webb 2013, Dvir 2014).

Treatment of patients with failed bioprosthetic valve is a clinical challenge. Re-operation is considered the standard of care, but a repeat cardiac surgery is associated with high risk of morbidity and mortality, not only of the complexity of the procedure, but also because of the comorbidities and advanced age of the patients who usually need it. The operative mortality for elective redo valve surgery is reported to range from 2-7%, and may increase to more than 30% among those at high-risk. Patients who are considered inoperable have no other effective treatment option; supportive medical therapy is associated with poor prognosis, and balloon valvuplasty...
Transcatheter aortic valve replacement (TAVR), also known as transcatheter aortic valve implantation (TAVI) has become an alternative less invasive treatment modality for patients with severe native aortic valve stenosis who are at high surgical risk due to advanced age, significant comorbidities, frailty, prior chest radiation and other factors. The current widespread use and success of TAVI in high-risk patients together with the major complications of redo aortic valve surgery in these patients; have led to considering the valve-in-valve TAVI (VIV-TAVI) (also referred to as TAV-in-SAV) approach as an option for patients with degenerated failed bioprosthetic valve. TAVI is performed with a beating heart and avoids the risks associated with using cardioplegia and cardiopulmonary bypass during redo surgery. Currently, the main transcatheter valves used for valve-in-valve procedures are the Edwards SAPIEN or SAPIEN XT (Edwards Lifesciences, Irvine, California), and the CoreValve (Medtronic, Minneapolis, Minnesota) (Eggebrecht 2011, Linke 2012, Dvir 2014).

Edwards SAPIEN XT Transcatheter Heart Valve (SAPIEN XT THV) system consists of a transcatheter aortic valve and the accessories used to implant it. The valve is made of cow tissue attached to a balloon-expandable, cobalt-chromium frame for support, and comes in three sizes: 23 mm, 26 mm, and 29 mm. The valve is compressed and placed on the end of a balloon catheter, which is then inserted through either the femoral artery or a small cut between the ribs and advanced through the blood vessels until it reaches the failed valve. The SAPIEN XT valve is then expanded with the balloon until it anchors to the failed valve (valve-in-valve). Once the new valve is in place, it opens and closes properly, allowing the blood to flow in the correct direction. According to the FDA The Edwards SAPIEN XT THV is indicated for patients with symptomatic heart disease due to either severe native calcific aortic stenosis, or more recently (in 2015) due failure of a surgical bioprosthetic aortic valve who are judged by a heart team to be at high or greater risk for open surgical therapy (i.e. Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days). It is contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen, have a mechanical artificial aortic valve, or have active bacterial endocarditis or other active infections in the heart or elsewhere (FDA and the manufacturer’s webpages).

The CoreValve system consists of a catheter-based artificial aortic heart valve and the accessories used to implant it. The valve is made of pig tissue attached to a flexible, self-expanding, nickel-titanium frame for support. The CoreValve is compressed and placed on the end of a delivery catheter, which is then inserted through the femoral artery. If the femoral arteries are not suitable, the valve can be inserted through other arteries or through the aorta. The catheter is pushed through the blood vessels until it reaches the diseased aortic valve. The valve is then released from the catheter, expands on its own and anchors to the diseased valve. The CoreValve functions the same as a normal valve, allowing the blood flow in the correct direction. The CoreValve System had been previously approved by the FDA to treat patients whose native aortic valve has become severely narrowed as a result of calcium buildup and who are considered to be at “extreme risk” or “high risk” for surgical aortic valve replacement. In March 2015 the FDA expanded the use of CoreValve system for aortic valve-in valve replacement inpatients who need replacement of a failed tissue aortic valve, but are at extreme or high risk of death or serious complications from traditional open-heart surgery based on the judgement of a heart medical team. The CoreValve System use is contraindicated in patients with a mechanical aortic heart valve, have any infection, cannot tolerate blood thinning medicines; or have sensitivity to titanium or nickel or contrast media (FDA News Release March 30, 2015).

Reported adverse events with of VIV-TAVI include death, stroke, acute kidney injury, myocardial infarction, major bleeding, and the need for a permanent pacemaker. Other limitations associated with VIV-TAVI are the increase risk of coronary obstruction (especially in patients with stentless valves); high residual gradients which may result from under expansion of the result transcatheter heart valve in smaller surgical bioprosthesis; and paravalvular leaks between the surgical and transcatheter valves. Successful outcome of the VIV procedure is thus dependent on patient selection, knowledge of prior cardiac surgery, internal diameter and material of the degenerated bioprosthetic valve as well as mode of valve failure, anticipation of complication, procedural planning, and experience of the cardiac team with TAVI (Bapat 2012, Webb 2013, Verhoey 2015, Phan 2016).

In 2015, the US Food and Drug administration (FDA) expanded the approved use of the SAPIEN XT (Edwards Lifesciences) and CoreValve System (Medtronic) to include "valve-in-valve" repair in patients who failed surgical bioprosthetic heart and are at high or extreme risk for complications associated with traditional open-heart surgery.
Evidence Conclusion: The published studies on transcatheter valve-in-valve implantation in a failed surgical bioprosthetic valve, as well as the two unpublished pivotal studies submitted to the FDA, were all descriptive, observational series that aimed at evaluating the feasibility, safety, and short-term outcomes of the procedure. The vast majority of the published studies was conducted in European countries and evaluated the Edwards SAPIEN or the CoreValve systems. The VIVID registry was initiated in 2010 to collect retrospective and prospective data on VIV-TAVI procedures performed in different centers worldwide.

Safety and outcomes of VIV-TAVI in patients with failed prosthetic aortic valve
The data provided in the meta-analyses as well as that collected in the international VIVID registry (Evidence Tables 1-3) indicate that the patients selected for valve-in-valve implantation due to a failed aortic bioprosthetic valve had a high risk profile. Their mean age was 77.5-78 years, and their mean logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) was 31-31.3. According to the pooled data presented in Phan and colleagues’ (2016) meta-analysis, 74.8% of the patients had a history of hypertension, 27.3% diabetes, 44.6%, chronic kidney disease, 50% coronary artery disease, 26.3% peripheral vascular disease, and 12.4% had a history of stroke. The following table summarizes the pooled results of the two published meta-analyses, and the aggregated data from the VIVID registry (more details and subanalyses are provided in evidence tables 1-3).

<table>
<thead>
<tr>
<th>Early/preoperative complications</th>
<th>Chen et al’s, meta-analysis (2016) N=15 studies on aortic VIV (861 patients) Rate % (95% CI)</th>
<th>Phan et al’s meta-analysis (2016) N=18 studies (823 patients) Pooled weighted estimate (95% CI)</th>
<th>Dvir, et al’s VIVID registry (2014) N=459 patients Rate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-day mortality</td>
<td>6.9% (4.3-10.0)</td>
<td>6.4% (4.8-8.2)</td>
<td>7.6%</td>
</tr>
<tr>
<td>Major stroke</td>
<td>1.8% (1.0-2.8)</td>
<td>2.0% (1.0-3.0)</td>
<td>1.7%</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>5.5% (4.0-7.2)</td>
<td>4.6% (1.7-7.4)</td>
<td>8.1%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>--</td>
<td>3.0% (1.0-5.0)</td>
<td>--</td>
</tr>
<tr>
<td>Major vascular complication</td>
<td>--</td>
<td>5.4% (2.6-8.1)</td>
<td>9.2%</td>
</tr>
<tr>
<td>Acute renal failure</td>
<td>6.7% (5.1-8.6)</td>
<td>7.0% (5.1-8.9)</td>
<td>7.4%</td>
</tr>
<tr>
<td>Need for permanent pacemaker</td>
<td>7.6% (5.9-9.6)</td>
<td>6.5% (4.3-8.7)</td>
<td>8.3%</td>
</tr>
<tr>
<td>Post-operative mean gradient (mmHg)</td>
<td>--</td>
<td>15.2 (95% CI; 13.4-17.1)</td>
<td>15.8 ±8.9 **</td>
</tr>
<tr>
<td>Late complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-year mortality</td>
<td>16.5% (12.0-21.6)</td>
<td>12.6% (5.6-21.4)</td>
<td>16.6%</td>
</tr>
</tbody>
</table>

Combined results of published studies on VIV-TAVI in patients with failed bioprosthetic aortic valves

*Mortality rate at latest follow-up

**Post-procedural gradients were assessed in 429 patients in VIVID registry. It was moderately elevated (mean ≥20 mmHg) among 26.8% of the patients, and was more common with the balloon expandable vs. self-expandable devices, and with small surgical valves.

- AV regurgitation: at least moderate degree in 5.4% (VIVID registry),
- Paravalvular leak: Mild in 13.1%, moderate in 3.5% (Phan meta-analysis)

- The majority of studies were conducted in Europe.
- The studies were single-center or multicenter observational series with population sizes ranging from 11 to 50.
- Most surgical bioprosthetic valves were stented (~ 82% vs 18% stentless), which may limit generalization of the results. VIV in stentless valves is reported to be a more challenging procedure.
- The two meta-analyses included the patients in the VIVID registry. There might be a potential of duplication of some results as it is unclear if the registry comprised data on patients included in the individual studies.
- The follow-up duration was generally insufficient to determine the long-term efficacy and the durability of the VIV implant.

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Subgroup analysis of data in the VIVID registry showed that patients with small surgical valves (label size <20 mm), and with stenosis as the mechanism of failure, had lower survival and worse outcomes. A multivariate analysis showed that surgical valve label size, type of valve failure, transapical access and STS score were significantly correlated with the overall 1-year mortality.

The FDA approval for the extended use of each of the Medtronic CoreValve and the Edwards SAPIEN in patients with failed prosthetic valves was based on the TAV-in-SAV registries for each of the two VIV systems (Data on methodology, analysis and results of the studies submitted to the FDA, were obtained from the FDA web pages). Both were prospective, non-randomized, observational studies that enrolled patients with symptomatic, failed bioprosthetic valves, and with an estimated harm exceeding the benefits (operative risk of death or serious irreversible complications as 50%) according to the judgement od on cardiologist and two cardiac surgeons (Evidence Tables 4 and 5).

VIV-TAVI versus conventional reoperation for replacing failing bioprosthetic aortic valve

There are no published studies, to date, that directly compared VIV-TAVI versus the conventional reoperation to replace the failing aortic bioprosthetic valve. However, it might not be feasible or ethical to directly compare VIV-TAVI to a redo surgery in high-risk patients with symptomatic degenerated bioprosthetic valve who are not suitable candidates for a repeat cardiac surgery that carries a high morbidity and mortality risk. Indirect comparisons between outcomes and safety VIV-TAVI and redo conventional atrial valve replacement (cAVR) in failed bioprosthetic aortic valves, were performed retrospectively by Phan and colleagues' meta-analysis (2016), and by Erlebach et al (2015) in a small retrospective study.

Phan and colleagues (Evidence Table 2) pooled the results of 18 observational studies (8 prospective and 10 retrospective) on VIV-TAVI and 6 studies on redo conventional aortic valve replacement (cAVR). Patients were not randomized to the interventions, and those in the VIV-TAVI were older and had significantly higher baseline morbidities. The population sizes were small and there were significant heterogeneity between the studies. The results of the analysis suggest that VIV-TAVI was associated with lower risk of stroke and bleeding and a higher risk of moderate paravalvular leak (PVL) compared to cAVR. There were no significant differences between the two procedures in the perioperative mortality. No sub-group analyses were performed to determine whether the outcomes varied according to mechanism or type of bioprosthetic valve failure, or other variables. The authors concluded that lower quality evidence suggests that VIV-TAVI may achieve similar hemodynamic outcomes while significantly reduces the risk of stroke and bleeding vs. redo cAVR, but with an increased rate of moderate PVL. They noted that RCTs and prospective registries are needed to compare the two procedures and examine the long-term effectiveness if VIV-TAVI.

Erlebach and colleagues (2015) retrospectively compared the outcomes of all patients after a valve-in-valve transcatheter aortic valve in surgical aortic valve (TAV-in-SAV) versus standard reoperation (surgical redo operation (SAV-in-SAV). Patient characteristics, preoperative data, post-procedural complications, and 30-day mortality were collected from a database that included data for 210 consecutive patients undergoing SAV-in-SAV from January 2001 to October 2014, and TAV-in-SAV starting from 2007. 108 patients were excluded if they had endocarditis, previous mechanical valves or TAVI, and or concomitant cardiac surgery. The analysis included 52 patients in the SAV-in-SAV group and 50 in TAV-in-SAV. This was a retrospective analysis of data for two groups of patients without randomization or matching. Patients in the TAV-in-SAV had a higher risk profile; they were significantly older, had higher mean logistic EuroSCORE, lower mean left ventricular ejection fraction, worse NYHA functional class, and higher rates of history of stroke, CAD, prior CABG, atrial fibrillation, and pulmonary hypertension than those in the SAV-in-SAV group.

Analysis of the results showed the following:

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>TAV-in-SAV N=50</th>
<th>SAV-in-SAV N=52</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day-all cause mortality, n (%)</td>
<td>2 4%</td>
<td>0</td>
<td>0.238</td>
</tr>
<tr>
<td>Kaplan-Meier 1-year survival</td>
<td>83%</td>
<td>96%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke, n (%)</td>
<td>2 4%</td>
<td>1 2%</td>
<td>0.614</td>
</tr>
<tr>
<td>Myocardial infarction, n (%)</td>
<td>1 2%</td>
<td>1 2%</td>
<td>0.490</td>
</tr>
<tr>
<td>Need for pacemaker implantation, n</td>
<td>3</td>
<td>11</td>
<td>0.042</td>
</tr>
</tbody>
</table>
All TAVI patients were grouped together and no subgroup analyses were made to determine the impact of the size of the failed valve, nature of failure, or the access route of TAVI on the outcome of the VIV procedures.

The study was a retrospective analysis of a small group of patients with significant differences in their baseline characteristics and risk profile. The results of this study as well as those of Phan et al’s meta-analysis should be interpreted with caution due to the lack of randomization, matching of patients, or adjusting for the confounding factors all of which may have an effect on the results.

**Conclusion:**
- There is fair evidence from a number of observational studies that valve-in-valve implant in a failed aortic prosthetic valve is feasible and relatively safe.
- There is insufficient direct evidence to determine whether the outcomes of valve-in-valve implantation in a failed aortic prosthetic valve are equivalent or superior to the outcomes of a redo conventional operation to replace the valve.
- There is insufficient published evidence to determine the long-term efficacy and durability of valve-in-valve implant in a failed aortic prosthetic valve.

**Articles:** The literature search for studies on valve-in-valve transcatheter aortic valve replacement in high risk patients with failed bioprosthetic valves identified a number of observational studies and case series from single institutions as well as registries for patients receiving a VIV-TAVI in various countries (Canadian registry, German registry, Italian registry, Germany/Switzerland registry, and a global registry that collects data form more than 60 countries worldwide). A recent systematic review with meta-analyses (Chen 2016) pooled the results of studies reporting on clinical outcomes of transcatheter VIV in failed surgical bioprosthetic aortic and mitral valves. Two other systematic reviews (with no meta-analyses) that summarized the results of studies on VIV-TAVI published through July 2014 were also identified (Tourmousoglou, et al, 2015, and Raval et al, 2014). To date, there are no published randomized controlled trials that directly compared the VIV-TAVI to surgical reoperation in patients with failed bioprosthetic aortic valves. The search identified a recent systematic review and meta-analysis (Phan, et al, 2016) that indirectly compared VIV-TAVI versus surgical valve redo operation (i.e. TAV-in-SAV versus SAV-in-SAV), and Erlebach et al, 2015 study that compared retrospective data on postoperative outcomes for patients with failing bioprosthetic valve who received a VIV-TAVI or underwent a redo aortic surgery in a single center in the period from January 2001 through October 2014. The two United States pivotal studies that were the basis of the FDA approvals of the systems are not published to date, but are available at the FDA website. The meta-analysis that pooled the results of the cohort studies on VIV-TAVI and the analysis that compared VIV-TAVI with reoperation, as well as the global VIVID registries and the two pivotal studies submitted to the FDA were selected for critical appraisal. Chen HL, Liu K. Clinical outcomes for transcatheter valve-in-valve in treating surgical bioprosthetic dysfunction: A meta-analysis. *Int J Cardiol*. 2016 Mar 18; 212:138-141. *(See Evidence Table 1)* Phan K, Zhao DF, Wang N, et al. Transcatheter valve-in-valve implantation versus re-operative conventional aortic valve replacement: a systematic review. *J Thorac Dis.* 2016 Jan; 8 (1):E83-93. *(See Evidence Table 2)* Dvir D, Webb JG, Bleiziffer S, et al. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. *JAMA.* 2014 Jul; 312(2):162-170. *(See Evidence Table 3).*

The use of Valve-in Valve Transcatheter Aortic Valve Implantation does meet the *Kaiser Permanente Medical Technology Assessment Criteria.*
<table>
<thead>
<tr>
<th>Date</th>
<th>Changes or Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/05/2015</td>
<td>Changed ejection fraction from &gt;15% to &gt;20%</td>
</tr>
<tr>
<td>03/01/2016</td>
<td>Added two indications to criteria</td>
</tr>
<tr>
<td>08/02/2016</td>
<td>Added MTAC review for Valve-in Valve Transcatheter Aortic Valve Implantation</td>
</tr>
<tr>
<td>09/06/2016</td>
<td>New policy for Valve-in-Valve Implantation was adopted</td>
</tr>
<tr>
<td>04/04/2017</td>
<td>Added indication for TAVR to clarify risk score and the ability for 2 cardiac surgeons to override risk scoring</td>
</tr>
</tbody>
</table>

**Codes**

CPT: 33361, 33362, 33363, 33364, 33365, 33366, 33367, 33368, 33369