Transcatheter Heart Valve Procedures

Policy Number: 2023T0557Z
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Instructions for Use

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Application

UnitedHealthcare Commercial

This Medical Policy applies to all UnitedHealthcare Commercial benefit plans.

UnitedHealthcare Individual Exchange

This Medical Policy applies to Individual Exchange benefit plans in all states except for Colorado.

Coverage Rationale

See Benefit Considerations

Aortic

Transcatheter aortic heart valve replacement is proven and medically necessary when performed according to U.S. Food and Drug Administration (FDA) labeled indications, contraindications, warnings and precautions and all of the following criteria are met:

- Diagnosis of severe calcific native aortic valve stenosis as indicated by **one** of the following:
  - Mean aortic valve gradient ≥ 40 mmHg; or
  - Peak aortic jet velocity ≥ 4.0 m/s; or
  - Aortic valve area of ≤ 0.8 cm^2
- Individual is symptomatic (New York Heart Association [NYHA] class II or greater) and symptoms are due to aortic valve stenosis
- An interventional cardiologist and an experienced cardiothoracic surgeon have determined that the procedure is appropriate
- Individual has engaged in a Shared Decision Making conversation with an interventional cardiologist and an experienced cardiothoracic surgeon

- Procedure is performed in a center that meets **all** of the following criteria:
  - On-site heart valve surgery and interventional cardiology programs; and
  - Post-procedure intensive care unit with personnel experienced in managing individuals who have undergone open-heart valve procedures; and
  - Volume Requirements consistent with the Centers for Medicare and Medicaid Services (CMS); for additional information, refer to the corresponding CMS National Coverage Determination and the Society of Thoracic Surgeons/American College of Cardiology (STS/ACC) Transcatheter Valve Therapy (TVT) Registry.

Transcatheter valve-in-valve (ViV) replacement within a failed bioprosthetic aortic valve is proven and medically necessary for individuals at high or prohibitive surgical risk (Predicted Risk of Mortality [PROM] score of ≥ 8%) when performed according to FDA labeled indications, contraindications, warnings and precautions.

Note: Requests for transcatheter aortic heart valve replacement for low-flow/low-gradient aortic stenosis will be evaluated on a case-by-case basis.

Mitral

Transcatheter mitral valve repair is proven and medically necessary when used according to FDA labeled indications, contraindications, warnings and precautions in individuals with one of the following clinical indications for intervention:

- Primary (degenerative) mitral regurgitation (MR) when **all** of the following criteria are met:
  - Moderate-to-severe or severe MR (grade ≥ 3); and
  - Symptomatic NYHA class III or IV; and
  - Prohibitive surgical risk as defined by ONE of the following:
    - PROM score of ≥ 8% for individuals deemed likely to undergo mitral valve replacement; or
    - PROM score of ≥ 6% for individuals deemed likely to undergo mitral valve repair; or
    - Predicted risk of death or major morbidity at 1 year of over 50%;

    and
  - Care directed by a multidisciplinary heart team which includes a heart failure specialist, interventional cardiologist and cardiothoracic surgeon experienced in the evaluation and treatment of heart failure and mitral valve disease.
- Secondary (functional) MR when **all** of the following criteria are met:
  - Moderate-to-severe or severe MR (grade ≥ 3) with left ventricular ejection fraction (LVEF) ≥ 20 and ≤ 50; and
  - Symptomatic NYHA class II –IV (ambulatory); and
  - Optimal evidence-based management which includes pharmacologic therapy plus cardiac resynchronization therapy as indicated; and
  - High surgical risk (PROM score of ≥ 8%); and
  - Care directed by a multidisciplinary heart team which includes a heart failure specialist, interventional cardiologist and cardiothoracic surgeon experienced in the evaluation and treatment of heart failure and mitral valve disease.

Pulmonary

Transcatheter pulmonary heart valve replacement, using the Melody™ or Sapien valves, is proven and medically necessary, when used according to FDA labeled indications, contraindications, warnings and precautions, in individuals with right ventricular outflow tract (RVOT) dysfunction with one of the following clinical indications for intervention:

- Moderate or greater pulmonary regurgitation; and/or
- Pulmonary stenosis with a mean RVOT gradient ≥ 35 mmHg

The following transcatheter heart valve devices and/or procedures are unproven and not medically necessary due to insufficient evidence of efficacy:

- Cerebral protection devices (e.g., Sentinel™)
- Mitral valve repair, reconstruction or replacement, except where noted above
- Tricuspid valve repair, reconstruction or replacement
- Valve-in-Valve (ViV) replacement within a failed bio-prosthesis for mitral, pulmonary, or tricuspid valves
- Transcatheter pulmonary heart valve replacement using the Harmony™ valve

Documentation Requirements

Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The documentation requirements outlined below are used to assess whether the member meets the clinical criteria for coverage but do not guarantee coverage of the service requested.

CPT Codes*	Required Clinical Information
Transcatheter Heart Valve Procedures	

33361
33362
33363
33364
33365
33366
33369
33477
	For **all** transcatheter valve procedures, provide medical notes documenting the following, when applicable:
	• Name of device being used, if available
	• Diagnosis
	• Co-morbidities
	• Treatments tried, failed, or contraindicated
	• Physician treatment plan
	
	In addition to the above, provide medical notes documenting the following for:
	• **Aortic Heart Valve**
	  ○ New York Heart Association (NYHA) Classification
	  ○ One of the following:
	    ▪ Mean aortic valve gradient
	    ▪ Peak aortic jet velocity
	    ▪ Aortic valve area
	  ○ Member surgical status related to bicuspid aortic value procedure(s)
	  ○ Member has engaged in a shared decision-making conversation with an interventional cardiologist and an experienced cardiothoracic surgeon who have determined procedure is appropriate
	  ○ Facility where procedure will be performed
	• **Aortic Transcatheter Valve-in-Valve (ViV) Replacement**
	  ○ Name of failed device
	  ○ Surgical risk using PROM score
	• **Pulmonary Heart Valve**
	  ○ Right ventricular outflow tract (RVOT) gradient or pulmonary regurgitation rate

*For code descriptions, refer to the Applicable Codes section.

Definitions

CMS Volume Requirements for Transcatheter Aortic Heart Valve Replacement (TAVR):
To begin a TAVR program for *hospitals without TAVR experience*, the hospital program must have the following:
- ≥ 50 open heart surgeries in the previous year prior to TAVR program initiation; and
- ≥ 20 aortic valve related procedures in the 2 years prior to TAVR program initiation; and
- ≥ 2 physicians with cardiac surgery privileges; and
- ≥ 1 physician with interventional cardiology privileges; and
- ≥ 300 percutaneous coronary interventions per year.

To begin a TAVR program for *heart teams without TAVR experience*, the heart team must include:
- Cardiovascular surgeon with ≥ 100 career open heart surgeries of which ≥ 25 are aortic valve related; and
- Interventional cardiologist with:
  - Professional experience of ≥ 100 career structural heart disease procedures; or, ≥ 30 left-sided structural procedures per year; and
  - Device-specific training as required by the manufacturer.

For *hospital programs with TAVR experience*, the hospital program must maintain the following:

- ≥ 50 aortic valve replacements (TAVR or surgical aortic valve replacement [SAVR]) per year including ≥ 20 TAVR procedures in the prior year; or
- ≥ 100 aortic valve replacements (TAVR or SAVR) every 2 years, including ≥ 40 TAVR procedures in the prior 2 years; and
- ≥ 2 physicians with cardiac surgery privileges; and
- ≥ 1 physician with interventional cardiology privileges; and
- ≥ 300 percutaneous coronary interventions per year.

(CMS National Coverage Determination [NCD] for TAVR)

New York Heart Association (NYHA) Heart Failure Classification (NYHA, 1994):

- I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
- II: Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
- III: Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
- IV: Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

Predicted Risk of Mortality (PROM): The Society of Thoracic Surgeons (STS) PROM score is a predictor of 30-day mortality after cardiac procedures (Otto et al., 2020).

Shared Decision-Making (SDM): SDM is a process by which physicians and individuals work together to choose the treatment option that best reflects the clinical evidence and the individual's values and preferences (Coylewright et al., 2020).

Applicable Codes

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0345T	Transcatheter mitral valve repair percutaneous approach via the coronary sinus
0483T	Transcatheter mitral valve implantation/replacement (TMVI) with prosthetic valve; percutaneous approach, including transseptal puncture, when performed
0484T	Transcatheter mitral valve implantation/replacement (TMVI) with prosthetic valve; transthoracic exposure (e.g., thoracotomy, transapical)
0543T	Transapical mitral valve repair, including transthoracic echocardiography, when performed, with placement of artificial chordae tendineae
0544T	Transcatheter mitral valve annulus reconstruction, with implantation of adjustable annulus reconstruction device, percutaneous approach including transseptal puncture
0545T	Transcatheter tricuspid valve annulus reconstruction with implantation of adjustable annulus reconstruction device, percutaneous approach
0569T	Transcatheter tricuspid valve repair, percutaneous approach; initial prosthesis
0570T	Transcatheter tricuspid valve repair, percutaneous approach; each additional prosthesis during same session (List separately in addition to code for primary procedure)
0646T	Transcatheter tricuspid valve implantation (TTVI)/replacement with prosthetic valve, percutaneous approach, including right heart catheterization, temporary pacemaker insertion, and selective right ventricular or right atrial angiography, when performed

CPT Code	Description
33361	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach
33362	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open femoral artery approach
33363	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open axillary artery approach
33364	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open iliac artery approach
33365	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transaortic approach (e.g., median sternotomy, mediastinotomy)
33366	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transapical exposure (e.g., left thoracotomy)
33367	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with percutaneous peripheral arterial and venous cannulation (e.g., femoral vessels) (List separately in addition to code for primary procedure)
33368	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with open peripheral arterial and venous cannulation (e.g., femoral, iliac, axillary vessels) (List separately in addition to code for primary procedure)
33369	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with central arterial and venous cannulation (e.g., aorta, right atrium, pulmonary artery) (List separately in addition to code for primary procedure)
33370	Transcatheter placement and subsequent removal of cerebral embolic protection device(s), including arterial access, catheterization, imaging, and radiological supervision and interpretation, percutaneous (List separately in addition to code for primary procedure)
33418	Transcatheter mitral valve repair, percutaneous approach, including transseptal puncture when performed; initial prosthesis
33419	Transcatheter mitral valve repair, percutaneous approach, including transseptal puncture when performed; additional prosthesis(es) during same session (List separately in addition to code for primary procedure)
33477	Transcatheter pulmonary valve implantation, percutaneous approach, including pre-stenting of the valve delivery site, when performed
33999	Unlisted procedure, cardiac surgery
93799	Unlisted cardiovascular service or procedure

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Description of Services

The four natural valves of the heart (aortic, pulmonary, mitral and tricuspid) act as one-way valves to direct the flow of blood to the lungs and aorta. Heart valves with congenital defects or those that become diseased over time can result in either a leaky valve (regurgitation/incompetence/insufficiency) or a valve that does not open wide enough (stenosis).

Conventional treatment of structural heart valve disorders is surgical repair or replacement requiring open-heart surgery using cardiopulmonary bypass. Transcatheter (percutaneous or catheter-based) valve procedures use catheter technology to access the heart and manage heart valve disorders without the need for open-heart surgery and cardiopulmonary bypass. During the procedure, a compressed artificial heart valve or other device is attached to a wire frame and guided by a catheter to the heart. Once in position, the wire frame expands, allowing the device to fully open.

Aortic Valve

The aortic valve directs blood flow from the left ventricle into the aorta. Aortic valve stenosis, a common valvular disorder in older adults, is a narrowing or obstruction of the aortic valve that prevents the valve leaflets from opening normally. When the aortic valve does not open properly, the left ventricle has to work harder to pump enough blood through the narrowed opening to the rest of the body. Reduced blood flow can cause chest pain, shortness of breath, excess fluid retention and other symptoms. Left untreated, severe aortic stenosis can lead to left ventricular hypertrophy and heart failure. The various stages of valvular aortic stenosis are addressed by Otto et al. (2020).

The standard for treating severe, symptomatic aortic stenosis is surgical replacement with a prosthetic valve. Transcatheter aortic valve replacement (TAVR) is a minimally invasive alternative to surgical valve replacement. Transcatheter aortic valves feature a metal, stent-like scaffold that contains a bioprosthetic valve. Depending on individual anatomy, possible access routes to the aortic valve include transfemoral (percutaneous or endovascular approach), transapical, subaxillary or transaortic approaches. The procedure is done without removing the diseased native valve.

Bicuspid Aortic ValveBicuspid aortic valve (BAV) is common, and many patients have left-sided heart obstructive disease of varying severity, from hypoplastic left-sided heart syndrome to minimal aortic stenosis or coarctation of the aorta. Significant enlargement of the thoracic aorta may progress to catastrophic aortic dissection and rupture (Silberbach et al., 2018). The aortic valve separates the left ventricle and the aorta. Flaps of tissue (cusps) on the valve open and close with each heartbeat and make sure blood flows in the right direction. The aortic valve usually has three cusps (tricuspid aortic valve) but sometimes has two cups (bicuspid). On rare occasions, some individuals are born with an aortic valve that has one cusp (unicuspid) or four cusps (quadricuspid) (Mayo Clinic, 2022). Congenital BAV is characterized by the presence of a low ridge or raphe along the aortic aspect of the conjoined cusp. Acquired BAV may result from acquired fibrous tissue fusion of the adjacent halves of two cusps and is characterized by a tall raphe, the upper edge of which corresponds with the upper level of the aortic cusps. In other cases, the ridge is a protrusion of the aorta and not derived from fused cuspid tissue. Such valves are considered to portray a condition which may be termed pseudo-acquired congenital BAV. The acquired BAV in some cases is combined of this congenital process and acquired fusion of cuspid tissue (Waller et al., 1973). A BAV may cause heart problems including 1) aortic valve stenosis, where the valve may not open fully and blood flow from the heart to the body is reduced or blocked; 2) aortic valve regurgitation, where the aortic valve does not close tightly causing blood to flow backward; and 3) aortopathy, when an enlarged aorta increases the risk of aortic dissection. Individuals with BAV are more likely to develop infective endocarditis (Mayo Clinic, 2022).

Mitral Valve

The mitral valve directs blood flow from the left atrium into the left ventricle. Mitral regurgitation (MR) occurs when the mitral valve does not close properly, allowing blood to flow backwards from the ventricle to the atrium. MR is sometimes referred to as mitral incompetence or mitral insufficiency. Primary, or degenerative, MR is usually caused by damage to the valve components (e.g., leaflets, attached chords or adjacent supporting tissue). Secondary, or functional, MR is typically due to changes in the shape of the left ventricle that pull the leaflets apart, preventing complete closure. Left untreated, moderate to severe MR can lead to congestive heart failure. MR that cannot be managed conservatively may require surgical valve repair or replacement.

Transcatheter mitral valve replacement (TMVR) is a minimally invasive alternative to surgical valve replacement. Transcatheter mitral valves feature a metal, stent-like scaffold that contains a bioprosthetic valve. Depending on individual anatomy, possible access routes to the mitral valve include transfemoral (percutaneous or endovascular approach), transseptal, transapical or transthoracic approaches. The procedure is done without removing the diseased native valve.

Transcatheter leaflet repair, percutaneous annuloplasty, artificial chordae tendineae and annulus reconstruction are minimally invasive approaches to repair damaged mitral valves. Transcatheter leaflet repair keeps the two valve leaflets more closely fitted together, thereby reducing regurgitation. The procedure, based on the surgical edge-to-edge technique, creates a double orifice using a clip instead of a suture to secure the leaflets. The device consists of a steerable guide catheter, including a clip delivery device and a two-armed, flexible metal clip covered in polyester fabric. A transseptal puncture is required to implant the device in the left side of the heart. Access to the mitral valve is achieved via the femoral vein.

Percutaneous transcatheter annuloplasty attempts to replicate the functional effects of open surgical annuloplasty by reshaping the mitral annulus from within the coronary sinus. The coronary sinus is a large vein located along the heart's outer wall, between the left atrium and left ventricle, adjacent to the mitral valve.

Various artificial chordae tendineae and annulus reconstruction devices are in the early stages of development.

Pulmonary Valve

The pulmonary valve directs blood flow from the right ventricle into the lungs. Disorders of the pulmonary valve are often due to congenital heart disease such as tetralogy of Fallot, pulmonary atresia, transposition of the great arteries and double-outlet right ventricle. Surgery to replace the valve with a bio-prosthesis may also include a conduit (graft) to open the RVOT. Over time, the valved conduit may fail, leading to pulmonary valve stenosis (narrowing), pulmonary valve regurgitation (incompetence/insufficiency) or a combination of the two. Because individuals undergoing this procedure are typically children or adolescents, the bioprosthetic valve will require revisions as the individual grows.

Transcatheter pulmonary valve implantation, a minimally invasive alternative to surgical valve repair or replacement, is designed to reduce the number of surgeries needed throughout an individual's lifetime. Transcatheter pulmonary valves feature a metal, stent-like scaffold that contains a bioprosthetic valve. Access to the pulmonary valve is most often achieved via the femoral vein. Depending on the device, the replacement valve can be positioned in a native or surgically repaired RVOT.

Tricuspid Valve

The tricuspid valve directs blood flow from the right atrium into the right ventricle. Tricuspid regurgitation (TR) occurs when the tricuspid valve does not close properly, allowing blood to flow backwards from the ventricle to the atrium. TR is sometimes referred to as tricuspid incompetence or tricuspid insufficiency. The gold standard for treating tricuspid valve disease is surgical annuloplasty. Devices for transcatheter tricuspid valve repair, reconstruction and replacement are in development.

Valve-in-Valve Procedures

Transcatheter heart valve implantation within an existing bioprosthetic valve, also called a valve-in-valve procedure, replaces a previously implanted bioprosthetic heart valve that has failed or degenerated over time.

Cerebral Protection

Transcatheter cerebral embolic protection devices are designed to filter and collect debris released during TAVR procedures. These devices are intended to reduce the risk of stroke and decline in cognitive function following surgery.

Benefit Considerations

Some benefit documents allow coverage of experimental/investigational/unproven treatments for life-threatening illnesses when certain conditions are met. Benefit coverage for an otherwise unproven service for the treatment of serious rare diseases may occur when certain conditions are met. The member specific benefit plan document must be consulted to make coverage decisions for this service.

Clinical Evidence

Aortic Valve

Koch et al. (2022) performed a single-center, retrospective cohort study of patients undergoing transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) for native aortic insufficiency (AI) between 2014 and 2020, to compare in-hospital and 30-day outcomes. Data were obtained from the Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database, Transcatheter Valve Therapy (TVT) registry, and chart review. In-hospital and 30-day outcomes were reported. Of 125 total patients, 91 underwent SAVR and 34 underwent TAVR. The TAVR group had a higher STS predictive risk of mortality (PROM) (TAVR = 3.96 %, SAVR = 1.25 %, P < 0.0001). In the postoperative period, the SAVR group had higher rates of new-onset atrial fibrillation (20.9 % vs. 0 %, P < 0.001), while the TAVR group had higher rates of complete heart block requiring permanent pacemaker implantation (20.6 % vs. 2.2 %, P < 0.001). There was no difference in in-hospital or 30-day mortality, stroke, myocardial infarction, residual AI, or repeat valve intervention. The authors concluded that despite higher STS PROM and more comorbidities, patients who underwent TAVR for AI had similar in-hospital and 30-day outcomes as patients who underwent SAVR for AI. They also concluded that these results support TAVR in selected high-risk patients with AI, with the knowledge that pacemaker needs may be higher than patients undergoing SAVR. This study is limited by its retrospective observations, non-randomization, and small sample size (n = 125). Long-term evaluations of the results and prospective randomized studies are needed to validate these findings.

Saito et al. (2022) completed a retrospective cohort study to compare the short-term outcomes of TAVR and SAVR in high-, intermediate-, and low-preoperative risk patients. A total of 454 patients who underwent TAVR or SAVR were included. Patients were categorized into high-, intermediate-, and low-risk according to the Society of Thoracic Surgery-Predicted Risk of Mortality score and clinical outcomes were compared between TAVR and SAVR groups. TAVR was less invasive, with less bleeding and transfusion (P < 0.001), less frequent new-onset atrial fibrillation (P < 0.001), and shorter intensive care unit stay (P < 0.001). Furthermore, transcatheter valves performed better than surgical valves, with lower peak velocity (P =0.003) and pressure gradient (P < 0.001) and higher effective orifice area index (P < 0.001). The clinical outcomes of TAVR were comparable to or even superior to those of SAVR in high- and intermediate-risk patients. In low-risk patients, the 1- and 2-year mortality rates were 6.3% and 12.1%, respectively, in the TAVR group and 0% and 0.9%, respectively, in the SAVR group (P < 0.001). Mild or greater paravalvular leakage was a risk factor for mortality (hazard ratio 35.78; P < 0.001). The authors concluded that TAVR was superior to SAVR in the sense of less invasiveness and valvular function. However, the indication of TAVR in low-risk patients should be carefully discussed, because paravalvular leakage was a risk factor for short-term mortality. This study is limited by its retrospective observational design, and short-term follow-up did not allow for assessment of intermediate and long-term outcomes.

In a meta-analysis of seven landmark RCTs, Siontis et al. (2019) compared the safety and efficacy of TAVR versus SAVR across the entire spectrum of surgical risk patients. Across the seven trials, 8,020 participants with severe, symptomatic aortic stenosis were enrolled: TAVR (n = 4,014) and SAVR (n = 4,006). The primary endpoint was all-cause mortality up to 2 years. The authors reported a lower risk of all-cause mortality (12% relative risk reduction) and stroke (19% relative risk reduction), regardless of underlying surgical risk, up to two years of follow-up. TAVR was linked to a higher risk of permanent pacemaker implantation and major vascular complications, but a reduced risk of major bleeding, new onset atrial fibrillation and acute kidney injury.

A Hayes comparative effectiveness review evaluated TAVR and SAVR for aortic stenosis in low and intermediate risk patients. The report concluded that for treatment of severe calcific aortic stenosis in patients with intermediate surgical risk for complications during open valve replacement, TAVR may be a suitable alternative to SAVR in patients for whom a dedicated heart team determines it is appropriate as described in clinical practice guidelines. Moderate-quality evidence indicates mortality, stroke and myocardial infarction are not significantly different in intermediate-risk patients treated with TAVR or SAVR at follow-up of at least 2 years. Further, evidence indicates that the incidence of acute kidney injury and atrial fibrillation are lower after TAVR than after SAVR. However, new pacemaker implantation, vascular complications and aortic insufficiency are higher after TAVR than after SAVR. For patients with low surgical risk, the available evidence of moderate quality indicates a higher incidence of mortality after TAVR than SAVR at 1 to 3 years follow-up. Additional well-designed randomized controlled trials that provide data on the long-term durability and safety of TAVR are needed (Hayes, 2018a; updated 2020).

Several systematic reviews and/or meta-analyses comparing TAVR and SAVR in intermediate-risk patients with severe aortic stenosis reported similar clinical efficacy in the two groups (Lazkani et al., 2019; Singh et al., 2018; Sardar et al., 2017).

Witberg et al. (2018) conducted a systematic review and meta-analysis of randomized controlled trials and observational studies of TAVR versus SAVR in patients at low surgical risk. The primary outcome was all-cause mortality. The secondary outcomes included stroke, myocardial infarction, bleeding and various procedural complications. Six studies including 3,484 patients were included. The short-term mortality was similar with either TAVR or SAVR; however, TAVR was associated with increased risk for intermediate-term mortality. TAVR was associated with reduced risk for bleeding and renal failure but an increased risk for vascular complications and pacemaker implantation. The authors noted that until more data is available, SAVR should remain the treatment of choice for low-risk patients.

Using registry data, Ribeiro et al. (2018) evaluated clinical outcomes and changes in LVEF following TAVR in patients with classic low-flow, low-gradient aortic stenosis (LFLG-AS). A total of 287 patients were included in the analysis. Clinical follow-up was obtained at 1 and 12 months, and yearly thereafter. TAVR was associated with good periprocedural outcomes among patients with LFLG-AS and reduced LVEF. However, approximately one third of patients with LFLG AS who underwent TAVR had died by 2-year follow-up; with pulmonary disease, anemia and residual paravalvular leak associated with worse outcomes. LVEF improved following TAVR, but dobutamine stress echocardiography (DSE) did not predict clinical outcomes or LVEF changes over time. Data from this multicenter registry supports an expanding role for TAVR among patients with LFLG severe AS and reduced LVEF. NCT01835028

Arora et al. (2017) performed a systematic review and meta-analysis comparing the 30-day risk of clinical outcomes between TAVR and SAVR in the lower surgical risk population. Four studies were included. Compared to SAVR, TAVR had a significantly lower risk of bleeding complications and acute kidney injury. However, a higher risk of vascular complications, moderate or severe paravalvular leak and permanent pacemaker implantations was noted for TAVR. The authors noted that additional high-quality studies are needed to further explore the feasibility and long-term durability of TAVR in low-risk patients.

PARTNER (Placement of AoRtic TraNscathetER) Valves Study

The PARTNER trial is a two-part, multicenter, randomized controlled trial funded by Edwards Lifesciences. Cohort A compared transcatheter aortic valve replacement to surgical valve replacement. Cohort B compared transcatheter aortic valve replacement to medical therapy in patients with severe aortic stenosis who were unable to undergo surgery. NCT00530894.

Cohort A

In a multicenter, noninferiority, open-label, randomized controlled trial, Smith et al. (2011) randomly assigned 699 high-risk patients with severe aortic stenosis to undergo either TAVR with a balloon-expandable bovine pericardial valve (n = 348; transfemoral n = 244; transapical n = 104) or surgical replacement (n = 351). The primary end point was death from any cause at 1 year. The rates of death from any cause were 3.4% in the transcatheter group and 6.5% in the surgical group at 30 days and 24.2% and 26.8%, respectively, at 1 year. The rates of major stroke were 3.8% in the transcatheter group and 2.1% in the surgical group at 30 days and 5.1% and 2.4%, respectively, at 1 year. At 30 days, major vascular complications were significantly more frequent with transcatheter replacement (11.0% vs. 3.2%). Adverse events that were more frequent after surgical replacement included major bleeding (9.3% vs. 19.5%) and new-onset atrial fibrillation (8.6% vs. 16.0%). 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 periprocedural risks.

A 2-year follow-up of patients in Cohort A did not report significantly different outcomes in the two groups with respect to mortality, reduction in cardiac symptoms and improved valve hemodynamics. Paravalvular regurgitation was more frequent after TAVR and was associated with increased late mortality. An early increase in the risk of stroke with TAVR was attenuated over time. The authors concluded that these results support TAVR as an alternative to surgery in high-risk patients (Kodali et al., 2012).

At 5 years, the risk of death was 67.8% in the TAVR group compared with 62.4% in the surgical group. There were no structural valve deteriorations requiring surgical valve replacement in either group. Moderate or severe aortic regurgitation occurred in 40 (14%) of 280 patients in the TAVR group and two (1%) of 228 in the surgical group and was associated with increased 5-year risk of mortality in the TAVR group (72.4% for moderate or severe aortic regurgitation versus 56.6% for those with mild aortic regurgitation or less) (Mack et al., 2015).

Cohort B

In the same multicenter, open label, randomized controlled trial, Leon et al. (2010) evaluated TAVR in patients with severe aortic stenosis who were not candidates for surgery. A total of 358 patients were randomized to standard therapy (including balloon aortic valvuloplasty) (n = 179) or transfemoral transcatheter implantation of a balloon-expandable bovine pericardial valve (n = 179). At 1 year, the rate of death from any cause was 30.7% with TAVR, as compared with 50.7% with standard therapy (hazard ratio with transcatheter aortic valve implantation (TAVI), 0.55; 95% confidence interval [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 TAVR as compared with 71.6% with standard therapy. Among survivors at 1 year, the rate of cardiac symptoms (NYHA class III or IV) was lower among patients who had undergone TAVR than among those who had received standard therapy (25.2% vs. 58.0%). At 30 days, TAVR, as compared with standard therapy, was associated with a higher incidence of major strokes (5.0% vs. 1.1%) and major vascular complications (16.2% vs. 1.1%). In the year after TAVR, there was no deterioration in the functioning of the bioprosthetic valve. The authors concluded that in patients with severe aortic stenosis who were not suitable candidates for surgery, TAVR, 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.

At 2 years, the mortality rates in Cohort B were 43.3% in the TAVR group and 68.0% in the standard therapy group ($P < 0.001$). The corresponding rates of cardiac death were 31.0% and 62.4% ($P < 0.001$). The survival advantage associated with TAVR at 1 year remained significant among patients who survived beyond the first year. The rate of stroke was higher after TAVR than with standard therapy (13.8% vs. 5.5%). There was an increased frequency of early ischemic strokes (≤ 30 days) but little change in the rate of late ischemic strokes (> 30 days). At 2 years, the rate of rehospitalization was 35.0% in the TAVR group and 72.5% in the standard-therapy group. TAVR, as compared with standard therapy, was also associated with improved functional status. The data suggest that the mortality benefit after TAVR may be limited to patients who do not have extensive coexisting conditions. The authors concluded that among appropriately selected patients with severe aortic stenosis who were not suitable candidates for surgery, TAVR reduced the rates of death and hospitalization, with a decrease in symptoms and an improvement in valve hemodynamics that were sustained at 2 years of follow-up (Makkar et al., 2012).

Using a longitudinal echocardiographic analysis of patients in the PARTNER trial, Daubert et al. (2016) reported that valve performance and cardiac hemodynamics were stable 5 years after implantation of both the SAPIEN TAVR and SAVR valves. Eighty-six TAVR and 48 SAVR patients with paired first post-implant and 5-year echocardiograms were analyzed.

PARTNER II Study

The PARTNER II study is a two-part, multicenter, randomized controlled trial, also funded by Edwards Lifesciences, evaluating a second-generation transcatheter valve system in intermediate-risk patients. The newer, low-profile SAPIEN XT system was developed to reduce adverse events noted in the PARTNER study. Cohort A compared TAVR to conventional surgery in patients with severe aortic stenosis and intermediate surgical risk. Cohort B compared the SAPIEN XT valve with the first-generation SAPIEN valve in patients with severe aortic stenosis who were unable to undergo surgery. NCT01314313.

Cohort A

Leon et al. (2016) evaluated TAVR and SAVR in a multicenter, noninferiority, open-label, randomized controlled trial involving intermediate-risk patients. A total of 2,032 intermediate-risk patients with severe aortic stenosis were randomly assigned to undergo either TAVR with the SAPIEN XT valve (n = 1011) or SAVR (n = 1021). The primary end point was death from any cause or disabling stroke at 2 years. The primary hypothesis was that TAVR would not be inferior to surgical replacement. Before randomization, patients were entered into one of two cohorts on the basis of clinical and imaging findings: transfemoral access (76.3%) and transthoracic access (23.7%). The rate of death from any cause or disabling stroke was similar in the TAVR group and the surgery group. At 2 years, the event rates were 19.3% in the TAVR group and 21.1% in the surgery group. In the transfemoral access cohort, TAVR resulted in a lower rate of death or disabling stroke than surgery, whereas in the transthoracic access cohort, outcomes were similar in the two groups. TAVR resulted in larger aortic-valve areas than did surgery and also resulted in lower rates of acute kidney injury, severe bleeding and new-onset atrial fibrillation. Surgery resulted in fewer major vascular complications and less paravalvular aortic regurgitation.

At 5 years, there was no significant difference in the incidence of death from any cause or disabling stroke between the TAVR and SAVR groups. More patients in the TAVR group had at least mild paravalvular aortic regurgitation (33.3% vs. 6.3%). Repeat hospitalizations were more frequent after TAVR than after SAVR (33.3% vs. 25.2%), as were aortic valve reinterventions (3.2% vs. 0.8%) (Makkar et al., 2020).

Cohort B

Webb et al. (2015) evaluated the safety and effectiveness of the SAPIEN XT versus SAPIEN valve systems in patients with symptomatic, severe aortic stenosis who were not candidates for surgery. The primary endpoint was a composite of all-cause mortality, major stroke and rehospitalization. Secondary endpoints included cardiovascular death, NYHA functional class, myocardial infarction, stroke, acute kidney injury, vascular complications, bleeding, 6-min walk distance and valve performance. A total of 560 patients were randomized to receive the SAPIEN (n = 276) or SAPIEN XT (n = 284) systems. At 1-year follow-up, there was no difference in all-cause mortality, major stroke or rehospitalization between SAPIEN and SAPIEN XT, but the SAPIEN XT was associated with less vascular complications and bleeding requiring transfusion. No differences in the secondary endpoints were found. The authors concluded that in inoperable patients with severe, symptomatic aortic stenosis, the lower-profile SAPIEN XT system provided an incremental improvement from the prior generation of TAVR technology.

In a large, multicenter registry of inoperable, high-risk and intermediate-risk patients, Kodali et al. (2016) reported early outcomes following TAVR with the next-generation SAPIEN 3 valve. Patients with severe, symptomatic aortic stenosis (583 high surgical risk or inoperable and 1078 intermediate risk) were enrolled. All patients received the SAPIEN 3 valve via transfemoral (n = 1443) and transapical or transaortic (n = 218) access routes. The rate of 30-day all-cause mortality was 2.2% in high-risk/inoperable patients (mean STS score 8.7%) and 1.1% in intermediate-risk patients (mean STS score 5.3%). In high-risk/inoperable patients, the 30-day rate of major/disabling stroke was 0.9%, major bleeding 14.0%, major vascular complications 5.1% and requirement for permanent pacemaker 13.3%. In intermediate-risk patients, the 30-day rate of major/disabling stroke was 1.0%, major bleeding 10.6%, major vascular complications 6.1% and requirement for permanent pacemaker 10.1%. Overall, paravalvular regurgitation at 30 days was none/trace in 55.9% of patients, mild in 40.7%, moderate in 3.4% and severe in 0.0%. Mean gradients among patients with paired baseline and 30-day or discharge echocardiograms decreased from 45.8 mmHg at baseline to 11.4 mmHg at 30 days, while aortic valve area increased from 0.69 to 1.67 cm2.

PARTNER 3 Low Risk Study

The PARTNER 3 study, a multicenter, noninferiority, open label, randomized controlled trial, also funded by Edwards Lifesciences, evaluated the third generation SAPIEN 3 transcatheter valve system. The study compared outcomes of TAVR with those of SAVR in patients with severe aortic stenosis and a low risk of death with surgery. NCT02675114.

Mack et al. (2019) randomly assigned patients with severe aortic stenosis and low surgical risk to undergo either TAVR with a third-generation balloon-expandable valve (n = 503) or standard SAVR with a bioprosthetic valve (n = 497). The assigned procedure was performed in 950 patients (496 in the TAVR group and 454 in the SAVR group). The primary end point was a composite of death from any cause, stroke, or rehospitalization at one year after the procedure. At one year, TAVR using the SAPIEN 3 system was superior to surgery with regard to the primary composite end point of death, stroke, or rehospitalization (hazard ratio: 0.54; 95% CI, 0.37 to 0.79; p = 0.001). At 30 days, TAVR was associated with a significantly lower rate of new-onset atrial fibrillation, a shorter index hospitalization and a lower risk of a poor treatment outcome. There were no significant differences in major vascular complications, new permanent pacemaker insertions or moderate or severe paravalvular regurgitation.

The 2-year follow-up showed continued superiority of the composite outcome primary endpoint favoring TAVR versus surgery, but more frequent deaths, strokes, and valve thrombosis events in the TAVR group between 1 and 2 years. Disease-specific health status at 2 years was better after TAVR than surgery. Echocardiographic findings through 2 years indicated stable valve hemodynamics and no differences in valve durability parameters (Leon et al., 2021).

EVOLUT Low Risk Study

The EVOLUT study, a multicenter, randomized noninferiority trial funded by Medtronic, evaluated the safety and efficacy of TAVR with a self-expanding bio-prosthesis compared with SAVR in patients at low risk of death with surgery. NCT02701283.

Popma et al. (2019) performed a randomized noninferiority, open-label trial comparing TAVR with a self-expanding supra-annular bio-prosthesis with SAVR in patients with severe aortic stenosis who were at low surgical risk. Of the 1468 patients who underwent randomization, an attempted TAVR (n = 725) or SAVR (n = 678) was performed in 1403. When 850 patients reached the 12-month follow-up, data was analyzed regarding the primary end point, a composite of death or disabling stroke at 24 months. The authors reported no significant differences between the two treatment groups. In low-risk patients, TAVR was noninferior to surgery with respect to the risk of death or disabling stroke at 24 months. At 30 days, TAVR was associated with a lower incidence of disabling stroke, acute kidney injury, bleeding events and atrial fibrillation than surgery but with a higher incidence of aortic regurgitation and permanent pacemaker use. At 12 months, patients in the TAVR group had lower aortic-valve gradients than those in the surgery group and larger effective orifice areas. Patients were evaluated at baseline, at discharge and at 1, 6, 12, 18 and 24 months after the procedure. At the 12-month follow-up, data was available for 432 patients in the TAVR group and 352 in the surgery group. At the 24-month follow-up, data was available for 72 patients in the TAVR group and 65 patients in the surgery group. The median follow-up time in each group was 12.2 months. Long-term clinical and echocardiographic follow-up will continue through 10 years for all patients.

Nordic Aortic Valve Intervention Trial (NOTION)

The NOTION study, a multicenter, randomized controlled trial compared TAVR with a self-expanding bio-prosthesis with SAVR in patients with severe aortic stenosis from all risk categories. NCT01057173.

In the NOTION trial, 280 patients ≥ 70 years old with severe aortic valve stenosis and no significant coronary artery disease were randomized 1:1 to TAVR versus SAVR. The primary outcome was the composite rate of death from any cause, stroke or myocardial infarction. Results of the NOTION study at five years demonstrated no statistical difference for major clinical outcomes after TAVR with a self-expanding prosthesis compared to SAVR. However, higher rates of prosthetic regurgitation and pacemaker implantation were reported after TAVR (Thyregod et al., 2019). Earlier publications reported similar results (Thyregod et al., 2015; Søndergaard et al., 2016). At 6 years, the rates of all-cause mortality were not statistically different between patients undergoing TAVR (42.5%) and SAVR (37.7%). The rate of structural valve deterioration was higher for SAVR than TAVR (24.0% vs. 4.8%), whereas there were no differences in nonstructural valve deterioration (57.8% vs. 54.0%) or endocarditis (5.9% vs. 5.8%). Bioprosthetic valve failure rates were low and similar for both groups (Søndergaard et al., 2019). At 8 years, there were no significant differences in the risk for all-cause mortality, stroke, or myocardial infarction, as well as the risk of bioprosthetic valve failure. The risk of structural valve deterioration was lower after TAVR than after SAVR (13.9% vs. 28.3) (Jørgensen et al., 2021)

Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) Study

The SURTAVI study is a multicenter, randomized controlled trial, funded by Medtronic, to compare the safety and efficacy of TAVR performed with the use of a self-expanding bio-prosthesis with SAVR in patients at intermediate risk for surgery. NCT01586910.

In this randomized trial comparing TAVR with SAVR, Reardon et al. (2017) evaluated the clinical outcomes in intermediate-risk patients with severe, symptomatic aortic stenosis. The primary end point was a composite of death from any cause or disabling stroke. A total of 1,746 patients underwent randomization at 87 centers. Of these patients, 1,660 underwent an attempted TAVR or surgical procedure. The authors reported a large number of unplanned withdrawals in the surgery group, primarily due to the withdrawal of patient consent after randomization. At 24 months, the risk of death or disabling stroke ranged from 12.6% in the TAVR group to 14.0% in the surgery group. Surgery was associated with higher rates of acute kidney injury, atrial fibrillation and transfusion requirements, whereas TAVR had higher rates of residual aortic regurgitation and need for pacemaker implantation. TAVR resulted in lower mean gradients and larger aortic-valve areas than surgery. Structural valve deterioration at 24 months did not occur in either group. The authors concluded that TAVR was a noninferior alternative to surgery in patients at intermediate surgical risk.

CoreValve US Pivotal Trial

In a multicenter, randomized, noninferiority trial, Adams et al. (2014) reported that TAVR, using a self-expanding bio-prosthesis (CoreValve), had a significantly higher rate of survival at one year than SAVR in patients with severe aortic stenosis and an increased surgical risk. A total of 795 patients were randomly assigned in a 1:1 ratio to TAVR with the CoreValve (TAVR group) or to SAVR (surgical group). The rate of death from any cause at one year was significantly lower in the TAVR group than in the surgical group (14.2% vs. 19.1%) with an absolute reduction in risk of 4.9 percent. Results were similar in the intention-to-treat analysis where the event rate was 13.9 percent in the TAVR group compared to 18.7 percent in the surgical group. The survival benefit with TAVR was consistent across clinical subgroups. NCT01240902.

At 2 years, all-cause mortality was significantly lower in the TAVR group (22.2%) than in the surgical group (28.6%) in the as-treated cohort, with an absolute reduction in risk of 6.5 percentage points. Similar results were found in the intention-to-treat cohort. The rate of 2-year death or major stroke was significantly lower in the TAVR group (24.2%) than in the surgical group (32.5%) (Reardon et al., 2015).

At 3 years, all-cause mortality or stroke was significantly lower in TAVR patients (37.3% vs. 46.7% in SAVR). Adverse clinical outcome components were also reduced in TAVR patients compared with SAVR patients, including all-cause mortality (32.9% vs. 39.1%, respectively), all stroke (12.6% vs. 19.0%, respectively) and major adverse cardiovascular or cerebrovascular events (40.2% vs. 47.9%, respectively). Hemodynamics were better with TAVR patients (mean aortic valve gradient 7.62 ±3.57 mmHg vs. 11.40 ±6.81 mmHg in SAVR), although moderate or severe residual aortic regurgitation was higher in TAVR patients (6.8% vs. 0.0% in SAVR). There was no clinical evidence of valve thrombosis in either group (Deeb et al., 2016).

In a prospective, multicenter, nonrandomized study, Popma et al. (2014) evaluated the safety and efficacy of the CoreValve transcatheter heart valve for the treatment of severe aortic stenosis in patients at extreme risk for surgery. Forty-one sites recruited 506 patients, of whom 489 underwent treatment with the CoreValve device. The rate of all-cause mortality or major stroke at 12 months was 26.0% vs. 43.0%. Individual 30-day and 12-month events included all-cause mortality (8.4% and 24.3%, respectively) and major stroke (2.3% and 4.3%, respectively). Procedural events at 30 days included, life threatening/disabling bleeding (12.7%), major vascular complications (8.2%) and need for permanent pacemaker placement (21.6%). The frequency of moderate or severe paravalvular aortic regurgitation was lower 12-months after self-expanding TAVR (4.2%) than at discharge (9.7%).

Several national TAVR registries were identified in the literature. Published results indicate that use of the SAPIEN and CoreValve devices was fairly equal, and the transfemoral approach was used approximately 3 times as often as the transapical approach. Conversion to surgical valve replacement occurred in 0.4% to 4% of procedures. Procedural success was very high and ranged from 91% to 99%. Procedural mortality was low and ranged from 0.4% to 3%. Survival at 30 days ranged from 87% to 95% and at 1 year from 63% to 100%, depending on the device and approach used (Walther et al., 2015; Gilard et al., 2012; Ussia et al., 2012; Bosmans et al., 2011; Thomas et al., 2011; Eltchaninoff et al., 2011; Zahn et al., 2011; Moat et al., 2011; Rodés-Cabau et al., 2010).

A meta-analysis of the adverse effects associated with TAVR included over 16,000 patients in 49 studies. Khatri et al. (2013) found that the need for a permanent pacemaker was the most common adverse outcome (13.1%) and was 5 times more common with the CoreValve than the Edwards SAPIEN valve. Vascular complications were also common (10.4%) and was highest with the trans arterial implantation of the Edwards SAPIEN valve (22.3%). Acute renal failure was the third most common complication, occurring in 4.9% of patients. Overall, 30-day and 1-year survival after TAVR were 91.9% and 79.2%, respectively.

Bicuspid Aortic Valve

A systematic review and meta-analysis were conducted by Chan et al. (2022) to compare the outcomes of TAVI in stenotic bicuspid aortic valve (BAV) against tricuspid aortic valve (TAV). The authors performed an electronic literature search in PubMed, MEDLINE, EMBASE, and Scopus to identify all studies comparing TAVI in stenotic BAV versus TAV. Only studies comparing TAVI in BAV versus TAV were included, without any limit on the study date. Primary endpoints were 30-day and 1-year mortality, while secondary endpoints were postoperative rates of stroke, acute kidney injury (AKI), and permanent pacemaker (PPM) requirement. A trial sequential analysis (TSA) was performed for all endpoints to understand their significance. A total of 13 studies met the inclusion criteria (917 BAV and 3,079 TAV patients). The BAV cohort was younger (76.8 ±7.43 years vs. 78.5 ±7.12 years, P = 0.02), had a higher trans-aortic valve gradient (P = 0.02), and larger ascending aortic diameters (P < 0.0001). No difference was shown for primary (30-day mortality [P = 0.45] and 1-year mortality [P = 0.41]) and secondary endpoints (postoperative stroke [P = 0.49], AKI [P = 0.14], and PPM requirement [P = 0.86]). The BAV group had a higher rate of post-operative aortic regurgitation (P = 0.002). TSA showed that there was sufficient evidence to conclude the lack of difference in PPM requirements, and 30-day and 1-year mortality between the two cohorts. The authors concluded TAVI should be considered clinically as it gives satisfactory outcomes for treating stenotic BAV. Only one included study followed patients for more than 1 year. In addition, subgroup analysis by the type of valve used was not possible due to studies including a mixture of different valves, often from different generations. Reporting outcomes by the type of valve could give a better understanding of whether the benefits of newer generation valves in TAV were applicable in BAV. These should be considered in future studies. Further investigation is needed before clinical usefulness of this procedure is proven.

Chen et al. (2022) conducted a systematic review to analyze the available data for TAVR in BAV patients, targeting procedural outcomes, clinical outcomes and mortality with up to two years of follow-up. A literature search of five databases was performed and all primary studies published between 2002 and 2021 that reported procedural, clinical or mortality outcome data were identified. Following data extraction, a meta-analysis of means or proportions was performed using a random effects model. Heterogeneity was assessed using the I2 statistic. A total of 22 studies with 1,945 BAV patients were identified. The mean age was 74.1 years and 58.8% of patients were male. Device success rate was 87.5%. Moderate to severe paravalvular leak (PVL) was seen in 3.7% of procedures. Clinical outcomes included new permanent pacemaker insertion (PPI) (11.8%), major bleeding (3.5%), major vascular complications (2.5%), stroke (2.3%), acute kidney injury (2.1%) and coronary obstruction (0.1%). Mortality in hospital, at 30-days, one and two years of follow-up were 1.9%, 2.1%, 9.6% and 12.9%, respectively. The authors concluded that the available data on TAVR for BAV shows promising outcomes and low rates of complications. BAV patients in this systematic review were studied as a single cohort, and subgroup analyses were not performed between different groups of BAV patients. There was significant heterogeneity within the baseline characteristics of the study population. Further investigation is needed before clinical usefulness of this procedure is proven.

Zhang et al. (2022) conducted a systematic review and meta-analysis of clinical adverse events in patients undergoing TAVR with BAV vs. tricuspid aortic valve (TAV) anatomy and the efficacy of balloon-expandable (BE) vs. self-expanding (SE) valves in the BAV population. Observational studies and a randomized controlled trial of patients with BAV undergoing TAVR were included according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. A total of 43 studies were included in the analysis. In patients undergoing TAVR, type 1 BAV was the most common phenotype and type 2 BAV accounted for the least. Higher risks of conversion to surgical aortic valve replacement (SAVR), the need of a second valve, a moderate or severe paravalvular leakage (PVL), device failure, acute kidney injury (AKI), and stroke were observed in patients with BAV than in patients with TAV during hospitalization. BAV had a higher risk of new permanent pacemaker implantation (PPI) both at hospitalization and a 30-day follow-up. Risk of 1-year mortality was lower in patients with BAV than those with TAV [odds ratio (OR) = 0.85, 95% CI 0.75-0.97, P = 0.01]. Balloon-expandible (BE) transcatheter heart valves (THVs) had higher risks of annular rupture but a lower risk of the need of a second valve and a new PPI than self-expanding (SE) THVs. Moreover, BE THV was less expanded and more elliptical in BAV than in TAV. In general, the rates of clinical adverse events were lower in new-generation THVs than in early-generation THVs in both BAV and TAV. The authors concluded despite higher risks of conversion to SAVR, the need of a second valve, moderate or severe PVL, device failure, AKI, stroke, and new PPI, TAVR seems to be a viable option for selected patients with severe bicuspid aortic stenosis (AS), which demonstrated a potential benefit of 1-year survival, especially among lower surgical risk population using new-generation devices. Limitations include heterogeneity in some analyses, choice of prosthesis was up to the physician's discretion, and the majority of included studies were not randomized trials in design. Further research with randomized controlled trials is needed to validate these findings.

An ECRI Clinical Evidence Assessment was conducted to evaluate SAPIENs safety and effectiveness and how they compare with those of other TAVR devices (including the second-generation SAPIEN XT valve) and SAVR. Review and meta-analysis found no statistical difference in technical success, periprocedural mortality, complications, and regurgitation resolution in patients with bicuspid native aortic valves and treated with SAPIEN 3, SAPIEN XT, CoreValve, Evolut R or Pro, Lotus, Direct Flow, or Venus (ECRI 2022; Quintana et al., 2020).

A systematic review and meta-analysis conducted by Du et al. (2021) aimed to compare procedural and 30-day outcomes after TAVI between type 0 and type 1 BAV. Studies comparing the outcomes of TAVI in Sievers type 0 vs. type 1 BAV were retrieved from PubMed, EMBASE, Cochrane Library, and Web of Science from inception to May 2021. The data were extracted regarding the study characteristics and outcomes. The odds ratios (ORs) with 95% CIs were pooled for procedural and 30-day outcomes. Six observational studies were included with determined type 0 BAV in 226 patients and type 1 BAV in 902 patients. The patients with type 0 BAV were slightly younger, had larger supra-annular structure, and more frequently implanted self-expanding prosthesis compared with type 1 BAV. In the pooled analyses, the patients with type 0 BAV had a similar incidence of procedural death (OR = 2.6, 95% CI 0.7-10.3), device success (OR = 0.6; 95% CI 0.3-1.3), and ≥ mild (OR = 0.8; 95% CI 0.4-1.6) or moderate (OR = 0.9, 95% CI 0.4-1.8) paravalvular leak, whereas higher mean aortic gradient (mean difference = 1.4 mmHg, 95% CI 0.03-2.7) and increased coronary compromise risk (OR = 7.2; 95% CI 1.5-34.9), compared with type 1 BAV. The incidence of death (OR = 1.2; 95% CI 0.5-3.1), stroke (OR = 0.5; 95% CI 0.1-2.4), and new pacemaker (OR = 0.6; 95% CI 0.2-2.2) at 30 days were not different between the BAV morphologies (P > 0.05). The treatment effect heterogeneity across the studies for the above outcomes were low. The authors concluded that patients with type 0 BAV appeared to have similar short-term outcomes after TAVI compared with type 1 BAV. In addition, the authors stated TAVI for type 0 BAV aortic stenosis might lead to an elevated coronary obstruction risk and suboptimal aortic valvular hemodynamics. Limitations include selection bias as the trials included were either small feasibility studies or large retrospective registries, with inconsistent inclusion and exclusion criteria. The short-term follow-up did not allow for assessment of intermediate and long-term outcomes. Further investigation is needed before clinical usefulness of this procedure is proven.

An ECRI Clinical Evidence Assessment found inconclusive evidence on the HAART 200 aortic annuloplasty device (BioStable Science & Engineering, Inc.) due to too few or no data on outcomes and comparisons of interest to treat moderate to severe aortic insufficiency in patients with bicuspid aortic valve disease. Study results were at high risk of bias due to small sample size and lack of controls, blinding and randomization. No studies reported on long-term follow-up or comparison of aortic valve repair using HAART 200 with aortic valve replacement (ECRI, 2020).

Quintana et al. (2019) conducted a meta-analysis to assess 1-year mortality after TAVR in patients with bicuspid AS using a literature search from the Cochrane, PubMed, Clinical Trials, SCOPUS, and EMBASE databases. Short-term outcomes that could potentially impact one-year mortality were analyzed. After evaluating 380 potential articles, 5 observational studies were selected. A total of 3,890 patients treated with TAVR were included: 721 had bicuspid and 3,169 had tricuspid AS. No statistical difference between the baseline characteristics of the two groups of patients was seen outside of mean aortic gradient. The primary endpoint of 1-year all-cause mortality revealed 85 deaths in 719 patients (11.82%) with bicuspid AS compared to 467 deaths in 3,100 patients (15.06%) with tricuspid AS, with no statistically significant difference between both groups [relative risk (RR) 1.03; 95% CI 0.70-1.51]. Bicuspid AS was associated with a decrease in device success (RR 0.62; 95% CI 0.45-0.84) and an increase in moderate-to-severe prosthetic valve regurgitation (RR 1.55; 95% CI 1.07-2.22) after TAVR compared to tricuspid AS. The effect of meta-regression coefficients on 1-year all-cause mortality was not statistically substantial for any patient baseline characteristics. The authors concluded when comparing TAVR procedure in tricuspid AS versus bicuspid AS, there was no difference noted in 1-year all-cause mortality. The small number of patients in each study and the observational nature of studies evaluating 1-year outcomes in patients with bicuspid AS undergoing TAVR are limitations of this meta-analysis.

Kanjanahattakij et al. (2018) conducted a systematic review and meta-analysis to evaluate evidence of TAVR in patients with severe aortic stenosis and BAV stenosis compared with TAV. Using professional databases, the authors searched for relevant articles featuring cohort studies that included patients with BAV and TAV who underwent TAVR studies, of which reported outcomes of interest included mortality and complications in both groups. Pooled effect size was calculated with a random-effect model and weighted for the inverse of variance, to compare outcomes post-TAVR between BAV and TAV. Nine studies were included in the meta-analysis. There was no statistically significant difference in the 30-day mortality rate in patients with BAV compared with TAV (OR: 1.27, 95% CI: 0.84-1.93, I2 = 0). Patients with BAV were more likely to have a moderate to severe paravalvular leak (9 studies; OR: 1.42, 95% CI: 1.08-1.87, I2 = 0) and conversion to surgery (5 studies; OR: 5.48, 95% CI: 1.74-17.27, I2 = 0), and less likely to have device success compared with patients with TAV (5 studies; OR: 0.57, 95% CI: 0.40-0.81, I2 = 0%). The authors concluded there was no difference in mortality post-TAVR in patients with BAV compared with TAV. The short-term follow-up did not allow for assessment of intermediate and long-term outcomes. Further research with randomized controlled trials is needed to validate these findings.

Mitral Valve

Transcatheter Mitral Valve Replacement

There is insufficient quality evidence in the clinical literature demonstrating the long-term efficacy of catheter-delivered mitral valve prostheses for treating mitral disease. Further results from prospective, randomized controlled trials are needed to determine device durability and the ideal candidates for the procedure. Several clinical trials are in progress.

A single-center, retrospective cohort study by Taha et al. (2022) was performed to evaluate the feasibility and safety of transcatheter mitral valve replacement (TMVR) in patients with high surgical risk with degenerated mitral bio-prostheses (TMViV), failed surgical rings (TMViR), and mitral annular calcification (TMViMAC). Patients with high surgical risk who underwent TMVR from February 2017 to September 2020, were enrolled in this study. The TMVR procedure was performed using Edwards SAPIEN-3 valves through the transseptal approach. Sixty-four patients aged 62.7 ±16.1 years with an STS score of 9.2 ±3.7% underwent TMVR [35 (55%) TMViV, 16 (25%) TMViR, and 13 (20%) TMViMAC]. Mitral stenosis was more frequent in TMViV, mitral regurgitation was more frequent in TMViR, and combined mitral stenosis and regurgitation were more frequent in TMViMAC (P < 0.05). (e MV gradient was 14.3 ±5.3 mmHg and the MV area was 1.5 ±0.6 cm2. The 29 mm valve was frequently used in TMViV and TMViMAC, while the 23 mm valve was frequently used in TMViR (P = 0.003). The procedural and fluoroscopy times were 58.7 ±8.9 and 41.1 ±8.2 minutes, respectively. Technical success was reported in 62 (98.4%) patients; 1 TMViR patient experienced valve embolization and salvage surgery, and 1 TMViMAC patient experienced slight valve malposition. At 3 months, 2 (3.1%) patients showed valve thrombosis (treated with anticoagulation), and 1 (1.6%) patient developed a paravalvular leak (underwent surgical MV replacement). At 6 months, 3 (4.7%) patients showed valve degeneration (underwent surgical MV replacement). Throughout follow-up, no patient exhibited mortality. The authors concluded that TMVR is a feasible and safe approach in patients with high surgical risk. TMViV and TMViR are reasonable as the first treatment approaches, and TMViMAC seems encouraging. Limitations include lack of comparison with other therapeutic approaches, small sample size (n = 64), short duration of follow-up (6 months), and single-center design. Further research is needed to determine the clinical relevance of these findings.

A Hayes report concluded that there is insufficient evidence to draw conclusions regarding the effectiveness and safety of TMVR for treating patients with MR. Substantial uncertainty remains due to a small body of evidence and lack of studies comparing TMVR with clinical alternatives (Hayes, 2021).

Regueiro et al. (2017) evaluated outcomes in 13 patients with severe native mitral regurgitation (MR) who underwent TMVR with the FORTIS valve. The multicenter registry included consecutive patients under a compassionate clinical use program. Clinical and echocardiographic data were collected at baseline, 30-day, 1-year and 2-year follow-up. MR was of ischemic origin in most patients, and the mean LVEF was 34 ±9%. Surgery was a technical success in 10 patients (76.9%). Five patients (38.5%) died within 30 days. At the 30-day follow-up, mean transmitral gradient was 3 ±1 mmHg, and there were no cases of moderate-severe residual MR or left ventricular outflow tract obstruction. At the 2-year follow-up, all-cause mortality was 54%, there were no cases of valve malfunction, and, with one exception, all patients were in NYHA functional class II. At the 2-year follow-up, computed tomography exams performed in 3 patients showed no valve prosthesis fractures or displacement. This study is limited by lack of a control group and small sample size.

In a multicenter global registry, Guerrero et al. (2016) evaluated the outcomes of TMVR in patients with severe mitral annular calcification. Sixty-four patients in 32 centers underwent TMVR with compassionate use of balloon-expandable valves. Mean age was 73 ±13 years, 66% were female and mean STS score was 14.4 ±9.5%. The mean mitral gradient was 11.45 ±4.4 mmHg, and the mean mitral area was 1.18 ±0.5 cm2. SAPIEN valves were used in 7.8%, SAPIEN XT in 59.4%, SAPIEN 3 in 28.1% and Inovare in 4.7%. Access was transatrial in 15.6%, transapical in 43.8% and transseptal in 40.6%. Technical success was achieved in 46 (72%) patients, primarily limited by the need for a second valve in 11 (17.2%). Six (9.3%) had left ventricular outflow tract obstruction with hemodynamic compromise. Mean mitral gradient post-procedure was 4 ±2.2 mmHg, and paravalvular regurgitation was mild or absent in all. Thirty-day all-cause mortality was 29.7%. Eighty-four percent of the survivors with follow-up data available were in NYHA functional class I or II at 30 days (n = 25). The authors concluded that TMVR with balloon-expandable valves in patients with severe mitral annular calcification is feasible but may be associated with significant adverse events. This study is limited by retrospective design, lack of comparison group, short-term follow-up and small sample size.

Puri et al. (2016) conducted a systematic review of TMVR for inoperable severely calcified native mitral valve disease. Nine publications describing 11 patients (82% severe mitral stenosis; 18% severe mitral regurgitation) were identified. The procedural success rate was 73%, without residual paravalvular leaks. Successful immediate re-deployment of a 2nd valve was needed in 2 instances, following significant paravalvular leak detection. All patients survived the procedure, with 2 non-cardiac-related deaths reported on days 10 and 41 post-TMVR. Mid-term follow-up, reported in 8 patients, revealed 6 patients were alive at 3-months with much improved functional status. Further studies with a larger number of patients and longer follow-up are warranted.

Percutaneous Leaflet Repair

Marmagkiolis et al. (2019) performed a meta-analysis to evaluate the safety and efficacy of percutaneous mitral valve repair for the management of functional MR. Seven studies (two RCTs and 5 observational studies) comparing percutaneous mitral valve repair using the MitraClip device (n = 1174) against conservative therapy (n = 1015) for the management of functional MR were included. The 12-month mortality rate in the MitraClip group was 18.4% compared with 25.9% in the medical therapy group. The rate of readmission at 12 months was 29.9% in the MitraClip group compared with 54.1% in the medical therapy group.

According to Hayes, a large body of low-quality evidence indicates that the MitraClip procedure is reasonably safe and may be beneficial for high-risk patients with moderate or severe MR, who are not acceptable candidates for conventional surgery. Several nonrandomized studies that compared MitraClip with optimal medical management found benefits, such as improved survival, after the MitraClip procedure; however, randomized controlled trials are needed to confirm these promising findings. Additional well-designed studies are needed to establish the clinical role of the MitraClip procedure, particularly relative to optimal medical management and minimally invasive open surgery in patients who are not candidates for open heart surgery (Hayes, 2018b; updated 2021).

The multicenter randomized controlled COAPT study enrolled patients with heart failure and moderate-to-severe or severe secondary mitral regurgitation who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy. Patients were randomly assigned to transcatheter mitral valve repair plus medical therapy (device group) or medical therapy alone (control group). Of the 614 patients who were enrolled in the trial, 302 were assigned to the device group and 312 to the control group. The primary effectiveness end point was all hospitalizations for heart failure within 24 months of follow-up. The primary safety end point was freedom from device-related complications at 12 months. Transcatheter mitral valve repair resulted in a lower rate of hospitalization for heart failure (hazard ratio, 0.53; 95% confidence interval [CI], 0.40 to 0.70; P < 0.001) and lower all-cause mortality (hazard ratio, 0.62; 95% CI, 0.46 to 0.82; P < 0.001) within 24 months of follow-up than medical therapy alone. The rate of freedom from device-related complications (96.6%) exceeded a prespecified safety threshold (Stone et al., 2018). With extended follow-up through 36 months, there was no loss of effectiveness with MitraClip treatment nor did new safety concerns emerge. Additionally, among 58 patients assigned to medical therapy alone who crossed over and were treated with MitraClip, the subsequent composite rate of mortality or hospitalizations for heart failure was reduced compared with those who continued on medical therapy alone (Mack et al., 2021). NCT01626079.

In the MITRA-FR study, patients with severe secondary MR were randomly assigned to undergo percutaneous mitral valve repair plus medical therapy (n = 152) or medical therapy alone (n = 152). Severe secondary MR was defined as an effective regurgitant orifice area of > 20 mm^2 or a regurgitant volume of > 30 ml per beat, a LVEF between 15 and 40% and symptomatic heart failure. Among patients with severe secondary MR, the rate of death or unplanned hospitalization for heart failure at 1 year did not differ significantly between the two groups. The rate of death from any cause was 24.3% (37 of 152 patients) in the intervention group and 22.4% (34 of 152 patients) in the control group. The rate of unplanned hospitalization for heart failure was 48.7% (74 of 152 patients) in the intervention group and 47.4% (72 of 152 patients) in the control group (Obadia et al., 2018). NCT01920698.

Bail (2015) performed a meta-analysis of the safety and efficacy of the MitraClip device. Twenty-six observational studies (n = 3821) were included in the analysis. Based on the analysis, the authors reported that treatment with MitraClip is associated with good short-term success and low mortality. The procedure is safe and effective for patients with limited surgical options. The results are comparable with open mitral valve repair, but patients are markedly older and have a higher risk profile than patients who undergo open mitral valve repair. These findings are limited by the lack of randomization of the included studies.

EVEREST II (Endovascular Valve Edge-to-Edge Repair Study)

EVEREST II is a two-part multicenter, randomized controlled trial and registry to evaluate the safety and efficacy of endovascular mitral valve repair using the MitraClip device compared with conventional mitral valve surgery in patients with moderate to severe mitral regurgitation (MR). The study is funded by Abbott Vascular. EVEREST II consists of a randomized arm and a high-risk registry arm. NCT00209274.

EVEREST II Randomized Arm

Feldman et al. (2011) randomly assigned 279 patients with moderately severe or severe (grade 3-4 +) MR in a 2:1 ratio to undergo either percutaneous repair (n = 184) or conventional surgery (n = 95) for repair or replacement of the mitral valve. The patients enrolled in this trial had a normal surgical risk and mainly degenerative MR with preserved left ventricular function. The primary end point for efficacy was freedom from death, from surgery for mitral-valve dysfunction and from grade 3-4 + MR at 12 months. The primary safety end point was a composite of major adverse events within 30 days. At 12 months, the rates of the primary end point for efficacy were 55% in the percutaneous-repair group and 73% in the surgery group. The respective rates of the components of the primary end point were as follows: death, 6% in each group; surgery for mitral-valve dysfunction, 20% versus 2%; and grade 3-4 + MR, 21% versus 20%. Major adverse events occurred in 15% of patients in the percutaneous-repair group and 48% of patients in the surgery group at 30 days. At 12 months, both groups had improved left ventricular size, NYHA functional class and quality-of-life measures, as compared with baseline. Although percutaneous repair was less effective at reducing MR than conventional surgery at 12 and 24 months, the procedure was associated with a lower adverse event rate and similar improvements in clinical outcomes.

At 4 years follow-up, Mauri et al. (2013) reported no significant differences between the MitraClip and conventional surgery treatment groups in all-cause mortality, presence of moderate or severe MR or event-free survival. However, at 4 years follow-up, additional mitral valve surgery was needed for 25% of MitraClip patients versus 6% of conventional surgery patients.

At 5 years follow-up, Feldman et al. (2015) reported that, although mitral valve repair surgery is superior to percutaneous mitral valve intervention using the MitraClip device in reducing the severity of MR, the device reduces symptoms, produces durable reduction of MR and promotes favorable reverse remodeling of the left ventricle 5 years after intervention.

EVEREST II High Risk Registry Arm

Using registry data from the EVEREST II High-Risk registry and the REALISM Continued Access Study High-Risk Arm registry, Glower et al. (2014) reported 12-month outcomes in high-risk patients treated with the MitraClip device for MR. Patients with grades 3 to 4 + MR and a surgical mortality risk of ≥ 12% were enrolled. In the studies, 327 of 351 patients completed 12 months of follow-up. Patients were elderly (76 ±11 years of age), with 70% having functional MR and 60% having prior cardiac surgery. The mitral valve device reduced MR to ≤ 2 + in 86% of patients at discharge (n = 325). Major adverse events at 30 days included death in 4.8%, myocardial infarction in 1.1% and stroke in 2.6%. At 12 months, MR was ≤ 2 + in 84% of patients (n = 225). From baseline to 12 months, left ventricular (LV) end-diastolic volume improved from 161 ±56 ml to 143 ±53 ml (n = 203) and LV end-systolic volume improved from 87 ±47 ml to 79 ±44 ml (n = 202). NYHA functional class improved from 82% in class III/IV at baseline to 83% in class I/II at 12 months (n = 234). Survival estimate at 12 months was 77.2%.

Whitlow et al. (2012) evaluated 78 high-risk symptomatic patients with severe (Grade 3 or 4 +) MR and an estimated surgical mortality rate of ≥ 12%. Percutaneous mitral valve leaflet repair, using the MitraClip device, was compared with 36 patients with similar degrees of MR, risks and comorbidities who were screened for the study but were not enrolled for various reasons. The devices were successfully placed in 96% of patients. Procedure-related mortality rate at 30 days was similar in the patients who underwent MitraClip placement and the comparator group (7.7% versus 8.3%), but the MitraClip patients appeared to have a better 1-year survival (76% versus 55%). In surviving patients with matched baseline and 12-month data, 78% had an MR grade of ≤ 2 +. Left ventricular end-diastolic volume improved from 172 ml to 140 ml, and end-systolic volume improved from 82 ml to 73 ml. NYHA functional class improved from III/IV at baseline in 89% to class I/II in 74%. Quality of life improved (Short Form-36 physical component score increased from 32.1 to 36.1), and the mental component score increased from 45.5 to 48.7 at 12 months. The annual rate of hospitalization for congestive heart failure in surviving patients with matched data decreased from 0.59 to 0.32. The authors concluded that the MitraClip device reduced MR in a majority of patients deemed at high risk of surgery, resulting in improvement in clinical symptoms and significant left ventricular reverse remodeling over 12 months. The findings are however limited by lack of randomization.

At 5 years, clinical follow-up was achieved in 90% of 78 enrolled patients. The rate of post-procedural adverse events declined from 30 days to 1-year follow-up and was stable thereafter through 5 years. Two patients developed mitral stenosis. Two patients underwent mitral valve surgery. A total of 42 deaths were reported through 5 years most likely a consequence of the advanced age and comorbidity profile of the enrolled patients. Effectiveness measures at 5 years showed reductions in MR severity to ≤ 2 + in 75% of patients, left ventricular end-diastolic volume and left ventricular end-systolic volume compared with baseline. NYHA functional class improved from baseline to 5 years, and septal-lateral annular dimensions remained stable with no indication of mitral annular dilation through 5 years (Kar et al., 2019).

EVEREST (Endovascular Valve Edge-to-Edge Repair Study)

EVEREST is a multicenter, prospective single-arm study to evaluate the feasibility, safety and efficacy of a percutaneous mitral valve repair system (MitraClip) for treating MR. Patients will undergo 30-day, 6-month, 12-month, and 5-year clinical follow-up. The study is funded by Abbott Vascular. NCT00209339.

Feldman et al. (2009) conducted an analysis of this prospective, multicenter single-arm study to evaluate the feasibility, safety and efficacy of the MitraClip system. A total of 107 patients with moderate to severe (grade 3-4 +) MR or compromised left ventricular function (if asymptomatic) underwent percutaneous valve repair with the MitraClip device. Ten (9%) had a major adverse event, including 1 nonprocedural death. Freedom from clip embolization was 100%. Partial clip detachment occurred in 10 (9%) patients. Overall, 74% of patients achieved acute success and 64% were discharged with MR of ≤ 1 +. Thirty-two patients (30%) had mitral valve surgery during the 3.2 years after clip procedures. When repair was planned, 84% (21 of 25) were successful. Thus, surgical options were preserved. A total of 50 of 76 (66%) successfully treated patients were free from death, mitral valve surgery or MR > 2 + at 12 months (primary efficacy end point). Kaplan-Meier freedom from death was 95.9%, 94.0% and 90.1%, and Kaplan-Meier freedom from surgery was 88.5%, 83.2% and 76.3% at 1, 2 and 3 years, respectively. The findings are limited by lack of comparison group.

Maisano et al. (2013) and Reichenspurner et al. (2013) reported early outcomes from the ACCESS-EU trial. The prospective, multicenter, single-arm post-approval study enrolled 567 patients with MR. Maisano et al. reported an implant success rate of 99.6%. Nineteen patients (3.4%) died within 30 days after the MitraClip procedure. Survival at 1 year was 81.8%. Thirty-six patients (6.3%) required mitral valve surgery within 12 months after the implant procedure. There was improvement in the severity of MR at 12 months, compared with baseline. In a subset of 117 patients with severe degenerative MR, Reichenspurner et al. reported that the MitraClip procedure resulted in significant reductions in MR and improvements in clinical outcomes at 12 months. Limitations of this study include lack of randomization, absence of a control group and short-term follow-up. Additionally, patient selection criteria varied at participating centers.

Cohort studies have compared the MitraClip procedure in high-risk patients with conventional surgery in patients at normal risk. The largest of these studies enrolled 171 patients with secondary MR and found that after 6 months, the MitraClip procedure was associated with lower survival (87% versus 96% of patients) and lower freedom from moderate or severe MR (88% versus 97% of patients). These differences may have been due to the poorer health status of patients who underwent the MitraClip procedure. Adjustment for these differences eliminated the statistically significant difference in survival (Conradi et al., 2013). Similar results were obtained by Taramasso et al. (2012) in a cohort study that enrolled 143 patients and preferentially assigned higher-risk patients to the MitraClip procedure. At 1-year follow-up, there were no significant differences between the treatment groups in patient survival, but the MitraClip group was more likely to have moderate or severe MR (21% versus 6% of patients). Again, these differences may have been due to the poorer health status of patients who underwent the MitraClip procedure.

Percutaneous Annuloplasty

There is insufficient quality evidence in the clinical literature demonstrating the long-term efficacy of coronary sinus annuloplasty devices for treating mitral regurgitation. Further results from prospective, randomized controlled trials are needed to determine safety, efficacy, durability and the ideal candidates for the procedure.

In the REDUCE FMR trial, Witte et al. (2019) evaluated the effects of the Carillon device on MR severity and left ventricular remodeling. In this blinded, randomized, proof-of-concept, sham-controlled trial, patients receiving optimal heart failure medical therapy were assigned to a coronary sinus-based mitral annular reduction approach for functional MR or sham. The primary endpoint was change in mitral regurgitant volume at 12 months, measured by echocardiography. Patients (n = 120) were randomized to either the treatment (n = 87) or the sham-controlled (n = 33) arm. There were no significant differences in baseline characteristics between the groups. In the treatment group, 73 of 87 (84%) had the device implanted. The primary endpoint was met with a statistically significant reduction in mitral regurgitant volume in the treatment group compared to the control group. Additionally, there was a significant reduction in left ventricular volumes in patients receiving the device versus those in the control group. This study was not powered to evaluate clinical endpoints. Studies are underway to assess the effect of this approach on mortality and hospitalization in patients with FMR. NCT02325830.

A Hayes report concluded that there is insufficient evidence to evaluate the Carillon procedure for percutaneous mitral valve repair (Hayes, 2018b; updated 2021).

Siminiak et al. (2012) evaluated whether percutaneous mitral annuloplasty (Carillon Mitral Contour System) could safely and effectively reduce functional mitral regurgitation (FMR) and yield durable long-term clinical benefit. Patients in whom the device was placed then acutely recaptured for clinical reasons served as a comparator group. Quantitative measures of FMR, left ventricular (LV) dimensions, NYHA class, 6 min walk distance (6MWD), and quality of life were assessed in both groups up to 12 months. Safety and key functional data were assessed in the implanted cohort up to 24 months. Thirty-six patients received a permanent implant; 17 had the device recaptured. The 30-day major adverse event rate was 1.9%. In contrast to the comparison group, the implanted cohort demonstrated significant reductions in FMR as represented by regurgitant volume. There was a corresponding reduction in LV diastolic volume and systolic volume compared with progressive LV dilation in the comparator. The 6MWD markedly improved for the implanted patients by 102.5 ±164 m at 12 months and 131.9 ±80 m at 24 months. The authors concluded that percutaneous reduction of FMR using a coronary sinus approach is associated with reverse LV remodeling. Significant clinical improvements persisted up to 24 months. While this study provides a comparator group with which to evaluate the hemodynamic and clinical significance of treating FMR, the lack of a randomized and blinded comparator also remains the primary limitation of the study. According to the authors, a randomized trial comparing intervention with a medically managed control group is warranted.

Schofer et al. (2009) evaluated patients with moderate heart disease who were enrolled in the CARILLON Mitral Annuloplasty Device European Union Study (AMADEUS). Percutaneous mitral annuloplasty was achieved through the coronary sinus with the CARILLON Mitral Contour System. Of the 48 patients enrolled in the trial, 30 received the CARILLON device. Eighteen patients did not receive a device because of access issues, insufficient acute FMR reduction, or coronary artery compromise. Echocardiographic FMR grade, exercise tolerance, NYHA class, and quality of life were assessed at baseline and 1 and 6 months. The major adverse event rate was 13% at 30 days. At 6 months, the degree of FMR reduction among 5 different quantitative echocardiographic measures ranged from 22% to 32%. Six-minute walk distance improved from 307+/-87 m at baseline to 403+/-137 m at 6 months. Quality of life, measured by the Kansas City Cardiomyopathy Questionnaire, improved from 47+/-16 points at baseline to 69+/-15 points at 6 months. The authors concluded that percutaneous reduction in FMR with a novel coronary sinus-based mitral annuloplasty device is feasible in patients with heart failure, is associated with a low rate of major adverse events and is associated with improvement in quality of life and exercise tolerance. Study limitations include the lack of a randomized, blinded control group with whom to compare safety and efficacy results.

Several other minimally invasive mitral valve repair devices are in the early stages of development. Large, prospective studies with long-term follow-up are needed to establish their clinical role.

Small case series from a single research group reported early results with the Harpoon expanded polytetrafluoroethylene (ePTFE) chordal implantation system. The results were promising; however, larger prospective studies with long-term follow-up are needed to establish their clinical role (Gammie et al., 2021; Gammie et al., 2016; Gammie et al., 2018).

Messika-Zeitoun et al. (2019) reported the 1-year outcomes of 60 consecutive patients with moderate or severe secondary MR who underwent the Cardioband procedure. At 1 year, most patients had moderate or less MR and experienced significant functional improvements. There were two in-hospital deaths (no device-related), one stroke, two coronary artery complications and one tamponade. Anchor disengagement, observed in 10 patients, resulted in device inefficacy in five patients and led to device modification halfway through the study to mitigate this issue. Study limitations include lack of randomization and control and short-term follow-up.

Colli et al. (2018) reported early results of the NeoChord mitral valve repair system for treating degenerative MR. In a consecutive case series of patients, 213 participants were enrolled in the NeoChord Independent International Registry. All participants presented with severe MR. The primary end points were procedural success, freedom from mortality, stroke, reintervention, recurrence of severe MR, rehospitalization and decrease of at least 1 NYHA functional class at 1-year follow-up. Procedural success was achieved in 206 (96.7%) patients. At 1-year follow-up, overall survival was 98 ±1%. Composite end point was achieved in 84 ±2.5% for the overall population. Study limitations include lack of randomization and control and short-term follow-up.

Pulmonary Valve

A Hayes report concluded that there is insufficient evidence to draw conclusions regarding the effectiveness and safety of percutaneous pulmonary valve implantation (PPVI) using SAPIEN 3 and SAPIEN XT valves for the treatment of right ventricular outflow tract (RVOT). Substantial uncertainty exists regarding the long-term durability and efficacy compared with open heart surgery (Hayes, 2022).

Chatterjee et al. (2017) performed a systematic review and meta-analyses of observational studies evaluating transcatheter pulmonary valve implantation. Nineteen studies (n = 1044) with 5 or more patients and at least 6 months of follow-up were included. Thirteen studies used the Melody valve, three used the Edwards SAPIEN or SAPIEN XT valves and three used both Melody and Edwards valve systems. Procedural success rate was 96.2% with a conduit rupture rate of 4.1% and coronary complication rate of 1.3%. The authors reported favorable updated estimates of procedural and follow-up outcomes after transcatheter pulmonary valve implantation. They also noted that widespread adoption of pre-stenting has improved long-term outcomes in these patients. (This systematic review includes Cheatham et al. 2015, Armstrong et al. 2014, Butera et al. 2013 and Eicken et al. 2011 which were previously cited in this policy.)

Harmony

There is insufficient quality evidence in the clinical literature demonstrating the long-term safety and efficacy of the Harmony transcatheter pulmonary valve. Further results from comparative studies or randomized controlled trials are needed to determine safety, efficacy and durability of the device.

Benson et al. (2020) reported 3-year clinical and hemodynamic outcomes in a follow-up to the Bergersen et al. (2017) feasibility study. Of the original 20 implanted patients, 17 completed 3-year follow-up. Results showed good valve function in most, and the absence of moderate/severe paravalvular leak and significant late frame fractures. Two patients developed significant neointimal tissue ingrowth requiring ViV treatment, while all others had no clinically significant RVOT obstruction. The authors noted that these results are encouraging, but further follow-up is required. At 5 years, Gillespie et al. (2021) reported in a letter to the editor sustained valve function with freedom from moderate-to-severe valve or perivalvular leak and no reports of endocarditis. Two patients underwent surgical explant. There were 3 catheter-based reinterventions performed in 2 patients who both ultimately underwent Melody ViV procedures. One patient passed away shortly after the 3-year follow-up assessment. These and the original publication described below are limited by lack of a comparison group undergoing a different therapeutic approach.

Bergersen et al. (2017) reported clinical outcomes from an early feasibility study to assess the self-expanding Harmony transcatheter pulmonary valve. Of sixty-six enrolled participants, 21 patients were approved for implant and 20 received the Harmony device. Most patients had been diagnosed with tetralogy of Fallot and had augmented RVOTs or transannular patch repairs. Clinical assessments were collected at baseline and after 1-month, 3-month and 6-month follow-ups. In the 20 implanted patients, the device was implanted in the intended location; however, proximal migration occurred in one participant during delivery system removal. Two devices were surgically explanted. Premature ventricular contractions related to the procedure were reported in three patients; two were resolved without treatment. One patient had ventricular arrhythmias that required treatment and were later resolved. Eighteen patients returned for the 3- and 6-month follow-up assessments.

Echocardiographic data remained consistent with those observed at the 1-month visit. Compared with baseline, patients had significant improvements in pulmonary regurgitation. By the 6-month follow-up, there were minimal changes in incidence of paravalvular leak, mean RVOT gradient or tricuspid regurgitation. Study limitations include lack of randomization, control group and small sample size. Additionally, enrollment was limited to three sites, each with an experienced catheterization cardiologist performing the procedure. The authors noted that further studies with larger patient populations are needed to assess long-term durability, function and safety of the Harmony device.

Melody

McElhinney et al. (2010) conducted a single-arm multicenter trial of 136 patients (median age, 19 years) who underwent catheterization for intended Melody valve implantation. Implantation was attempted in 124 patients. In the other 12, transcatheter pulmonary valve placement was not attempted because of the risk of coronary artery compression (n = 6) or other clinical or protocol contraindications. There was 1 death and 1 explanted valve after conduit rupture. The median peak RVOT gradient was 37 mmHg before implantation and 12 mmHg immediately after implantation. Before implantation, pulmonary regurgitation was moderate or severe in 92 patients. No patient had more than mild pulmonary regurgitation early after implantation or during follow-up. Freedom from stent fracture was 77.8+/-4.3% at 14 months. Freedom from valve dysfunction or reintervention was 93.5+/-2.4% at 1 year. A higher RVOT gradient at discharge and younger age were associated with shorter freedom from dysfunction. The results demonstrated an ongoing high rate of procedural success and encouraging short-term valve function. All re-interventions in this series were for RVOT obstruction, highlighting the importance of patient selection, adequate relief of obstruction, and measures to prevent and manage stent fracture. Jones et al. (2022) reported on 58 patients at 10 years. The estimated freedom from mortality was 90%, from reoperation 79%, and from any reintervention 60%. Ten-year freedom from TPV dysfunction was 53% and was significantly shorter in children than in adults. Estimated freedom from TPV-related endocarditis was 81% at 10 years, with an annualized rate of 2.0% per patient-year. NCT00740870.

SAPIEN

Kenny et al. (2018) reported 3-year follow-up results of the COMPASSION (Congenital Multicenter Trial of Pulmonic Valve Regurgitation Studying the SAPIEN Transcatheter Heart Valve) trial. Patients with moderate to severe pulmonary regurgitation and/or RVOT conduit obstruction were implanted with the SAPIEN transcatheter heart valve. Fifty-seven of the 63 eligible patients were accounted for at the 3-year follow-up visit from a total of 69 implantations in 81 enrolled patients. Indications for implantation were pulmonary stenosis (7.6%), regurgitation (12.7%) or both (79.7%). Functional improvement in NYHA functional class was observed in 93.5% of patients. Mean peak conduit gradient decreased from 37.5 ±25.4 to 17.8 ±12.4 mmHg, and mean right ventricular systolic pressure decreased from 59.6 ±17.7 to 42.9 ±13.4 mmHg. Pulmonary regurgitation was mild or less in 91.1% of patients. When implanted in patients with moderate to severe pulmonary regurgitation and/or RVOT conduit obstruction, the SAPIEN valve was associated with favorable outcomes at 3 years, with low rates of all-cause mortality, reintervention and endocarditis and no stent fractures.

Tricuspid Valve

There is insufficient quality evidence in the clinical literature demonstrating the long-term safety and efficacy of transcatheter procedures for treating tricuspid valve disease. Further results from prospective, randomized controlled trials are needed to determine safety, efficacy, durability and the ideal candidates for the procedure.

Bugan et al. (2022) completed a systematic review and meta-analysis to evaluate the feasibility of orthotopic transcatheter tricuspid valve replacement (TTVR) devices, echocardiographic, functional improvements, and mortality rates following replacement in patients with significant tricuspid valve regurgitation. The authors systematically searched for the studies evaluating the efficacy and safety of transcatheter tricuspid valve replacement for significant tricuspid valve regurgitation. The efficacy and safety outcomes were the improvements in New York Heart Association functional class, 6-minute walking distance, all-cause death, and periprocedural and long-term complications. In addition, a random-effect meta-analysis was performed comparing outcomes before and after transcatheter tricuspid valve replacement. Nine studies with 321 patients were included in this study. The mean age was 75.8 years, and the mean European System for Cardiac Operative Risk Evaluation II score was 8.2% (95% CI: 6.1 to 10.3). Severe, massive, and torrential tricuspid valve regurgitation was diagnosed in 95% of patients (95% CI: 89% to 98%), and 83% (95% CI: 73% to 90%) of patients were in New York Heart Association functional class III or IV. At a weighted mean follow-up of 122 days, New York Heart Association functional class (risk ratio = 0.20; 95% CI: 0.11 to 0.35; P < .001) and 6-minute walking distance (mean difference = 91.1 m; 95% CI: 37.3 to 144.9 m; P < .001) improved. The prevalence of severe or greater tricuspid valve regurgitation was reduced after transcatheter tricuspid valve replacement (baseline risk ratio= 0.19; 95% CI: 0.10 to 0.36; P < .001). In total, 28 patients (10%; 95% CI: 6% to 17%) died.

Pooled analyses demonstrated non-significant differences in hospital and 30-day mortality and > 30-day mortality than predicted operative mortality (risk ratio = 1.03; 95% CI: 0.41 to 2.59; P = .95, risk ratio = 1.39; 95% CI: 0.69 to 2.81; P = .35, respectively). The authors concluded that transcatheter tricuspid valve replacement could be an emerging treatment option for patients with severe tricuspid regurgitation who are not eligible for transcatheter repair or surgical replacement because of high surgical risk. Limitations include a potential for bias as the analysis only included single-arm interventional studies case series, and no randomized controlled trials (RCTs). Moderate heterogeneity was found in the consistency of results. In addition, there are no specific guideline recommendations for patient selection for TTVR, therefore, this meta-analysis is limited by the lack of uniformity in the definition of procedural success. Further research with randomized controlled trials is needed to validate these findings.

An ECRI Clinical Evidence Assessment found very low-quality evidence on percutaneous tricuspid valve repair for treating TR in patients who are ineligible for surgery. Study results were at high risk of bias due to small sample size and lack of controls and randomization (ECRI, 2022).

Bocchino et al. (2021) performed a meta-analysis to assess the pooled clinical and echocardiographic outcomes of different isolated transcatheter tricuspid valve repair strategies for moderate or greater TR in patients who were ineligible for surgery. Fourteen observational studies (n = 771) were included. At a mean follow-up of 212 days, 209 patients (35%) were in NYHA functional class III or IV compared with 586 patients (84%) at baseline. Six-minute walking distance significantly improved by a mean 50 meters. One hundred forty-seven patients (24%) showed severe or greater TR after isolated transcatheter tricuspid valve repair compared with 616 (96%) at baseline. The included studies are at a high risk of bias due to several factors: small sample size, single-center focus, retrospective design, and/or lack of controls, randomization and blinding. Further results from prospective, randomized controlled trials are needed to confirm these findings.

The international TriValve Registry (n = 312) was developed to evaluate several transcatheter tricuspid valve interventions in high-risk patients with severe TR (predominantly functional). Interventions included leaflet repair, annulus repair, coaptation and replacement. Implanted devices included MitraClip (n = 210), Trialign (n = 18), TriCinch first generation (n = 14), caval valve implantation (n = 30), FORMA (n = 24), Cardioband (n = 13), NaviGate (n = 6) and PASCAL (n = 1). Preliminary results of transcatheter tricuspid valve interventions were promising in terms of safety and feasibility. Mid-term survival was favorable in this high-risk population. However, long-term outcomes and better patient selection are needed to better understand the clinical role of these procedures for treating TR (Taramasso et al., 2019).

In an observational study of 64 consecutive patients, Nickenig et al. (2017) evaluated the safety and feasibility of transcatheter repair of chronic severe TR using edge-to-edge clipping. The procedure was successfully performed in 97% of the patients. After the procedure, TR was reduced by at least 1 grade in 91% of the patients, with significant improvements in NYHA class and 6-minute walk test. In 13% of patients, TR remained severe after the procedure. Significant reductions in effective regurgitant orifice area, vena contracta width and regurgitant volume were observed. This study is limited by small sample size, lack of randomization and control, and limited follow-up.

Valve-in-Valve (ViV) Procedures

There is insufficient quality evidence in the clinical literature demonstrating the long-term efficacy of ViV procedures for mitral, pulmonary, or tricuspid valves. The evidence for these procedures is still evolving. Evidence supporting ViV procedures for aortic valves is stronger.

Al-Abcha et al. (2021) performed a meta-analysis to compare clinical outcomes of ViV TAVR versus redo SAVR in failed bioprosthetic aortic valves. Twelve observational studies were included (n = 8430). Compared to redo SAVR, ViV TAVR was associated with a similar risk of all-cause mortality, cardiovascular mortality, myocardial infarction, permanent pacemaker implantation, and the rate of moderate to severe paravalvular leakage. However, the rates of major bleeding, stroke, procedural mortality and 30-day mortality were significantly lower in the ViV group. Randomized clinical trials are needed to confirm the safety and efficacy of ViV TAVR in patients with failed bioprosthetic aortic valves.

Gozdek et al. (2018) performed a systematic review and meta-analysis to compare redo SAVR with ViV TAVR for patients with failed aortic bio-prostheses. Five observational studies (n = 342) were included in the analysis. Although there was no statistical difference in procedural mortality, 30-day mortality, and cardiovascular mortality at a mean follow-up period of 18 months, cumulative survival analysis favored surgery. ViV procedures were associated with a significantly lower rate of permanent pacemaker implantations and shorter intensive care unit and hospital stays. Redo SAVR offered superior echocardiographic outcomes, lower incidence of patient-prosthesis mismatch, fewer paravalvular leaks, and lower mean postoperative aortic valve gradients. The authors concluded that ViV approach is a safe, feasible alternative to conventional surgery that may offer an effective, less invasive treatment for patients with failed surgical aortic bio-prostheses who are inoperable or at high risk, but that SAVR should remain the standard of care, particularly in the low-risk population, because it offers superior hemodynamic outcomes with low mortality rates.

Tam et al. (2018) performed a systematic review and meta-analysis to determine the safety and efficacy of ViV TAVR versus redo SAVR for the treatment of previously failed aortic bio-prostheses. Four unadjusted (n = 298) and two propensity-matched (n = 200) observational studies were included. Despite higher predicted surgical risk of ViV patients, there was no difference in perioperative mortality (4.4% versus 5.7%) or late mortality, reported at median one-year follow-up. The incidence of permanent pacemaker implantation (8.3% versus 14.6%) and dialysis (3.2% versus 10.3%) were lower in ViV. There was a reduction in the incidence of severe patient-prosthesis mismatch (3.3% versus 13.5%) and mild or greater paravalvular leak (5.5% versus 21.1%) in the redo SAVR group compared to ViV.

Using patient data from the STS/American College of Cardiology Transcatheter Valve Therapy Registry, Tuzcu et al. (2018) evaluated the safety and effectiveness of ViV TAVR for failed surgically implanted bio-prostheses by comparing it with the benchmark of native valve (NV) TAVR. Patients who underwent ViV TAVR (n = 1,150) were matched 1:2 to patients undergoing NV TAVR (n = 2,259). Unadjusted analysis revealed lower 30-day mortality (2.9% vs. 4.8%), stroke (1.7% vs. 3.0%) and heart failure hospitalizations (2.4% vs. 4.6%) in the ViV TAVR compared with the NV TAVR group. Adjusted analysis revealed lower 30-day mortality, lower 1-year mortality and hospitalization for heart failure in the ViV TAVR group. Patients in the ViV TAVR group had higher post-TAVR mean gradient (16 vs. 9 mmHg), but less moderate or severe aortic regurgitation (3.5% vs. 6.6%). Post-TAVR gradients were highest in small SAVRs and stenotic SAVRs.

Eleid et al. (2017) reported 1-year outcomes of percutaneous balloon-expandable transcatheter heart valve implantation in a failed mitral bio-prosthesis (n = 60), previous ring annuloplasty (n = 15) and severe mitral annular calcification (n = 12). Acute procedural success was achieved in 97% of the ViV group and 74% in the valve in ring/valve in mitral annular calcification (MAC) group. Thirty-day survival free of death and cardiovascular surgery was 95% in the ViV subgroup and 78% in the valve in ring/valve in MAC group. One-year survival free of death and cardiovascular surgery was 86% in the ViV group compared with 68%. At 1 year, 90% had NYHA functional class I or II symptoms, no patients had more than mild residual mitral prosthetic or periprosthetic regurgitation and the mean transvalvular gradient was 7 ±3 mmHg. The procedure for failed annuloplasty rings and severe MAC was feasible but associated with significant rates of left ventricular outflow tract obstruction, need for a second valve and/or cardiac surgery. This study reflects very early results with the procedure and is limited by small sample size and lack of randomization. Further studies of a larger number of patients treated using similar techniques and with longer follow-up duration will be necessary to continually assess outcomes of this novel therapy.

In an observational study, Yoon et al. (2017) evaluated the outcomes of TMVR in 248 patients with failed mitral bioprosthetic valves (ViV) and annuloplasty rings. The TMVR procedure provided acceptable outcomes in high-risk patients with degenerated bio-prostheses or failed annuloplasty rings, but mitral valve-in-ring was associated with higher rates of procedural complications and mid-term mortality compared with mitral ViV. This study is limited by lack of randomization and control. Further studies evaluating the long-term outcomes of patients undergoing TMVR for degenerated bio-prostheses or failed annuloplasty rings are needed.

Deeb et al. (2017) evaluated the safety and effectiveness of the CoreValve in patients with failed surgical aortic bio-prostheses. The CoreValve U.S. Expanded Use Study was a prospective, nonrandomized study that enrolled 233 patients with symptomatic surgical valve failure who were deemed unsuitable for reoperation. Patients were treated with the CoreValve and evaluated for 30-day and 1-year outcomes after the procedure. Surgical valve failure occurred through stenosis (56.4%), regurgitation (22.0%) or a combination (21.6%). A total of 227 patients underwent attempted TAVR and successful TAVR was achieved in 225 (99.1%) patients. Patients were elderly (76.7 ±10.8 years), had an STS PROM score of 9.0 ±6.7% and were severely symptomatic (86.8% NYHA functional class III or IV). The all-cause mortality rate was 2.2% at 30 days and 14.6% at 1 year; major stroke rate was 0.4% at 30 days and 1.8% at 1 year. Moderate aortic regurgitation occurred in 3.5% of patients at 30 days and 7.4% of patients at 1 year, with no severe aortic regurgitation. The rate of new permanent pacemaker implantation was 8.1% at 30 days and 11.0% at 1 year. The mean valve gradient was 17.0 ±8.8 mmHg at 30 days and 16.6 ±8.9 mmHg at 1 year.

Webb et al. (2017) evaluated 30-day and 1-year outcomes in high-risk patients undergoing ViV TAVR using the SAPIEN XT valve. Patients with symptomatic degeneration of surgical aortic bio-prostheses at high risk (≥ 50% major morbidity or mortality) for reoperative surgery were prospectively enrolled in the multicenter PARTNER 2 ViV trial and continued access registries. ViV procedures were performed in 365 patients (96 initial registry, 269 continued access patients). Mean age was 78.9 ±10.2 years, and mean STS score was 9.1 ±4.7%. At 30 days, all-cause mortality was 2.7%, stroke was 2.7%, major vascular complication was 4.1%, conversion to surgery was 0.6%, coronary occlusion was 0.8% and new pacemaker insertion was 1.9%. One-year all-cause mortality was 12.4%. Mortality fell from the initial registry to the subsequent continued access registry, both at 30 days (8.2% vs. 0.7%, respectively) and at 1 year (19.7% vs. 9.8%, respectively). At 1-year, mean gradient was 17.6 mmHg, and effective orifice area was 1.16 cm2, with greater than mild paravalvular regurgitation of 1.9%. LVEF increased (50.6% to 54.2%), and mass index decreased (135.7 to 117.6 g/m2), with reductions in both mitral (34.9% vs. 12.7%) and tricuspid (31.8% vs. 21.2%) moderate or severe regurgitation.

Phan et al. (2016) conducted a systematic review to compare outcomes and safety of transcatheter ViV implantation with reoperative conventional aortic valve replacement. A total of 18 relevant observational studies (823 patients) were included. Pooled analysis suggested that transcatheter ViV implantation achieved similar hemodynamic outcomes, with lower risk of strokes and bleeding, but higher rates of paravalvular leaks compared to reoperative conventional aortic valve replacement. The authors noted that future randomized studies and prospective registries are essential to compare the effectiveness of these procedures.

Using VIVID registry data, Dvir et al. (2014) determined the survival of patients after transcatheter aortic ViV implantation inside failed surgical bioprosthetic valves. Correlates for survival were evaluated using a multinational registry that included 459 patients with degenerated bioprosthetic valves undergoing ViV implantation. Modes of bio-prosthesis failure were stenosis (n = 181), regurgitation (n = 139) and combined (n = 139). The stenosis group had a higher percentage of small valves (37% vs 20.9% and 26.6% in the regurgitation and combined groups, respectively). Within 1 month following ViV implantation, 35 (7.6%) patients died, 8 (1.7%) had major stroke and 313 (92.6%) of surviving patients had good functional status (NYHA class I/II). The overall 1-year survival rate was 83.2%; 62 death events; 228 survivors). Patients in the stenosis group had worse 1-year survival (76.6%; 34 deaths; 86 survivors) in comparison with the regurgitation group (91.2%; 10 deaths; 76 survivors) and the combined group (83.9%; 18 deaths; 66 survivors). Similarly, patients with small valves had worse 1-year survival (74.8%; 27 deaths; 57 survivors) versus with intermediate-sized valves (81.8%; 26 deaths; 92 survivors) and with large valves (93.3%; 7 deaths; 73 survivors). Factors associated with mortality within 1 year included having small surgical bio-prosthesis (≤ 21 mm) and baseline stenosis (vs regurgitation). In a follow-up study, Bleiziffer et al. (2020) assessed long-term survival and reintervention outcomes after transcatheter aortic ViV procedures. A total of 1,006 aortic ViV procedures were included in the analysis. The primary endpoint was patient survival, and the main secondary endpoint was all-cause reintervention. Results showed that the size of the original failed valve may influence long-term mortality, and the type of transcatheter valve may influence the need for reintervention after aortic ViV procedures.

Cerebral Protection

There is insufficient quality evidence in the clinical literature demonstrating the long-term efficacy of transcatheter cerebral protection devices in improving neurological and cognitive function following transcatheter aortic valve replacement.

A prospective, post-market, multi-center, randomized controlled trial was conducted by Kapadia et al. (2022) to evaluate the Sentinel cerebral embolic protection (CEP) device in patients with aortic stenosis undergoing transfemoral transcatheter TAVR. A total of 3,000 patients with aortic stenosis across North America, Europe, and Australia underwent randomization in a 1:1 ratio to undergo transfemoral TAVR with CEP (CEP group) or without CEP (control group); 1,501 were assigned to the CEP group and 1499 to the control group. The primary end point was stroke within 72 hours after TAVR or before discharge (whichever came first) in the intention-to-treat population. Disabling stroke, death, transient ischemic attack, delirium, major or minor vascular complications at the CEP access site, and acute kidney injury were also assessed. A neurology professional examined all enrolled study patients at baseline and again after TAVR. A CEP device was successfully deployed in 1,406 of the 1,489 patients (94.4%) in whom an attempt was made. The incidence of stroke within 72 hours after TAVR or before discharge did not differ between the CEP group and the control group (2.3% vs. 2.9%; difference, −0.6 percentage points; 95% confidence interval, −1.7 to 0.5; P = 0.30). Disabling stroke occurred in 0.5% of the patients in the CEP group and in 1.3% of those in the control group. There were no sizeable differences between the CEP group and the control group in the percentage of patients who died (0.5% vs. 0.3%); had a stroke, a transient ischemic attack, or delirium (3.1% vs. 3.7%); or had acute kidney injury (0.5% vs. 0.5%). One patient (0.1%) had a vascular complication at the CEP access site. The authors concluded among patients with aortic stenosis undergoing transfemoral TAVR, the use of CEP did not influence the incidence of periprocedural stroke but based on the 95% confidence interval around this outcome, the results may not rule out a benefit of CEP during TAVR. Limitations include a greater percentage of female patients in the CEP group despite randomization and large number of enrolled patients. Female sex has been reported to be a risk factor for stroke with TAVR. Granular data on clinical outcomes were restricted to a small number of endpoints, with only short-term follow-up. In addition, the trial results apply only to the Sentinel CEP device and cannot be generalized to other CEP devices. There are additional ongoing clinical trials including the BHF PROTECT-TAVI (British Heart Foundation Randomized Trial of Routine Cerebral Embolic Protection in Transcatheter Aortic Valve Implantation; ISRCTN Registry number, ISRCTN16665769) in which additional data on the effectiveness of CEP during TAVR are forthcoming.

In a letter to the editor, Radwan et al. (2021) performed a meta-analysis of studies evaluating the safety and efficacy of the Sentinel cerebral protection system during TAVR. Three RCTs and four observational studies were included (n = 117,329). The Sentinel group was associated with lower risk of 30-day stroke, mortality and major bleeding. These short-term results were mainly driven from observational data as subgroup analysis from the RCTs showed a trend toward benefit without statistical significance. The rate of major vascular complications was similar between the 2 groups. Results from large RCTs are needed to confirm these results.

Ndunda et al. (2019) performed a systematic review and meta-analysis to compare the clinical outcomes following TAVR with and without the use of the Sentinel Cerebral Protection System (Sentinel CPS). Four studies (three RCTs and one propensity score-matched cohort study) comparing patients undergoing TAVR with Sentinel CPS (n = 606) to those without any embolic protection device (n = 724) were included. Sentinel CPS use was associated with lower rates of 30-day mortality, 30-day symptomatic stroke and major or life-threatening bleeding. There was no significant difference between the two arms in the incidence of acute kidney injury and major vascular complications. The authors noted limitations for the analyzed studies including lack of a control group for some studies, small sample sizes, lack of patient-level data and missing outcomes data. Furthermore, not all included studies were randomized.

An ECRI product brief on the Sentinel device reported that the evidence suggests that device placement is relatively safe, but whether it benefits patients undergoing TAVR is unclear. Studies reported inconsistent findings on the device's impact on reducing stroke risk and too few data are available on the long-term neurocognitive burden of brain microinfarction in patients treated with the device. Additional controlled studies that report on these outcomes are needed to assess the device's effectiveness (ECRI, 2017d; updated 2019).

Bagur et al. (2017) performed a systematic review and meta-analysis evaluating the impact of embolic protection devices on cerebrovascular events during TAVR. Sixteen studies (5 RCTs and 11 observational studies) involving 1,170 patients (865/305 with/without embolic protection devices) were included. The embolic protection device delivery success rate was reported in all studies and was achieved in 94.5% of patients. Meta-analyses comparing the two methods showed no significant differences between patients undergoing TAVR with or without embolic protection devices with respect to clinically evident stroke and 30-day mortality. Embolic protection during TAVR may be associated with smaller volume of silent ischemic lesions and smaller total volume of silent ischemic lesions. However, it may not reduce the number of new-single, multiple or total number of lesions.

In an observational cohort study, Seeger et al. (2017) evaluated the impact of cerebral embolic protection on stroke-free survival in 802 consecutive patients undergoing TAVR for severe aortic stenosis. The Sentinel cerebral embolic protection device was used in 34.9% (n = 280) of patients. In the remaining group of patients, TAVR was performed without cerebral embolic protection. In patients undergoing TAVR, use of a cerebral embolic protection device demonstrated a significantly higher rate of stroke-free survival compared with unprotected TAVR. This study is limited by lack of randomization.

In two randomized, controlled trials (Kapadia et al., 2017; Van Mieghem et al., 2016), the primary efficacy endpoint was reduction in volume of new cerebral lesions on diffusion-weighted magnetic resonance imaging (DW-evaluation) up to 7 days post-TAVR, a surrogate endpoint for cerebral damage. This endpoint was not met in either trial, although both trials demonstrated a nonsignificant numerical reduction in new cerebral lesions favoring the Sentinel device over no transcatheter cerebral embolic protection. In addition, both trials were limited by small sample sizes and poor compliance with DW-MRI follow-up, which was missing for 21% of SENTINEL trial patients (Kapadia et al., 2017) and 43% of MISTRAL-C trial patients (Van Mieghem et al., 2016).

In the Claret Embolic Protection and TAVI (CLEAN-TAVI) trial, Haussig et al. (2016) evaluated the effect of a cerebral protection device on the number and volume of cerebral lesions in patients undergoing TAVR. One hundred patients were randomly assigned to undergo TAVR with a cerebral protection device (filter group; n = 50) or without a cerebral protection device (control group; n = 50). Brain MRI was performed at baseline, 2 days and 7 days after TAVR. The use of a cerebral protection device reduced the frequency of ischemic cerebral lesions in potentially protected regions. The number of new lesions was 4.00 in the filter group and 10.00 in the control group. New lesion volume after TAVR was 242 mm^3 in the filter group and 527 mm^3 in the control group. One patient in the control group died prior to the 30-day visit. Life-threatening hemorrhages occurred in 1 patient in the filter group and 1 in the control group. Major vascular complications occurred in 5 patients in the filter group and 6 patients in the control group. One patient in the filter group and 5 in the control group had acute kidney injury, and 3 patients in the filter group had a thoracotomy. Larger studies, with longer follow-up are needed to assess the effect of cerebral protection device use on neurological and cognitive function after TAVR. NCT01833052.

Giustino et al. (2016) conducted a systematic review and meta-analysis of four randomized controlled trials (n = 252) that tested the safety and efficacy of embolic protection during TAVR. Use of embolic protection was associated with lower total lesion volume and smaller number of new ischemic lesions. Embolic protection was associated with a trend toward lower risk for deterioration in National Institutes of Health Stroke Scale score at discharge and higher Montreal Cognitive Assessment score. Risk for overt stroke and all-cause mortality were not significantly lower in the embolic protection group. The authors noted that the findings are subject to the inherent limitations of the included trials due to study design, length of follow-up, imaging and neurocognitive assessment dropout. Some of the endpoints were not available in all of the included trials. Most of the valves used were first-generation TAVR devices. Given the substantial limitations of the included studies, the results are only hypothesis generating. Further prospective, adequately powered randomized controlled trials are needed to establish the role of embolic protection during TAVR.

Clinical Practice Guidelines

American College of Cardiology (ACC)/American Heart Association (AHA)

ACC/AHA guidelines for the management of patients with valvular heart disease (Otto et al., 2020) make the following recommendations regarding transcatheter valve therapies:

Aortic

In patients with an indication for aortic valve replacement, the choice of prosthetic valve should be based on a shared decision-making process that accounts for the patient's values and preferences and includes discussion of the indications for and risks of anticoagulant therapy and the potential need for and risks associated with valve reintervention.

Bicuspid Aortic Valve

2020 ACC/AHA guideline (updated 2021) for intervention recommends patients with BAV and severe AR who meet criteria for AVR, aortic valve repair may be considered in selected patients if the surgery is performed at a Comprehensive Valve Center. In patients with BAV and symptomatic, severe AS, TAVI may be considered as an alternative to SAVR after consideration of patient-specific procedural risks, values, trade-offs, and preferences, and when the surgery is performed at a Comprehensive Valve Center. RCTs are needed to obtain full clarity on the optimal use of TAVI in this population, as well as long-term outcomes.

Mitral

In severely symptomatic patients (NYHA class III or IV) with primary severe MR and high or prohibitive surgical risk, transcatheter edge-to-edge repair is reasonable if mitral valve anatomy is favorable for the repair procedure and patient life expectancy is at least 1 year.

In patients with chronic severe secondary MR related to left ventricular systolic dysfunction (LVEF < 50%) who have persistent symptoms (NYHA class II, III, or IV) while on optimal guideline-directed management and therapy for heart failure, transcatheter edge-to-edge repair is reasonable in patients with appropriate anatomy as defined on transesophageal echocardiography and with LVEF between 20% and 50%, left ventricular end-systolic dimension ≤ 70 mm, and pulmonary artery systolic pressure ≤ 70 mmHg.

Pulmonary

Transcatheter pulmonary valve replacement is outside the scope of these guidelines. See Stout et al., 2019.

Tricuspid

The guideline does not address the transcatheter approach for tricuspid valve replacement.

ViV

For severely symptomatic patients with bioprosthetic aortic valve stenosis and high or prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a Comprehensive Valve Center.

For patients with severe heart failure symptoms caused by bioprosthetic valve regurgitation who are at high to prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a Comprehensive Valve Center.

The ACC and STS, along with the Society for Cardiovascular Angiography and Interventions (SCAI) and the American Association for Thoracic Surgery (AATS), released an expert consensus statement outlining operator and institutional recommendations and requirements for creating and maintaining transcatheter aortic valve replacement programs. The recommendations are aimed at ensuring optimal patient care (Bavaria et al., 2018). The same organizations released similar statements addressing transcatheter therapies for mitral valve procedures (Bonow et al., 2020) and pulmonary valve procedures (Hijazi et al., 2015).

ACC guidelines on the management of adults with congenital heart disease address interventions for patients with RVOT dysfunction. Interventions include surgical replacement or percutaneous stenting and/or transcatheter valve placement. Patients with moderate or greater conduit stenosis and/or regurgitation who have reduced exercise capacity or arrhythmias can benefit from surgical or transcatheter conduit intervention to relieve stenosis and/or regurgitation. Transcatheter stenting and pulmonary valve replacement may be performed with high procedural success and low mortality rates, and result in improved hemodynamics and improved exercise capacity. Surgical conduit replacement carries a higher risk of periprocedural complications with good long-term outcomes. Predictors of conduit dysfunction and reoperation include placement of small diameter conduits; therefore, insertion of conduits with the largest possible diameter should be attempted, anticipating that subsequent valve replacement may be via a transcatheter approach (Stout et al., 2019).

ACC appropriate use criteria for the treatment of severe aortic stenosis include criteria for patients with LFLG-AS (Bonow et al., 2017).

European Society of Cardiology (ESC)

ESC guidelines for the management of adult congenital heart disease state that transcatheter pulmonary valve implantation techniques are an alternative to open heart surgery in patients with RVOT conduit stenosis/regurgitation. Transcatheter replacement, when technically feasible, provides outcomes comparable to surgical pulmonary valve replacement and is intended to extend the lifetime of a conduit, reducing the number of reoperations during a patient's lifetime (Baumgartner et al., 2020).

European Society of Cardiology (ESC)/European Association for Cardio-Thoracic Surgery (EACTS)

In their joint guideline for the management of valvular heart disease, the ESC and the EACTS (Vahanian, 2022) recommend the following with regard to transcatheter heart valve procedures:

Aortic

The guideline recommends that the choice between surgical and transcatheter intervention for aortic stenosis be based upon careful evaluation of clinical, anatomical and procedural factors by the cardiac treatment team, weighing the risks and benefits of each approach for the individual patient.

They recommend SAVR in younger patients who are low risk for surgery (< 75 years and STSPROM/ EuroSCORE II < 4%) or in patients who are operable and unsuitable for transfemoral TAVI; however, they recommend TAVI for older patients (>_75 years), or for those who are high-risk (STS-PROM/EuroSCORE II > 8%) or unsuitable for surgery. SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical and procedural characteristics.

Tricuspid

The guideline indicates that transcatheter treatment of symptomatic secondary severe tricuspid regurgitation has a IIb recommendation which indicates the procedure may be considered in inoperable patients at a heart valve center with expertise in the treatment of tricuspid valve disease. This level of recommendation indicates that the usefulness or efficacy of this approach is less well established by evidence/opinion.

National Institute for Health and Care Excellence (NICE)

NICE published an interventional procedures guidance (IPG) for transcatheter tricuspid valve annuloplasty for tricuspid regurgitation in which they state that the evidence on efficacy of transcatheter tricuspid valve annuloplasty is limited in quantity and quality and that the evidence on safety shows there are serious but well-recognized complications when this procedure is done on people with severe and symptomatic tricuspid regurgitation. For people with mild or moderate tricuspid regurgitation, the evidence is inadequate in quantity and quality on the safety and efficacy of this procedure (NICE, 2022a)

In another IPG published by NICE that addresses transcatheter tricuspid valve leaflet repair for tricuspid regurgitation, NICE states that the evidence on efficacy of transcatheter valve leaflet repair is limited in quantity and quality for people with severe and symptomatic tricuspid regurgitation. The IPG also states that the evidence on its safety shows there are serious but well-recognized complications. For people with mild or moderate tricuspid regurgitation, the IPG states that the evidence is inadequate in quantity and quality for the safety and efficacy of transcatheter tricuspid valve leaflet repair (NICE, 2022b).

NICE published an overarching guideline for heart valve disease presenting in adults. In the evidence review supporting documentation for the guideline, NICE states that transcatheter valve interventions may allow for quicker recovery if the procedure is uncomplicated and notes that the abnormal valve is not removed using the transcatheter approach, rather, the abnormal valve is pushed aside to allow for the prosthetic valve to be implanted.

For aortic valve disease, this guideline states that TAVI is clinically effective but not currently cost effective for patients defined as intermediate or low risk for cardiac surgery for aortic valve disease. For aortic stenosis, the guideline states that transcatheter interventions are currently only indicated for symptomatic patients; however, for aortic regurgitation, there is no current accepted transcatheter intervention. The guideline also stated that there is no evidence for TAVI valve durability beyond 6-7 years and that there is evidence of valve leaflet deterioration due to crimping which cannot be avoided when a valve is implanted through a catheter.

With regard to mitral stenosis, this guideline on heart valve disease in adults recommends transcatheter valvotomy for adults with rheumatic severe mitral stenosis if the valve is suitable for the procedure or surgical mitral valve replacement when the transcatheter valvotomy is not suitable. Transcatheter edge-to-edge repair is recommended, if suitable, for adults with severe primary mitral regurgitation and symptoms when surgery is unsuitable and for adults with heart failure and severe secondary mitral regurgitation if surgery is unsuitable and the patient remains symptomatic on medical management.

The guideline does not include any guidance for transcatheter tricuspid valve repair for tricuspid regurgitation (NICE, 2021a).

A NICE guidance document states that the current evidence on the safety of transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bio-prosthesis shows some serious but well-recognized complications. Evidence on its efficacy is limited in quality. This procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE, 2021b).

A NICE IPG on the transapical transcatheter mitral valve-in-ring implantation procedure states that the evidence on the safety of this procedure after failed mitral valve repair surgery is adequate and shows some serious but well recognized complications. It also states that the evidence on this procedure's efficacy is limited in quality and that the procedure should only be used with special arrangements for clinical governance, consent, and audit or research (NICE, 2021c).

A NICE guidance document states that the evidence on the safety and efficacy of ViV TAVR for aortic bioprosthetic dysfunction is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit. The report also notes that long-term evidence for ViV TAVR is from earlier-generation devices. The technology is evolving, and longer-term evidence is needed (NICE, 2019a).

A NICE guidance document states that transcatheter insertion of a cerebral protection device to prevent cerebral embolism during TAVR raises no major safety concerns other than those associated with the TAVR procedure. However, the evidence on efficacy for preventing TAVR-related stroke is inconclusive. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE, 2019b).

A NICE guidance document states that evidence on the safety and efficacy of percutaneous mitral valve leaflet repair for mitral regurgitation is adequate to support the use of this procedure, in patients for whom open surgery is contraindicated following risk assessment, provided that standard arrangements are in place for clinical governance, consent and audit (NICE, 2019c).

A NICE guidance document states that the evidence on the safety and efficacy of TAVR for aortic stenosis is adequate to support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit. Patient details should be entered into the national registry and adverse events should be reported. Patient selection should be carried out by an experienced multidisciplinary team, which must include interventional cardiologists experienced in the procedure, cardiac surgeons, an expert in cardiac imaging and, when appropriate, a cardiac anesthetist and a specialist in elderly medicine. The multidisciplinary team should determine the risk level for each patient and the TAVR device most suitable for them (NICE, 2017).

A NICE guidance document states that the evidence on percutaneous pulmonary valve implantation (PPVI) for RVOT dysfunction shows good short-term efficacy. There is little evidence on long-term efficacy, but it is well documented that these valves may need to be replaced in the longer term. With regard to safety there are well-recognized complications, particularly stent fractures in the longer term, which may or may not have clinical effects. Patients having this procedure are often very unwell and might otherwise need open heart surgery (typically reoperative) with its associated risks (NICE, 2013).

U.S. Food and Drug Administration (FDA)

This section is to be used for informational purposes only. FDA approval alone is not a basis for coverage.

Aortic

SAPIEN

The Edwards SAPIEN Transcatheter Heart Valve received FDA premarket approval (P100041) on November 2, 2011. The device is indicated for transfemoral delivery in patients with severe, symptomatic native aortic valve stenosis who have been determined by a cardiac surgeon to be inoperable for open aortic valve replacement and in whom existing comorbidities would not preclude the expected benefit from correction of the aortic stenosis. The device is contraindicated in patients who cannot tolerate an anticoagulation/antiplatelet regimen or who have active bacterial endocarditis or other active infections. Labeling also states that implantation of the transcatheter heart valve should be performed only by physicians who have received Edwards Lifesciences training. The implanting physician should be experienced in balloon aortic valvuloplasty. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100041. (Accessed September 21, 2022)

On October 19, 2012, the FDA approved an expanded indication for the Edwards SAPIEN valve to include patients with aortic stenosis who are eligible for surgery but who are at high risk for serious surgical complications or death (P110021). In this patient group, the valve is approved for both transfemoral and transapical delivery. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P110021. (Accessed September 21, 2022)

On September 23, 2013, the FDA approved revised labeling for the SAPIEN valve. The new labeling removes references to specific access points now making the device available for inoperable patients who need an alternate access point. The device is now indicated for patients with severe symptomatic calcified native aortic valve stenosis without severe aortic insufficiency and with ejection fraction > 20% who have been examined by a heart team including an experienced cardiac surgeon and a cardiologist and found to be: 1) inoperable and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis; or 2) be operative candidates for aortic valve replacement but who have a predicted operative risk score ≥ 8% or are judged by the heart team to be at a ≥ 15% risk of mortality for SAVR.

SAPIEN XT, SAPIEN 3, and SAPIEN 3 Ultra

The Edwards SAPIEN XT Transcatheter Heart Valve and accessories received FDA premarket approval (P130009) on June 16, 2014. The device is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient of ≥ 40 mmHg or a peak aortic-jet velocity of ≥ 4.0 m/s), and with native anatomy appropriate for the 23, 26 or 29 mm valve system, who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., STS operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days). Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130009. (Accessed September 21, 2022)

The Edwards SAPIEN 3 Transcatheter Heart Valve and accessories received FDA premarket approval (P140031) on June 17, 2015. The device is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., STS operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days). Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P140031. (Accessed September 21, 2022)

On August 18, 2016, the FDA granted expanded approval of the SAPIEN XT and SAPIEN 3 valves to include patients with intermediate surgical risk for aortic valve replacement.

CoreValve

The Medtronic CoreValve System received FDA premarket approval (P130021) on January 17, 2014. The device is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤ 0.8 cm^2, a mean aortic valve gradient of > 40 mmHg, or a peak aortic-jet velocity of > 4.0 m/s) and with native aortic annulus diameters between 18 and 29 mm who are judged by a heart team, including a cardiac surgeon, to be at extreme risk or inoperable for open surgical therapy (predicted risk of operative mortality and/or serious irreversible morbidity ≥ 50% at 30 days). The device is contraindicated for patients presenting with any of the following conditions:

- Known hypersensitivity or contraindication to aspirin, heparin (HIT/HITTS) and bivalirudin, ticlopidine, clopidogrel, Nitinol (titanium or nickel), or sensitivity to contrast media, which cannot be adequately premedicated
- Ongoing sepsis, including active endocarditis
- Preexisting mechanical heart valve in aortic position

Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130021. (Accessed September 21, 2022)

On June 12, 2014, the FDA approved an expanded indication for the Medtronic CoreValve System to include patients at high or greater risk for open surgical therapy (i.e., STS operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

On June 22, 2015, the FDA approved Medtronic's next-generation CoreValve Evolut™ R System which allows for the device to be recaptured and repositioned.

On March 20, 2017, the FDA approved Medtronic's CoreValve Evolut PRO valve for the treatment of severe aortic stenosis in symptomatic patients who are at high or extreme risk for open heart surgery. The valve design includes an outer wrap that adds surface area contact between the valve and the native aortic annulus to improve valve sealing performance.

On July 10, 2017, the FDA approved an expanded indication for the Medtronic CoreValve, Evolut R and Evolut PRO valves to include patients with intermediate surgical risk for aortic valve replacement.

LOTUS Edge

On November 17, 2020, Boston Scientific announced discontinuation of the LOTUS product due to complexities associated with the product delivery system. The Boston Scientific LOTUS Edge Valve System received FDA premarket approval (P180029) on April 23, 2019. The device is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤ 1.0 cm^2 or index of ≤ 0.6 cm^2/m^2) who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the STS risk score and other clinical comorbidities unmeasured by the STS risk calculator). Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P180029. (Accessed September 21, 2022)

Portico Transcatheter Aortic Valve Implantation System

The Portico Transcatheter Aortic Valve Implantation System received FDA premarket approval on September 17, 2021. The device is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the STS risk score and other clinical comorbidities unmeasured by the STS risk calculator). Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P190023. (Accessed September 21, 2022)

On August 16, 2019, the FDA granted expanded approval for 4 TAVR devices: CoreValve Evolut R and Evolut PRO (Medtronic), SAPIEN 3 and SAPIEN 3 Ultra (Edwards Lifesciences) for the treatment of patients with severe aortic stenosis who are at low risk for surgical aortic valve replacement. The devices are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy. Additional information available at:

- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130021S058
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P140031S085

(Accessed September 21, 2022)

FDA approval status for other brands of aortic valve prostheses, percutaneous delivered can be found on the FDA's Premarket Approval website using Product Code NPT: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm. (Accessed September 21, 2022)

Mitral

The MitraClip Mitral Valve Repair System received FDA premarket approval (P100009) on October 24, 2013. The device is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3 +) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100009. (Accessed September 21, 2022)

A 3rd generation MitraClip device was approved on July 12, 2018.

On March 14, 2019, the FDA approved an expanded indication for the MitraClip NT and MitraClip NTR/XTR Clip Delivery Systems to include secondary MR. The devices, when used with maximally tolerated GDMT, are indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (functional) mitral regurgitation (MR ≥ Grade III per American Society of Echocardiography criteria) in patients with a LVEF ≥ 20% and ≤ 50%, and a left ventricular end systolic dimension (LVESD) ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease. Additional information available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P100009S028. (Accessed September 21, 2022)

FDA approval status for other brands of mitral valve prostheses, percutaneous delivered can be found on the FDA's Premarket Approval website using Product Code NPU while other mitral valve repair devices can be found using Product Code NKM: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm. (Accessed September 21, 2022)

Pulmonary

Harmony

The Harmony™ TPV System received FDA premarket approval (P200046) on March 26, 2021. The Harmony valve is indicated for use in the management of pediatric and adult patients with severe pulmonary regurgitation (i.e., severe pulmonary regurgitation as determined by echocardiography and/or pulmonary regurgitant fraction ≥ 30% as determined by cardiac MRI) who have a native or surgically repaired right ventricular outflow tract (RVOT) and are clinically indicated for surgical pulmonary

valve replacement. Additional information is available at:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P200046. (Accessed September 21, 2022)

Melody

The Melody Transcatheter Pulmonary Valve (TPV) and the Ensemble Transcatheter Valve Delivery System received FDA premarket approval (P140017) on January 27, 2015. The Melody TPV is indicated for use as an adjunct to surgery in the management of pediatric and adult patients with the following clinical conditions:

- Existence of a full (circumferential) dysfunctional RVOT conduit that was equal to or greater than 16 mm in diameter when originally implanted; and
- Dysfunctional RVOT conduit with a clinical indication for intervention, and:
  - Regurgitation: ≥ moderate regurgitation; and/or
  - Stenosis: mean RVOT gradient ≥ 35 mmHg

Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P140017. (Accessed September 21, 2022)

The Melody TPV and the Ensemble Transcatheter Valve Delivery System were originally approved under Humanitarian Device Exemption (HDE) (H080002) on January 25, 2010. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H080002. (Accessed September 21, 2022)

SAPIEN XT

On February 29, 2016, the FDA granted expanded approval of the Edwards SAPIEN XT Transcatheter Heart Valve to include use in PPVI procedures (P130009). Additional information is available at:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130009. (Accessed September 21, 2022)

SAPIEN 3

On August 31, 2020, the FDA granted approval of the Edwards SAPIEN 3 Heart Valve System with Edwards Commander Delivery System for use in PPVI procedures (P200015). Additional information is available at:
https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P200015. (Accessed September 21, 2022)

FDA approval status for other brands of pulmonary valve prostheses, percutaneous delivered can be found on the FDA's Premarket Approval website using Product Code NPV: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm. (Accessed September 21, 2022)

Valve-In-Valve

On March 30, 2015, the FDA approved a second indication for the Medtronic CoreValve System. The device is approved for valve-in-valve replacement and is indicated for use in selected high-surgical risk patients with a degenerated bioprosthetic aortic valve who require another valve replacement procedure.

On October 9, 2015, the FDA granted expanded approval of the SAPIEN XT Transcatheter Heart Valve to include aortic valve-in-valve procedures in high- or extreme-risk candidates to replace a failing bioprosthetic valve.

On June 5, 2017, the FDA granted expanded approval of the SAPIEN 3 valve for aortic and mitral valve-in-valve procedures in high- or extreme-risk candidates to replace a failing bioprosthetic valve.

On February 24, 2017, the FDA granted expanded approval of the Melody Transcatheter Pulmonary Valve (TPV) for pulmonary valve-in-valve procedures to replace a failing bioprosthetic valve.

Cerebral Protection

Sentinel Cerebral Protection System (Claret Medical)

The FDA granted a de novo classification for the Sentinel device on June 1, 2017. Sentinel is indicated to capture and remove thrombus and debris during TAVR procedures in a manner that may prevent embolic material from traveling toward the cerebral circulation. Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/denovo.cfm?ID=DEN160043. (Accessed September 21, 2022)

Additional Products

The following products may not have full FDA approval:

- CardiAQ (Edwards Lifesciences)
- Cardioband™
- Carillon® Mitral Contour System™
- Fortis (Edwards Lifesciences)
- Harpoon
- NeoChord
- Tendyne (Abbott)
- Tiara™ (Neovasc, Inc.)
- TriGUARD 3™ (Keystone Heart) cerebral embolic protection device

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Policy History/Revision Information

Date	Summary of Changes
10/01/2023	**Application** ***Individual Exchange Plans*** • Removed language indicating this Medical Policy does not apply to Individual Exchange benefit plans in the states of Massachusetts, Nevada, and New York **Supporting Information** • Archived previous policy version 2023T0557Y

Instructions for Use

This Medical Policy provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

This Medical Policy may also be applied to Medicare Advantage plans in certain instances. In the absence of a Medicare National Coverage Determination (NCD), Local Coverage Determination (LCD), or other Medicare coverage guidance, CMS allows a Medicare Advantage Organization (MAO) to create its own coverage determinations, using objective evidence-based rationale relying on authoritative evidence (Medicare IOM Pub. No. 100-16, Ch. 4, §90.5).

UnitedHealthcare may also use tools developed by third parties, such as the InterQual® criteria, to assist us in administering health benefits. UnitedHealthcare Medical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.