TRANSCATHETER HEART VALVE PROCEDURES

Guideline Number: MMG129.L **Effective Date**: February 1, 2019

Instructions for Use

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Related Policies

None

COVERAGE RATIONALE

See Benefit Considerations

Transcatheter aortic heart valve replacement is proven and medically necessary for treating intermediate or higher risk* members, when used according to U.S. Food and Drug Administration (FDA) labeled indications, contraindications, warnings and precautions, and ALL of the following criteria are met:

- 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
- Member is symptomatic (New York Heart Association [NYHA] class II or greater) and symptoms are due to aortic valve stenosis
- Member requires valve replacement surgery but is at intermediate or higher risk* for serious surgical complications or death from open valve replacement surgery as determined by an interventional cardiologist and an experienced cardiothoracic surgeon.

*Society of Thoracic Surgeons (STS) risk categories are as follows (Nishimura et al., 2014):

- Intermediate - predicted risk of mortality (PROM) score of 4-8%
- High - PROM score of >8%

Transcatheter pulmonary heart valve replacement is proven and medically necessary, when used according to FDA labeled indications, contraindications, warnings and precautions, in members 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 or replacement
- Tricuspid valve repair or replacement
- Valve-in-Valve (ViV) replacement within a failed bioprosthesis.

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DEFINITIONS

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 STS PROM score is a predictor of 30-day mortality after cardiac procedures (Nishimura et al., 2014).

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 guideline 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)
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)
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)

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CPT Code	Description
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 (ECRI, 2012a; updated 2014). The various stages of valvular aortic stenosis are addressed by Nishimura et al. (2014).

The gold standard for treating severe, symptomatic aortic stenosis is surgical replacement with a prosthetic valve. However, some members are not candidates for open-heart surgery because they are too old, too frail or they suffer from another condition that would make the surgery too risky. 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.

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 bioprosthesis 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 member 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 achieved via the femoral vein. The replacement valve is usually positioned within a preexisting pulmonary conduit (graft) (NICE, 2013; Medtronic Melody website).

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 (Hayes, 2018). 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 (NICE, 2009).

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Transcatheter leaflet repair and percutaneous annuloplasty are two 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.

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. Devices for transcatheter tricuspid valve repair and replacement are in the early stages of 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

A Hayes report concluded that there is sufficient evidence to support the use of TAVR in patients with severe aortic stenosis who are deemed by a heart team to be at high or greater surgical risk. The overall quality of the evidence is moderate. Most studies showed no difference in mortality rates between TAVR and surgical aortic valve replacement (SAVR) in patients with aortic stenosis. Bleeding complications or events occurred less in TAVR-treated patients. Stroke and myocardial infarction rates between TAVR and SAVR did not differ; however, pacemaker implantation rates were higher in TAVR-treated patients. Renal impairment or injury rates were inconsistent. Definitive patient selection criteria for TAVR in patients with severe aortic stenosis have not been established (Hayes, 2015; updated 2017).

Nagaraja et al. (2014) conducted a systematic review and meta-analysis of 39 studies comparing TAVR and SAVR in patients with aortic stenosis. Among three randomized controlled trials, differences between the two cohorts were not statistically significant for the frequency of stroke, incidence of myocardial infarction, 30-day mortality rate, 1-year mortality rate and acute kidney injury. The remaining non-randomized controlled trials demonstrated that the TAVR group had an amplified frequency of aortic regurgitation at discharge. While differences between the two cohorts were not statistically significant for the incidence of myocardial infarction, stroke, acute renal failure requiring hemodialysis, 30-day mortality and the need for a pacemaker, fewer TAVR patients needed transfusions or experienced new-onset atrial fibrillation.

Biondi-Zoccai et al. (2014) performed a meta-analysis of four randomized controlled trials (n=1805) comparing survival rates and complications between TAVR and SAVR. Separate TAVR procedures were considered, including CoreValve, transfemoral SAPIEN and transapical SAPIEN. After a median of 8 months, risk of death and myocardial infarction was not different when comparing surgery versus transcatheter procedures, irrespective of device or access. Conversely, surgery was associated with higher rates of major bleeding and acute kidney injury, but lower rates of pacemaker implantation and moderate or severe aortic regurgitation. Strokes were less frequent with CoreValve than with transfemoral SAPIEN or transapical SAPIEN, whereas pacemaker implantation was more common with CoreValve. The authors concluded that survival after transcatheter or SAVR is similar, but there might be differences in the individual safety and effectiveness profile between the treatment strategies and the individual devices used in TAVR.

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PARTNER (Placement of AoRTic traNscatheterER 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. Clinicaltrials.gov number NCT00530894.

Cohort A

In a multicenter, 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 reported similar 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, 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. 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. The corresponding rates of cardiac death were 31.0% and 62.4%. 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 re-hospitalization 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.

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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. 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. ClinicalTrials.gov number NCT01314313.

Cohort A

Leon et al. (2016) evaluated TAVR and SAVR in a multicenter, randomized controlled trial involving intermediate-risk patients. A total of 2032 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.

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.

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 bioprosthesis with SAVR in patients at intermediate risk for surgery. ClinicalTrials.gov number NCT01586910.

In a 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 1746 patients underwent randomization at 87 centers. Of these patients, 1660 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

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occur in either group. The authors concluded that TAVR was a noninferior alternative to surgery in patients at intermediate surgical risk.

In a multicenter, randomized, noninferiority trial, Adams et al. (2014) reported that TAVR, using a self-expanding bioprosthesis (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. ClinicalTrials.gov number #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%).

Two nonrandomized studies compared specific TAVR devices (Attias et al., 2010; Wenaweser et al., 2011). Although there were no significant differences in mortality between the different treatment groups, further studies are needed to draw conclusions regarding the superiority of one device over another.

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 transarterial 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.

A National Institute for Health and Care Excellence (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).

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The Valve Academic Research Consortium (VARC), an independent collaboration between academic research organizations and specialty societies (cardiology and cardiac surgery) in the United States and Europe, is focused on creating consistent endpoint definitions and consensus recommendations for TAVR. In an effort to improve the quality of clinical research and to enable meaningful comparisons between clinical trials, consensus criteria were developed for the following endpoints: mortality, myocardial infarction, stroke, bleeding, acute kidney injury, vascular complications and prosthetic valve performance. Composite endpoints for safety and effectiveness were also recommended. The consensus document is not intended as a 'guidelines' or 'guidance' document and although thoroughly reviewed by individuals from seven cardiology and cardiac surgery societies, the content has not been subjected to a formal society guidelines review process (Leon et al. 2011). In a subsequent consensus document, Kappetein et al. (2012) provided additional detail on definitions to further standardize endpoint definitions.

Pulmonary Valve

An ECRI emerging technology evidence report states that studies using the Melody system indicate that percutaneous pulmonary valve implantation (PPVI) improves symptoms as indexed by the NYHA classification system in the short-term (<6 months), but longer-term results are not available. Studies using the Melody system also indicate that PPVI improves cardiac function on several measures (i.e., decreases RVOT pressure gradient, decreases regurgitation fraction through the pulmonary valve, and decreases right ventricular end-diastolic volume; data on maximal oxygen consumption are not consistent). No data were available to assess how PPVI affects quality of life. Ongoing clinical trials should help clarify questions not addressed by the available literature, including quality of life and long-term clinical outcomes (ECRI, 2012b).

A Hayes report concluded that the evidence evaluating PPVI was of low quality and consisted entirely of observational studies. Sample sizes were small, long-term follow-up was available for very few patients and there was considerable overlap in patient populations. No randomized or quasi-randomized controlled trials were identified in the literature. Study results showed consistent improvement in hemodynamics for patients with pulmonary valve insufficiency, stenosis or both, and for pulmonary regurgitation patients with pulmonary insufficiency following PPVI. Heart function was improved to a lesser extent while overall pulmonary function did not improve. Mid- to long-term follow-up was available in very few patients; however, the preliminary evidence suggests that in most patients, the benefits are maintained for a number of years. Valve failure rates range from 25% to 32% at 5 years. Additional evidence is needed to determine the impact of PPVI on disease-related survival and mortality. Complications were few, but some were potentially life threatening. There is a learning curve associated with PPVI, and experience with this technique improves outcomes and reduces the risk for complications. Although there is very limited evidence at this time, PPVI fills a gap in the management of patients with RVOT dysfunction following surgical repair for congenital heart defects. Although PPVI can cause severe complications, it is a treatment option used for patients who cannot undergo open heart surgery or to prolong the need for surgical valve replacement with its associated risks (Hayes, 2016; updated 2017).

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. 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.

Armstrong et al. (2014) conducted a one-year follow-up of the Melody transcatheter pulmonary valve (TPV) multicenter post-approval study to determine if real-world experience was equivalent to the historical results established in the initial Investigational Device Exemption trial. Patients with dysfunctional RVOT conduits were entered in this prospective, nonrandomized study at 10 centers. The primary endpoint was acceptable hemodynamic function at 6 months post-implantation, defined as a composite of RVOT echocardiographic mean gradient ≤30 mm Hg, pulmonary regurgitation less than moderate as measured by echocardiography, and freedom from conduit reintervention and reoperation. Cardiac catheterization was performed in 120 patients for potential implantation of the Melody TPV; of these, 100 patients were implanted, with a 98.0% procedural success rate. There were no procedure-related deaths. Acceptable hemodynamic function at 6 months was achieved in 96.7% of patients with evaluable data (87.9% of the entire implanted cohort), with results maintained through one year. No patient had moderate or severe pulmonary regurgitation after implantation. No patient required catheter reintervention in the first year after implantation, and 2 patients required reoperation for conduit replacement. The rate of freedom from TPV dysfunction was 96.9% at one year.

Butera et al. (2013) conducted a prospective, multicenter web-based registry study of percutaneous pulmonary valve implantation (PPVI). Between October 2007 and October 2010, 63 patients were included in the registry (median age: 24 years; range 11-65 years). Results suggest that PPVI has good procedural and mid-term success and might delay surgical intervention in more than 80% of patients. However, serious complications can occur and valve failure

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occurred in almost 20% of patients during follow-up. The authors concluded that longer follow-up and larger series are needed.

Eiken et al. (2011) reported on a two-center experience with percutaneous pulmonary valve implantation (PPVI) in 102 patients with RVOT dysfunction. Median weight was 63 kg (54.2-75.9 kg). Median age was 21.5 years (16.2-30.1 years). The median peak systolic RVOT gradient decreased from 37 mmHg (29-46 mmHg) to 14 mmHg (9-17 mmHg), and the ratio right ventricular (RV) pressure/aortic pressure (AoP) decreased from 62% (53-76%) to 36% (30-42%). The median end-diastolic RV-volume index decreased from 106 mL/m (2) (93-133 mL/m (2)) to 90 mL/m (2) (71-108 mL/m (2)). Pulmonary regurgitation was significantly reduced in all patients. One patient died due to compression of the left coronary artery. The incidence of stent fractures was 5 of 102 (5%). During follow-up [median: 352 days (99-390 days)] one percutaneous valve had to be removed surgically 6 months after implantation due to bacterial endocarditis. In 8 of 102 patients, a repeated dilatation of the valve was done due to a significant residual systolic pressure gradient, which resulted in a valve-in-valve procedure in four patients. The authors concluded that percutaneous pulmonary valve implantation can be performed by experienced interventionalists with similar results to previously published studies. The procedure is technically challenging and longer clinical follow-up is needed.

McElhinney et al. (2010) conducted a 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. Clinicaltrials.gov number NCT00740870.

Cheatham et al. (2015) reported clinical and hemodynamic outcomes up to 7 years after PPVI with the Melody valve. During a median follow-up of 4.5 years, 32 patients underwent RVOT reintervention for obstruction (n=27, with stent fracture in 22), endocarditis (n=3, 2 with stenosis and 1 with pulmonary regurgitation) or right ventricular dysfunction (n=2). Eleven patients had the valve explanted as an initial or second reintervention. Five-year freedom from reintervention and explantation was 76±4% and 92±3%, respectively. A conduit pre-stent and lower discharge RVOT gradient were associated with longer freedom from reintervention. In the 113 patients who were alive and reintervention free, the follow-up gradient was unchanged from early post-valve replacement, and all but 1 patient had mild or less pulmonary regurgitation. More severely impaired baseline spirometry was associated with a lower likelihood of improvement in exercise function after valve replacement. Clinicaltrials.gov number NCT00740870.

Zahn et al. (2009) evaluated the safety, procedural success and short-term effectiveness of the Melody transcatheter pulmonary valve in patients with dysfunctional RVOT conduits. Thirty four patients underwent catheterization for intended Melody valve implantation at 3 centers. Mean age was 19.4 +/- 7.7 years. Initial conduit Doppler mean gradient was 28.8 +/- 10.1 mmHg, and 94% of patients had moderate or severe pulmonary regurgitation (PR). Implantation was successful in 29 of 30 attempts and not attempted in 4 patients. Procedural complications included conduit rupture requiring urgent surgery and device removal (n = 1), wide-complex tachycardia (n = 1) and distal pulmonary artery guidewire perforation (n = 1). Peak systolic conduit gradient fell acutely from 37.2 +/- 16.3 mmHg to 17.3 +/- 7.3 mmHg, and no patient had more than mild PR. There were no deaths or further device explants. At 6-month follow-up, conduit Doppler mean gradient was 22.4 +/- 8.1 mmHg, and PR fraction by magnetic resonance imaging was significantly improved (3.3 +/- 3.6% vs. 27.6 +/- 13.3%). Stent fracture occurred in 8 of 29 implants; 3 of these were treated with a second Melody valve for recurrent stenosis later in follow-up. The authors concluded that implantation of the Melody valve for right ventricular outflow tract conduit dysfunction has encouraging acute and short-term outcomes when performed by experienced operators.

In a retrospective case series, Lurz et al. (2008) evaluated percutaneous pulmonary valve implantation in 155 patients with stenosis and/or regurgitation. The procedure led to significant reduction in right ventricular systolic pressure and RVOT gradient. Follow-up ranged from 0 to 83.7 months (median 28.4 months). Freedom from reoperation was 93% (+/-2%), 86% (+/-3%), 84% (+/-4%) and 70% (+/-13%) at 10, 30, 50 and 70 months, respectively. Freedom from transcatheter reintervention was 95% (+/-2%), 87% (+/-3%), 73% (+/-6%) and 73% (+/-6%) at 10, 30, 50 and 70 months, respectively. Survival at 83 months was 96.9%. The first series of 50 patients and patients with a residual gradient >25 mmHg were associated with a higher risk of reoperation.

In a retrospective case series, Khambadkone et al. (2005) evaluated percutaneous pulmonary valve implantation (PPVI) in 59 patients with pulmonary regurgitation with or without stenosis after repair of congenital heart disease.

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PPVI was performed successfully in 58 patients (32 male; median age of 16 years and median weight of 56 kg). The right ventricular (RV) pressure, RVOT gradient and pulmonary regurgitation (PR) decreased significantly after percutaneous pulmonary valve implantation. In 28 patients, magnetic resonance imaging showed significant reduction in PR fraction and in RV end-diastolic volume (EDV) and a significant increase in left ventricular EDV and effective RV stroke volume.

A National Institute for Health and Care Excellence (NICE) guidance document states that the evidence on percutaneous pulmonary valve implantation 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).

Mitral Valve

Transcatheter Mitral Valve Replacement

Transcatheter mitral valve replacement (TMVR) is in the early stages of development. Evidence at this time is limited to registry data and case-series with very small numbers. Further studies with a larger number of patients and longer follow-up are needed to determine device durability and the ideal candidates for the procedure.

Regueiro et al. (2017) evaluated outcomes in 13 patients with severe native mitral regurgitation (MR) who underwent transcatheter mitral valve replacement (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 left ventricular ejection fraction 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 mm Hg, 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 mm Hg 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 mm Hg, 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 policy is limited by retrospective design, 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.

Several clinical trials are in progress.

Percutaneous Leaflet Repair

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. Several large randomized controlled trials evaluating the MitraClip system are ongoing and are expected to provide valuable findings that will help establish the clinical roles of these technologies (Hayes, 2018).

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Bail (2015) performed a meta-analysis of the safety and efficacy of the MitraClip device. Twenty-six 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. Prospective randomized controlled trials are warranted to determine potential adverse events , device durability and long-term follow-up.

Munkholm-Larsen et al. (2014) performed a systematic review to assess the safety and efficacy of the MitraClip system for high surgical risk candidates with severe organic and/or functional MR. Twelve prospective observational studies were included. Immediate procedural success ranged from 72-100%. Thirty day mortality ranged from 0-7.8%. The authors noted a significant improvement in hemodynamic profile and functional status after implantation. One year survival ranged from 75-90%. The authors concluded that further prospective trials with mid- to long-term follow-up are required.

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%.

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

EVEREST II is a two-part multicenter, randomized controlled trial 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. Clinicaltrials.gov number 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

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

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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 study has several limitations, most notably a lack of randomization and a questionable comparator group that was recruited retrospectively.

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. Clinicaltrials.gov number NCT00209339.

Feldman et al. (2009) conducted a 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.

Maisano et al. (2013) and Reichenspurner et al. (2013) reported early outcomes from the ACCESS-EU trial. The prospective, multicenter, nonrandomized 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.

A National Institute for Health and Care Excellence (NICE) guidance document states that the evidence on the safety and efficacy of percutaneous mitral valve leaflet repair for MR is currently inadequate in quality and quantity. Therefore, this procedure should only be used with special arrangements for patients who are well enough for surgical mitral valve repair or in the context of research for patients who are not well enough for surgical mitral valve repair (NICE, 2009).

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

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

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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 remodelling. 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.

A National Institute for Health and Care Excellence (NICE) guidance document states that the current evidence on the safety and efficacy of percutaneous mitral valve annuloplasty is inadequate in quality and quantity. Therefore this procedure should only be used in the context of research, which should clearly describe patient selection, concomitant medical therapies and safety outcomes. Both objective measurements and clinical outcomes should be reported (NICE, 2010).

Tricuspid Valve

Devices for transcatheter tricuspid valve repair and replacement are in the early stages of development, and the evidence is evolving. Prospective, randomized controlled trials are needed to establish the role of these technologies in treating tricuspid disease.

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

The evidence base for transcatheter heart valve implantation within an existing bioprosthetic valve consists primarily of registries and case series.

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 bioprostheses 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 mm Hg), but less moderate or severe aortic regurgitation (3.5% vs. 6.6%). Post-TAVR gradients were highest in small SAVRs and stenotic SAVRs. This is a retrospective analysis of observational data. Longer-term follow-up studies are needed to clarify the durability of ViV TAVR.

Eleid et al. (2017) reported 1-year outcomes of percutaneous balloon-expandable transcatheter heart valve implantation in a failed mitral bioprosthesis (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

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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 mm Hg. 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 and control. 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 bioprostheses 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 bioprostheses or failed annuloplasty rings are needed.

Deeb et al. (2017) evaluated the safety and effectiveness of the CoreValve in patients with failed surgical bioprostheses. 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 a 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. Study limitations include lack of randomization and control and short-term follow-up.

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 bioprostheses 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%. Left ventricular ejection fraction 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. Study limitations include lack of randomization and control and short-term follow-up.

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 studies (823 patients) were included. Pooled analysis demonstrated 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 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 bioprosthesis 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 bioprosthesis (≤21 mm) and baseline stenosis (vs regurgitation).

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Raval et al. (2014) performed a systematic review to evaluate the effectiveness and outcomes of ViV implantation. Sixty-one studies were included: aortic (n=31), mitral (n=13), tricuspid (n=12) and pure native aortic valve regurgitation (n=9). The authors reported that ViV implantation can be considered an acceptable alternative to conventional open heart surgery for elderly high-risk surgical patients with bioprosthetic degeneration; however, most of the studies included were case reports with some case series. Long-term follow-up of treated patients will be necessary to establish the true role of ViV implantation for bioprosthetic degeneration.

Webb et al. (2010) evaluated transcatheter ViV implantation for failed bioprosthetic heart valves. ViV implantations were performed in 24 high-risk patients. Failed valves were aortic (n=10), mitral (n=7), pulmonary (n=6) or tricuspid (n=1) bioprostheses. Implantation was successful with immediate restoration of satisfactory valve function in all but one patient. No patient had more than mild regurgitation after implantation. No patients died during the procedure. Thirty-day mortality was 4.2%. Mortality was related primarily to learning-curve issues early in this high-risk experience. At baseline, 88% of patients were in NYHA functional class III or IV. At the last follow-up, 88% of patients were in class I or II. At a median follow-up of 135 days and a maximum follow-up of 1045 days, 91.7% of patients remained alive with satisfactory valve function. This study is limited by a small patient population and a lack of randomization and control.

A NICE guidance document states that for patients with aortic bioprosthetic valve dysfunction for whom SAVR is considered to be unsuitable, the evidence on the safety and efficacy of valve-in-valve (ViV) TAVR is adequate. For patients with aortic bioprosthetic valve dysfunction for whom SAVR is considered to be suitable but to pose a high risk, the evidence on the safety and efficacy of ViV TAVR is inadequate. For patients with aortic bioprosthetic valve dysfunction for whom SAVR is considered to be suitable and not to pose a high risk, the evidence on the safety and efficacy of ViV TAVR is inadequate (NICE, 2014).

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 bioprosthesis shows the potential for serious complications. However, this is in patients for whom open surgical valve implantation is unsuitable, who have severe symptoms and a high risk of death. The evidence on efficacy shows generally good symptom relief in the short term, but is based on very small numbers of patients. Therefore, this procedure should only be used with special arrangements for clinical governance, consent and audit or research (NICE, 2015).

Cerebral Protection

A Hayes prognosis overview (2018) concluded that the clinical benefits of the Sentinel cerebral embolic protection device are unclear. The best available evidence suggests that the device is safe and that it traps embolic debris in 99% of TAVR procedures. However, evidence is insufficient to definitively determine whether the device actually reduces risk for neurologic damage.

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, 2017).

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 involving 1170 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.

Seeger et al. (2017) evaluated the impact of cerebral embolic protection on stroke-free survival in 802 patients undergoing TAVR for severe aortic stenosis. The Sentinel cerebral embolic protection device was used in 34.9% (n=280) of consecutive 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-MRI) 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

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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. Clinicaltrials.gov number 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 nonsignificantly 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.

Professional Societies

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

ACC/AHA guidelines for the management of patients with valvular heart disease (Nishimura et al., 2014) make the following recommendations regarding transcatheter valve replacement:

Aortic

- Transcatheter aortic valve replacement (TAVR) is recommended in patients who meet an indication for aortic valve replacement (AVR) for aortic stenosis who have a prohibitive surgical risk and a predicted post-TAVR survival >12 mo. (Class I recommendation, level of evidence B - procedure is useful/effective based on evidence from a single randomized trial or nonrandomized studies.) See updates below.
- TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR and who have high surgical risk. (Class IIa recommendation, level of evidence B – procedure is reasonable but based on conflicting evidence from a single randomized trial or nonrandomized studies.) See updates below.
- TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of aortic stenosis. (Class III: no benefit, level of evidence B – procedure has no proven benefit based on evidence from a single randomized trial or nonrandomized studies.)
- For patients in whom TAVR or high-risk surgical AVR is being considered, members of a Heart Valve Team should collaborate to provide optimal patient care. (Class I recommendation, level of evidence C - based on expert opinion, case studies or standard of care.)

Mitral

Transcatheter mitral valve repair may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe primary MR (stage D) who have favorable anatomy for the repair procedure and a reasonable life expectancy but who have a prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal guideline-directed medical therapy for heart failure. (Class IIb recommendation, level of evidence B - procedure may be considered but usefulness/efficacy is less well established based on conflicting evidence from a single randomized trial or nonrandomized studies.)

Pulmonary

Transcatheter pulmonary valve replacement is outside the scope of these guidelines. See Warnes et al., 2008.

A 2017 focused update included the following areas of change (Nishimura et al., 2017):

- TAVR:
  - SAVR or TAVR is recommended for symptomatic patients with severe aortic stenosis (Stage D) and high risk for SAVR, depending on patient-specific procedural risks, values and preferences. Longer-term

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follow-up and additional randomized controlled trials have demonstrated that TAVR is equivalent to SAVR for severe symptomatic aortic stenosis when surgical risk is high. Class of recommendation updated from IIa to I (strong), level of evidence updated from B to A (high quality).
    - TAVR is recommended for symptomatic patients with severe aortic stenosis (Stage D) and a prohibitive risk for SAVR who have a predicted post-TAVR survival greater than 12 months. Longer-term follow-up from randomized controlled trials and additional observational studies has demonstrated the benefit of TAVR in patients with a prohibitive surgical risk. Level of evidence updated from B to A (high quality).
    - TAVR is a reasonable alternative to SAVR for symptomatic patients with severe aortic stenosis (Stage D) and an intermediate surgical risk, depending on patient-specific procedural risks, values and preferences. New evidence showed noninferiority of TAVR to SAVR in symptomatic patients with severe aortic stenosis at intermediate surgical risk.
- Valve-in-valve (ViV):
    - The use of a transcatheter ViV procedure may be considered for decision making on the type of valve, but long-term follow-up is not yet available, and not all bioprostheses are suitable for a ViV procedure. For severely symptomatic patients with bioprosthetic valve stenosis judged by the heart team to be at high or prohibitive risk of reoperation, and in whom improvement in hemodynamics is anticipated, a transcatheter ViV procedure is reasonable. (Class IIa recommendation, level of evidence B-NR - procedure is reasonable but based on evidence from nonrandomized studies).
    - In registries and case series comparing outcomes and safety of the transcatheter ViV procedure with repeat SAVR, the ViV procedure was found to have similar hemodynamic outcomes, lower stroke risk and reduced bleeding risk as compared with repeat surgery. However, no data is available yet on the durability and long-term outcomes after transcatheter ViV procedures.
    - A consensus-based decision pathway, provides additional details and practical guidance about TAVR with point-of-care checklists and algorithms (Otto et al., 2017).

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 (Tommaso et al., 2014) and pulmonary valve procedures (Hijazi et al., 2015).

In a separate publication, these organizations provide additional expert consensus recommendations for patient selection, screening and post-procedural care. These recommendations specify that TAVR is recommended for adults with severe, symptomatic, calcific stenosis of a trileaflet aortic valve who have aortic and vascular anatomy suitable for TAVR and a predicted survival of 12 months. TAVR is recommended in patients with prohibitive surgical risk and is a reasonable alternative to SAVR in patients at high surgical risk. Prohibitive surgical risk is defined by an estimated ≥ 50% risk of mortality or irreversible morbidity at 30 days or other factors such as frailty, prior radiation therapy, porcelain aorta and severe hepatic or pulmonary disease (Holmes et al., 2012).

In a joint consensus document, ACC and STS state that transcatheter valve therapy is a transformational technology with the potential to significantly impact the clinical management of patients with valvular heart disease in a less invasive manner.

Both ACC and STS strongly recommend the use of a "heart team" approach in which both a cardiothoracic surgeon and a cardiologist actively participate in the procedure. The consensus document makes recommendations for populating the heart team.

Participation in a national registry is also strongly recommended. The STS/ACCF TVT Registry is enrolling participant sites (https://www.ncdr.com/TVT/Home/Default.aspx). Data from this registry will provide clinical short-term and long-term follow-up information necessary to monitor outcomes as well as quality-of-life. The registry will also provide information that can be used to assess appropriateness of care as well as overuse (Holmes and Mack, 2011).

ACC guidelines on the management of adults with congenital heart disease address percutaneous therapies for reintervention in patients with RVOT dysfunction. Therapies include balloon dilation, stenting or percutaneous valve replacement. While promising, percutaneous valve replacement is considered investigational as it has yet to be proven in larger clinical trials (Warnes et al., 2008).

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

EACTS and ESC guidelines on the management of valvular heart disease make the following recommendations regarding transcatheter procedures (Baumgartner et al., 2017):

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Aortic
TAVR is recommended in patients who are not suitable for SAVR as assessed by an interdisciplinary team of specialists. The guidelines present a list of clinical characteristics and anatomical aspects to consider when deciding between TAVR and SAVR.

Mitral
Percutaneous edge-to-edge repair is generally safe and can improve symptoms and provide reverse left ventricular remodeling. However, the rate of residual mitral regurgitation up to 5 years is higher than with surgical repair. Percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe primary mitral regurgitation who fulfil the echocardiographic criteria of eligibility and are judged inoperable or at high surgical risk by an interdisciplinary team of specialists. Class IIb, level of evidence C – efficacy is less well established and based on consensus of opinion or small studies, retrospective studies or registries.

Experience with transcatheter annuloplasty, transapical chordal implantation or valve replacement is still limited and general recommendations cannot yet be made.

Very preliminary experience has suggested that transcatheter valve implantation in the mitral position is feasible in symptomatic elderly patients who are inoperable if the anatomy is suitable.

Tricuspid
Percutaneous repair techniques are in their infancy and must be further evaluated before any recommendations can be made.

ViV
Transcatheter ViV implantation in the aortic position should be considered by an interdisciplinary team of specialists depending on the risk of reoperation and the type and size of prosthesis. Class IIa, level of evidence C – evidence is in favor of efficacy but based on consensus of opinion or small studies, retrospective studies or registries. Experience is mostly for bioprostheses in the aortic position and remains limited in the mitral position and even more so in the tricuspid position. Long-term outcome data are needed.

European Society of Cardiology (ESC)
ESC guidelines for the management of adult congenital heart disease state that the decision to perform a percutaneous pulmonary valve implantation should involve a process of rigorous peer review and multidisciplinary discussion, as currently few data exist to demonstrate non-inferiority over surgery for many of these approaches. Mid-/long-term outcome data are not available yet for this procedure. Surgery is preferred over percutaneous methods when additional interventions are being considered (Baumgartner et al., 2010).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

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 August 17, 2018)

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 August 17, 2018)

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-

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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 and SAPIEN 3

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 August 17, 2018)

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 August 17, 2018)

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 mm Hg, 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 August 17, 2018)

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.

On February 12, 2013, the FDA granted the STS and the American College of Cardiology (ACC) a unique investigational device exemption (IDE) to study "alternative access" approaches for transcatheter aortic valve replacement (TAVR) using the STS/ACC TVT Registry™. Currently, only the transfemoral approach to TAVR using the Edwards SAPIEN valve has been approved for inoperable patients. Both the transfemoral and transapical approaches have been approved for high risk patients. An estimated 1 in 4 patients is ineligible for these procedures because of inadequate vessel size, vessel disease or other considerations. The new STS/ACC study protocol, as approved by CMS, allows Medicare reimbursement for alternative access to the aortic valve via the heart muscle or the aorta (transaortic approach) in inoperable patients involved in the study. The goal of the study is controlled off-label use of an approved

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device (STS press release, 2013). Available at: http://www.sts.org/sites/default/files/press-releases/STS_ACC_IDEannouncement.pdf. (Accessed August 17, 2018)

Pulmonary

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 right ventricular outflow tract (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 August 17, 2018)

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 August 17, 2018)

SAPIEN XT

On February 29, 2016, the FDA granted expanded approval of the Edwards SAPIEN XT Transcatheter Heart Valve to include use in percutaneous pulmonary valve implantation procedures (P130009).

Additional information is available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130009. (Accessed August 17, 2018)

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 August 17, 2018)

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

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 August 17, 2018)

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Additional Products

- CardiAQ (Edwards Lifesciences) – not FDA approved
- Carillon® Mitral Contour System™ for percutaneous annuloplasty – not FDA approved
- Fortis (Edwards Lifesciences) – not FDA approved
- Portico™ (St. Jude Medical) – not FDA approved
- Tiara™ (Neovasc, Inc.) - not FDA approved

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GUIDELINE HISTORY/REVISION INFORMATION

Date	Action/Description

02/01/2019	• Reorganized policy template; simplified and relocated *Instructions for Use* and *Benefit Considerations* section
	• Replaced references of "individual(s)" with "member(s)"
	• Simplified coverage rationale (no change to guidelines)
	• Added definition of:
	  ○ New York Heart Association (NYHA) Heart Failure Classification
	  ○ Predicted Risk of Mortality (PROM)
	• Updated supporting information to reflect the most current references
	• Archived previous policy version MMG129.K

INSTRUCTIONS FOR USE

This Medical Management Guideline 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 benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, 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 Management Guideline is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare West Medical Management Guidelines 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.

Member benefit coverage and limitations may vary based on the member's benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.

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