Transcatheter Heart Valve Procedures

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Coverage Policy

Transcatheter aortic valve implantation using a U.S. Food and Drug Administration (FDA) approved device is considered medically necessary when the following device-specific criteria are met:

- Edwards SAPIEN™ Transcatheter Heart Valve [Edwards Lifesciences, LLC, Irvine, CA] for ALL of the following:
  - severe symptomatic calcified native aortic valve stenosis without severe aortic insufficiency
  - ejection fraction > 20%
  - EITHER of the following:
    - inoperable as determined by the heart team, including an experienced cardiac surgeon and a cardiologist, and existing comorbidities would not preclude the expected benefit from correction of the aortic stenosis
    - operative candidate for aortic valve replacement but with a Society of Thoracic Surgeons predicted operative risk score ≥ 8%, or are judged by the heart team to be at a ≥ 15% risk of mortality for surgical aortic valve replacement

- Edwards SAPIEN™ XT Transcatheter Heart Valve [Edwards Lifesciences, LLC, Irvine, CA] OR Medtronic CoreValve System Transcatheter Aortic Valve [Medtronic CoreValve LLC, Santa Rosa, CA]) for ALL of the following:
  - symptomatic heart disease due to severe native calcific aortic stenosis (i.e., aortic valve area ≤ 1.0 cm² or aortic valve area index ≤ 0.6 cm²/m², a mean aortic valve gradient of ≥ 40mm Hg, or a peak aortic-jet velocity of ≥ 4.0 m/s)
- appropriate native anatomy
- judged by a heart team, including a cardiac surgeon, to be at high (or greater) risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days)

- Edwards SAPIEN 3 Transcatheter Heart Valve [Edwards Lifesciences, LLC, Irvine, CA] for ALL of the following:
  - severe symptomatic calcified native aortic valve stenosis
  - judged by a heart team, including a cardiac surgeon, to be at high (or greater) risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days)

Transcatheter aortic valve implantation for any other indication is considered experimental, investigational or unproven.

Transcatheter pulmonary valve implantation using a U.S. Food and Drug Administration (FDA) approved device is considered medically necessary when the following device-specific criteria are met:

- Medtronic Melody® Transcatheter Pulmonary Valve (Medtronic, Inc., Santa Ana, CA) for ALL of the following:
  - existence of a full (circumferential) right ventricular outflow tract (RVOT) conduit that was equal to or greater than 16 mm in diameter when originally implanted
  - dysfunctional RVOT conduit with a clinical indication for intervention, and EITHER of the following:
    - moderate or greater regurgitation
    - stenosis, with mean RVOT gradient ≥ 35 mmHg

- Edwards SAPIEN™ XT Transcatheter Heart Valve and Accessories [Edwards Lifesciences, LLC, Irvine, CA] for ALL of the following:
  - dysfunctional, non-compliant RVOT conduit with a clinical indication for intervention
  - pulmonary regurgitation ≥ moderate and/or mean RVOT gradient ≥ 35 mmHg

Transcatheter pulmonary valve implantation for any other indication is considered experimental, investigational or unproven.

Percutaneous mitral valve repair (e.g., MitraClip Clip Delivery System (MitraClip CDS) (Abbott Vascular, Menlo Park, CA) is considered experimental, investigational or unproven.

Percutaneous tricuspid valve repair or replacement for any indication is considered experimental, investigational or unproven.

Overview

This Coverage Policy addresses the transcatheter (percutaneous or catheter-based) approach for aortic or pulmonary heart valve replacement, percutaneous mitral valve repair and percutaneous tricuspid valve repair or replacement.

General Background

Aortic Valve

Valvular aortic stenosis is a narrowing or obstruction of the aortic valve that prevents the valve leaflets from opening normally. Medication is prescribed to alleviate symptoms. Surgical aortic valve replacement reduces symptoms and improves survival in patients with severe aortic stenosis, and is considered the surgical treatment of choice for most adults. As many as a third of patients with severe heart valve disease are considered too high risk for conventional surgical valve replacement. Transcatheter aortic valve implantation (TAVI), also referred to
as transcatheter aortic valve replacement (TAVR) or percutaneous aortic valve replacement, was first accomplished in 2002. TAVI or TAVR has been proposed as a less invasive alternative to open surgical aortic valve replacement in a specific subset of patients. TAVI or TAVR is a minimally invasive surgical procedure that repairs the valve without removing the old, damaged valve. Instead, it wedges a replacement valve into the aortic valve’s place. This is referred to a valve-in-valve procedure. Somewhat similar to a stent placed in an artery, the TAVI approach delivers a fully collapsible replacement valve to the valve site through a catheter. Once the new valve is expanded, it pushes the old valve leaflets out of the way and the tissue in the replacement valve takes over the job of regulating blood flow. The long-term durability of the TAVI bioprosthetic valves has not been adequately defined, so at present, conventional surgical aortic valve replacement remains the procedure of choice in patients at low or intermediate surgical risk (American Heart Association (AHA), 2017; Otto, et al., 2015; Webb, et al., 2015).

Several techniques for TAVI have been described in the literature. In early stages of development, valves were delivered via the femoral vein using an antegrade approach, with the catheter directed to the heart thorough the venous system in the direction of blood flow. With this procedure, a catheter is passed through the septum to reach the aortic valve. More recently, valves have been implanted through the heart wall (i.e., transapical approach), and via the femoral artery using a retrograde approach, against the direction of blood flow. The transapical procedure is performed by a cardiac surgeon, using direct left ventricular apical puncture though a small thoracotomy, and does not require a sternotomy. Retrograde approaches via the subclavian or axillary artery or the ascending aorta may also be used (Otto, et al., 2015; Webb, et al., 2015; Williams, 2010).

TAVR has been studied in patients who are not candidates for surgery or who are at high risk for complications due to surgery. Increased operator experience and enhanced transcatheter valve systems have led to a worldwide trend to use TAVR in patients who are at low or intermediate risk. This trend has been evaluated in randomized controlled and small observational studies. Since most patients who are currently recommended for surgery are at low or intermediate risk, the expansion of the use of TAVR requires rigorous clinical-trial validation with long-term follow-up (Leon, et al., 2015).

Presently there are two aortic valve systems that are available. The SAPIEN™ valve (Edwards Lifesciences, Irvine, CA) incorporates a balloon-expandable stainless steel stent frame within which are sewn bovine pericardial leaflets. A synthetic fabric sealing cuff surrounds the inflow of the valve to prevent paravalvular leaks. This is the valve evaluated in the PARTNER trial (Leon, et al., 2010) and it is currently approved for clinical use in the United States. Its successor, the SAPIEN XT™ valve, is constructed of a chromium alloy frame and has various minor improvements. This valve is compatible with newer low-profile delivery catheters. The next-generation SAPIEN 3 valve is compatible with even lower-profile delivery systems and has various improvements that facilitate accurate positioning and improve paravalvular sealing. The CoreValve System (Medtronic, Inc., Santa Rosa, CA) incorporates a self-expanding nitinol alloy frame within which are sewn porcine pericardial leaflets. A pericardial sealing cuff surrounds the inflow of the valve. The self-expanding frame is constrained within a delivery catheter. As the valve is released from the delivery catheter, the frame expands to assume its predetermined shape. The lower portion of the frame with its sealing cuff is positioned within the aortic annulus and displaces the native leaflets. The middle portion contains the pericardial valve. The upper portion extends above the coronaries to anchor and align the prosthesis within the ascending aorta (Webb, et al., 2015). These two aortic valve systems have undergone numerous design and labeling changes as described in the U.S. Food and Drug Administration (FDA) section of the Coverage Policy.

Numerous transcatheter aortic valves are currently in early clinical evaluation. These valves typically offer features that facilitate positioning, repositioning, fixation sealing, or a reduction in delivery catheter diameter. However, previous experience with surgical valves has shown that some enhancements may introduce the possibility of new mechanisms of failure, and therefore extensive evaluation will be necessary before widespread application (Webb, et al., 2015).

**U.S. Food and Drug Administration (FDA)–Edwards SAPIEN™ Transcatheter Heart Valve (Edwards Lifesiences, LLC, Irvine, CA):** The Edwards SAPIEN™ Transcatheter Heart Valve model 9000TFX, 23 and 26 mm, and accessories (RetroFlex™ 3 Delivery System, models 9120FS23 and 9120FS26 RetroFlex Balloon Catheter, models 9120BC20 and 9120BC23 Crimper, models 9100CR23 and 9100CR26) received FDA approval through the PMA process on November 2, 2011 (P100041). The SAPIEN Transcatheter Heart Valve
was approved for transfemoral delivery in patients with severe symptomatic native aortic valve stenosis, 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.

On October 19, 2012, an additional PMA approval (P110021) was granted, allowing a transapical delivery approach in addition to a transfemoral approach. Indications for use were also expanded. On September 23, 2013 (P11021/S026), the FDA approved removal of the access approach from the device labeling. As revised, the device is indicated for patients with severe symptomatic calcified native aortic valve stenosis without severe aortic insufficiency and with ejection fraction > 20% who have been examined by a heart team including an experienced cardiac surgeon and a cardiologist and found to be: 1) inoperable and in whom existing co-morbidities would not preclude the expected benefit from correction of the aortic stenosis; or 2) be operative candidates for aortic valve replacement but who have a predicted operative risk score ≥ 8% or are judged by the heart team to be at a ≥ 15% risk of mortality for surgical aortic valve replacement.

On October 25, 2015 (P130009/S034), the FDA expanded the indications for the Edwards SAPIEN XT Transcatheter Heart Valve, model 9300TFX, 23, 26, and 29 mm, to include use in patients with symptomatic heart disease due to severe native calcific aortic stenosis or failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

On June 17, 2015, the SAPIEN 3 Transcatheter Heart Valve and accessories model 9600TFX received FDA PMA approval (P140031). This third generation device has a major design change that adds a skirt at the base of the valve to minimize leakage around the valve. 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., Society of Thoracic Surgeons operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

In a PMA supplement approved on June 5, 2017 (P140031/S028) the FDA approved expanded use of the SAPIEN 3 Transcatheter Heart Valve, Model 9600TFX for treatment of individuals with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic or mitral valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

In the PARTNER II Trial Intermediate Risk Cohort A (denoted as PIIA) was the basis for the PMA approval decision for the SAPIEN XT. Data from the Partner II (denoted as PIIS3I) cohort were the basis for the SAPIEN 3 PMA approval. The manufacturer is required to follow these patients for 10 years to further monitor safety and effectiveness, as a condition of FDA approval.

In a PMA supplement approved on June 5, 2017 (P140031/S028) the FDA approved expanded use of the SAPIEN 3 Transcatheter Heart Valve, Model 9600TFX for treatment of individuals with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic or mitral valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).
data captured in the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry to establish a reasonable assurance of safety and effectiveness of transcatheter valve replacement with the Edwards SAPIEN 3 THV in patients with a failed surgical aortic or mitral bioprosthesis who are at high or greater surgical risk for reoperative aortic or mitral valve replacement. The data from the TVT Registry were the basis of the PMA supplemental approval decision. Valve function before valve-in-valve repair, upon discharge and 30 days post procedure was reported in the data.

**Medtronic CoreValve™ (MCS) System Transcatheter Aortic Valve (TAV) (Medtronic CoreValve LLC, Santa Rosa, CA):** The MCS TAV models MCS-P4-23-AOA (23 mm CoreValve Evolut), MCS-P3-26-AOA (26 mm), MCS-P3-29-AOA (29 mm) and MCS-P3-31-AOA (31 mm); Delivery Catheter System (DCS), Models DCS-C4-18FR and DCS-C4-18FR-23; and Compression Loading System Model CLS-3000-18FR received FDA approval through the PMA process on January 17, 2014 (P130021).

According to the FDA labeling, the Medtronic CoreValve™ System 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 cm², 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).

In a PMA supplement approved on June 12, 2014 (P130021/S002), the FDA expanded the indications for the CoreValve System. According to the revised PMA approval, the CoreValve 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 cm² or aortic valve area index ≤ 0.6 cm²/m², a mean aortic valve gradient of ≥ 40 mm Hg, or a peak aortic-jet velocity of ≥ 4.0 m/s) and with native anatomy appropriate for the 23, 26, 29, or 31 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., Society of Thoracic Surgeons operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

In a PMA supplement approved on March 20, 2015 (P130021/S010), the FDA expanded the indications for the CoreValve System to include the treatment of a failed surgical bioprosthesis (TAV-in-SAV). According to the revised PMA approval, the CoreValve is indicated for use in patients with symptomatic heart disease due to either severe native calcific aortic stenosis or failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days).

In a PMA supplement approved on June 22, 2015 (P130021/S014), the FDA approved a change in the design iteration of the 23, 26, and 29 mm Medtronic CoreValve System. According to the revised PMA approval, the new components include CoreValve™ Evolut R® transcatheter aortic valves, models Evolut R-23mm, Evolut R-26mm, and Evolut R-29mm, EnVeo R delivery catheter system, model EnVeo R, and EnVeo R loading systems. These components will be marketed under the trade name CoreValve Evolut R System.

In a PMA supplement approved on March 20, 2017 (P130021/S029), the FDA approved a design iteration of the 23, 26, and 29 mm Medtronic CoreValve Evolut R System. The new components include the CoreValve Evolut PRO Transcatheter Aortic Valves, models EVOLUTPRO-23-US, EVOLUTPRO-26-US, and EVOLUTPRO-29-US, and the EnVeo R Loading Systems, models LS-MDT2-23-US and LS-MDT2-2629-US.

In a PMA supplement approved on July 10, 2017 (P130021/S033), the FDA expanded FDA approval of the CoreValve System; CoreValve Evolut R System; CoreValve Evolut PRO System 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 intermediate or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥3% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator). The FDA approval is based on two year results from the SURTAVI trial (NCT01586910), a randomized study comparing TAVR (CoreValve System) with surgical aortic valve replacement in individuals with severe, symptomatic aortic stenosis at intermediate surgical risk.
Literature Review—Transcatheter Aortic Valve Implantation in High Risk Patients:

**PARTNER (Placement of AoRTic traNscatheterER valves) trial:** The PARTNER trial is a two-part, multicenter, randomized controlled trial. 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 parallel study (PARTNER Cohort A), Smith et al. (2011) randomly assigned 699 high-risk patients with severe aortic stenosis to TAVI using the SAPIEN heart valve system with either a transfemoral or transapical approach (n=348) or surgical replacement (n=351). The rates of death from any cause were 3.4% in the TAVI group and 6.5% in the surgical group at 30 days (p=0.07) and 24.2% vs. 26.8%, respectively, at one year. (p=0.07). The rates of stroke were 3.8% in the TAVI group and 2.1% in the surgical group at 30 days (p=0.20) and 5.1% vs. 2.4%, respectively, at one year (p=0.07). Major vascular complications were significantly more frequent with TAVR at 30 days (11.0% vs. 3.2%, p<0.001). Adverse events occurring more frequently after surgical replacement included major bleeding (9.3% vs. 19.5%, p<0.001) and new-onset atrial fibrillation 8.6% vs. 16.0%). More patients in the TAVI group had an improvement in symptoms at 30 days, but there was no significant difference between groups at one year.

Limitations of the study included an unexpected frequency of withdrawals and decisions to forego the procedure in patients assigned to surgical replacement, and approximately 5% of patients assigned to TAVI did not undergo the procedure. A balanced perspective on early outcomes therefore requires analysis of both the intention-to-treat and as-treated populations. However, for rates of death, neurological events, and procedural hazards, the two groups did not differ significantly in the as-treated population. The authors stated that in the absence of long-term follow-up data, recommendations for individual patients must balance the appeal of avoiding the known risks of open heart surgery with the transcatheter approach, which has different and less well understood risks, particularly regarding stroke. Additional randomized controlled trials are needed to determine whether transcatheter replacement is equivalent to surgical replacement in terms of clinical benefit for lower-risk patients with aortic stenosis.

Kodali et al. (2012) reported two year outcomes following TAVR or surgical aortic valve replacement in the high-risk patients with severe aortic stenosis in the PARTNER trial, Cohort A, (described above) who could undergo surgery (n=699). Patients at 25 centers were randomly assigned to surgical aortic-valve replacement (n=351) or TAVR (n=348). Patients assigned to TAVR were treated by either the transfemoral (n=244) or transapical (n=104) approach on the basis of whether peripheral arteries could accommodate the large sheath required. Patients assigned to surgical replacement were stratified according to whether a transfemoral or transapical approach would have been used. At two years there was no significant difference in mortality between the groups; 33.9% in the TAVR group and 35% in the surgery group (p=0.78). Paravalvular regurgitation was more frequent after TAVR (p < 0.001) and even mild regurgitation was associated with increased late mortality. The two treatments were similar in terms of reduction in cardiac symptoms and improved hemodynamics, and while there was an early increase in the risk of stroke with TAVR, this was attenuated over time.

Mack et al. (2015) reported five year outcomes following TAVR or surgical aortic valve replacement in the high-risk patients with severe aortic stenosis in the PARTNER trial, Cohort A, (described above). Patients at 25 centers were randomly assigned to surgical aortic-valve replacement (n=351) or TAVR (n=348). The risk of death was 62.4% in the surgical group versus 67.8% in the TAVR 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:** Leon et al. (2010) evaluated transcatheter aortic valve implantation for aortic stenosis in patients in the PARTNER (Placement of AoRTic TranScatheterER Valves) trial who were not suitable candidates for surgery (cohort B, n=358). In this randomized, unblinded, controlled multi-center trial patients with severe aortic stenosis, considered by surgeons not to be suitable candidates for surgery, were randomly assigned to standard therapy, including balloon valvuloplasty (n=179), or transfemoral transcatheter implantation of the Edwards SAPIEN heart-valve system (n=179). At one year, the rate of death from any cause (the primary endpoint) was 30.7% with TAVI vs. 50.7% with standard therapy (p<0.001). The rate of the composite end point of death from any
cause or repeat hospitalization was 42.5% with TAVI vs. 71.6% with standard therapy (p<0.001). The rate of cardiac symptoms (New York Heart Association class III or IV) was lower in patients in the TAVI group than in the standard therapy group (25.2% vs. 58.0% (p<0.001). However, at 30 days, TAVI was associated with a higher incidence of major strokes (5.0% vs. 1.1%, p=0.06) and major vascular complications (16.2% vs. 1.1%, p<0.001). The authors acknowledged limitations of the study, including the fact that important patient subgroups were excluded, including those requiring treatment of coronary stenosis and those with severe peripheral vascular disease, and also noted that an assessment of the durability and long-term clinical safety and effectiveness of the bioprosthetic valves will require more prolonged follow-up. The authors stated that the results of this study cannot be extrapolated to other patients with aortic stenosis. Additional randomized trials are needed to compare TAVI with aortic valve replacement among high-risk patients with aortic stenosis for whom surgery is a viable option and among low risk patients with aortic stenosis.

Five-year outcomes of transcatheter aortic valve replacement in inoperable patients in the PARTNER trial (Cohort B) were reported by Kapadia et al. (2015). The risk of all cause mortality at 5 years was 71.8% in the TAVR group versus 93.6% in the standard treatment group (p<0.0001). Risk of repeat hospital admission was 47.6% in the TAVR group compared with 87.3% in the standard treatment group (p<0.0001). At 5 years, 42 (86%) of 49 survivors in the TAVR group had New York Heart Association class 1 or 2 symptoms compared with three (60%) of five in the standard treatment group. Echocardiography after TAVR showed durable hemodynamic benefit (aortic valve area 1.52 cm² at 5 years, mean gradient 10.6 mm Hg at 5 years), with no evidence of structural valve deterioration.

Two-year outcomes of transcatheter aortic valve replacement in inoperable patients in the PARTNER trial (Cohort B) were reported by Makkar et al. (2012). The rates of death at two years were 43.3% in the TAVR group and 68.0% in the standard-therapy group (p< 0.001). The corresponding rate of cardiac death were 31.0% and 62.4% (p< 0.001).The survival advantage seen with TAVR at one year remained significant in patients who survived beyond the first year (p=0.02). The incidence of stroke was higher after TAVR then with standard therapy (13.8% vs. 5.5%, p=0.01), due in the first 30 days to more ischemic events, and beyond 30 days, to more hemorrhagic strokes. Rehospitalization rates were 35.0% in the TAVR group and 72.5% in the standard therapy group. TAVR was also associated with improved functional status (p<0.001).

Abdel-Wahab et al. (2014) conducted a multicenter randomized trial to assess the comparative performance of the balloon-expandable device and the self-expandable device regarding overall device success. Patients with severe aortic stenosis and an anatomy suitable for the transfemoral TAVR procedure were randomly assigned to receive a balloon-expandable valve (Edwards SAPIEN XT) or a self-expandable valve (Medtronic CoreValve). The primary endpoint was device success; a composite endpoint including successful vascular access and deployment of the device and retrieval of the delivery system, correct position of the device, intended performance of the heart valve without moderate or severe regurgitation, and only one valve implanted in the proper anatomical location. Device success occurred in 116 of 121 patients (95.9%) in the balloon-expandable group and 93 of 120 patients (77.5%) in the self-expandable valve group (relative risk 1.24, 95% CI 112-137, p<.001). The difference in success was attributed to a significantly lower frequency of residual moderate to severe aortic regurgitation (4.1% vs. 18.3%, p<.001) and less frequent need to implant more than one valve in the balloon expandable group. There were no significant differences in cardiovascular mortality, bleeding, or vascular complications. Placement of a new permanent pacemaker was less frequent in the balloon-expandable valve group (17.3% vs. 37.6%, p=.001).

Adams et al. (2014) conducted a multicenter, randomized non-inferiority trial to compare transcatheter aortic valve replacement (TAVR) using a self-expanding transcatheter aortic valve bioprosthesis (CoreValve) to surgical aortic valve replacement (n=795). Patients with severe aortic stenosis and symptoms of NYHA class II or higher were eligible if considered to be at increased risk for undergoing surgical AVR. Patients were determined to be at increased surgical risk if two cardiac surgeons and one interventional cardiologist estimated that the risk of death within 30 days after surgery was 15% or more and the risk of death or irreversible complications within 30 days was less than 50%. In the as-treated analysis, the primary end point, 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%, p<0.001 for noninferiority, p=0.04 for superiority). Results were similar in the intention to treat analysis. TAVR was non-inferior in terms of echocardiographic indexes of valve stenosis, functional status, and quality of life. Major vascular complications and permanent pacemaker implantations were significantly more frequent in
the TAVR group, while bleeding, acute kidney injury, and new onset or worsening atrial fibrillation were significantly more common than the surgical group. There were five cases of cardiac perforation in the TAVR group, and rates of paravalvular regurgitation were significantly higher in the TAVR group at all points. Deeb et al. (2016) reported that the rate of death or stroke at three years was lower with TAVR than with surgical AVR (37.3% versus 46.7%; p=0.0006).

Popma et al. (2014) conducted a multicenter nonrandomized study to evaluate the safety and efficacy of the CoreValve for treatment of severe aortic stenosis in patients at extreme risk for surgery (n=489). The primary endpoint was a composite of all-cause mortality or major stroke at 12 months, compared to a pre-specified objective performance goal (OPG). The OPG was determined based on a weighted meta-analysis performed of seven balloon aortic valvuloplasty studies and an analysis of inoperable patients in the PARTNER trial. At 12 months, the rate of all-cause mortality or major stroke was 26.0% compared to 43% with the OPG. The rates of all-cause mortality at 30 days and 12 months were 8.4% and 24.3%, respectively, and the rates of major stroke at 30 days and 12 months were 2.3% and 4.3%, respectively.

Rodes-Cabau et al. (2012) conducted a Canadian multicenter study of 339 patients considered to be inoperable or at very high surgical risk (Society of Thoracic Surgeons score: 9.8 ± 6.4%) who underwent TAVI with the Edwards valve (transfemoral: 48%, transapical: 52%). Follow-up was available in 99% of the patients. At a mean follow-up of 42 ±15 months 188 patients (55.5%) had died. The causes of late death (152 patients) were noncardiac (59.2%), cardiac (23.0%), and unknown (17.8%). Chronic obstructive pulmonary disease, chronic kidney disease, chronic atrial fibrillation, and frailty were predictors of late mortality. A mild decrease in valve area occurred at two year follow-up (p < 0.01), but was not clinically significant, and no further reduction in valve area was observed up to four years follow-up. There were no changes in residual aortic regurgitation and no cases of structural valve failure observed during the follow-up period.

Reynolds et al. (2011) conducted a prospective quality of life substudy in the PARTNER trial (detailed above). Health-related quality of life was assessed at baseline and at one, six and twelve months using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the 12-item Short Form-12 General Health Survey (SF-12). At baseline, mean KCCQ summary scores (35 ± 20) and SF-12 physical summary scores (28 ± 7)) were significantly depressed. The KCCQ summary scores improved in both groups, but improvement was greater after TAVI compared to control at 1 month (mean between-group difference, 13 points, p<0.001), six months (mean difference, 21 points; p<0.001) and twelve months (mean difference, 26 points; p<0.001). At twelve months, TAVI patients also reported higher SF-12 physical and mental health scores with mean differences compared with control of 5.7 and 6.4 points, respectively (p<0.001 for both comparisons).

A prospective single-center registry (Wenaweser et al., 2011) assessed the role of TAVI compared to medical treatment and surgical aortic valve replacement (SAVR) in patients with severe aortic stenosis at increased surgical risk (n=442). Patients with severe aortic stenosis (age 81.7 ± 6 years, mean logistic European System for Cardiac Operative Risk Evaluation: 22.3 ± 14.6%) were allocated to medical treatment (n=78), SAVR (n=107), or TAVI (n=257) on the basis of a comprehensive evaluation protocol. Baseline characteristics of patients allocated to medical treatment and TAVI were similar, while patients allocated to SAVR were younger and had a lower predicted peri-operative risk. Unadjusted rates of all-cause mortality at 30 months were lower for SAVR (22.4%) and TAVI (22.6%) compared to medical treatment (61.5%). Medical treatment, older age, peripheral vascular disease, and atrial fibrillation were significantly associated with all-cause mortality at 30 months in multivariate analysis.

Moat et al. (2011) published data from the United Kingdom Transcatheter Aortic Valve Implantation (U.K. TAVI) Registry. Data were collected prospectively on 870 patients undergoing 877 TAVI procedures through December 2009. Survival was 92.9% at 30 days, 78% at one year, and 73.7% at two years. In univariate analysis, survival was significantly adversely affected by renal dysfunction, presence of coronary artery disease, and a nontransfemoral approach. In the multivariate model, left ejection fraction of < 30%, presence of moderate/sever aortic regurgitation, and chronic obstructive pulmonary disease remained the only independent predictors of mortality.

**Literature Review–Transcatheter Aortic Valve Implantation in Intermediate Risk Patients:**
Intermediate Risk-Cohort A (PIIA) SAPIEN XT: In a randomized controlled study (Cohort A), Leon et al. (2016) reported the results in which TAVR with a transthoracic or transfemoral implanted second-generation valve system, SAPIEN XT (n=1011), was compared with conventional aortic valve surgery (n=1021). Patients included those with severe aortic stenosis and intermediate-risk clinical profiles. The primary endpoint was death from any cause or disabling stroke at two years. The rates of death from any cause or disabling stroke were 6.1% in the TAVR group and 8.0% in the surgery group at 30 days (p=0.11) and 14.5% vs. 16.4%, respectively, at one year (p=0.04) and 19.3% vs. 21.1%, respectively, at two years (p=0.33). All-cause death and disabling stroke at 2 years were clinically comparable between TAVR and surgery (16.7% vs. 18.0% for all-cause death; 6.2% vs. 6.4% for disabling stroke). Life-threatening or disabling bleeding was significantly more with the surgical group at two years 47.0% vs. 17.3% in the TAVR group (p<0.001). New atrial fibrillation was significantly more with the surgical group at two years 27.3% vs. 11.3% in the TAVR group (p<0.001). Acute kidney injury was more with the surgical group 6.2% vs. 3.8% in the TAVR group (p=0.02).

Limitations of the study include high frequency of unexpected withdrawals in patients who were scheduled to undergo surgery. A total of 94 patients (4.6%) were enrolled but did not undergo the assigned procedure, including 17 patients in the TAVR group and 77 in the surgery group. The main reason for nontreatment was withdrawal from the trial. The authors reported that further technological advances may favorably influence the outcomes with TAVR in the future, and the SAPIEN XT valve that was used in this trial has already been replaced by the SAPIEN 3 valve system. Long-term assessments of the durability of bioprosthetic transcatheter valves (i.e., through 10 years) remain a limitation, although 5-year echocardiographic evaluations from the earlier PARTNER trials indicate no evidence of important premature or accelerated structural valve deterioration.

Intermediate Risk-Partner II SAPIEN 3 (PIIS3i): Thourani et al. (2016) reported longer-term data in intermediate-risk patients given SAPIEN 3 TAVR and compared outcomes to those of intermediate risk patients given surgical aortic valve replacement. In the SAPIEN 3 observational study, 1077 intermediate-risk patients at 51 sites in the USA and Canada were assigned to receive TAVR with the SAPIEN 3 valve (952 [88%] via transfemoral access). In this population all-cause mortality and incidence of strokes, re-intervention, and aortic
valve regurgitation at year after implantation was assessed. One year outcomes in this population were compared with those for intermediate-risk patients treated with surgical valve replacement in the PARTNER 2A trial (Cohort A PIIA study above), using a prespecified propensity score analysis to account for between-trial differences in baseline characteristics. The primary endpoint was the composite of death from any cause, all strokes, and incidence of moderate or severe aortic regurgitation. At 1 year follow-up of the SAPIEN 3 observational study, 79 of 1077 patients who initiated the TAVR procedure had died (all-cause mortality 7.4%; 6.5% in the transfemoral access subgroup), and disabling strokes had occurred in 24 (2%), aortic valve reintervention in six (1%), and moderate or severe paravalvular regurgitation in 13 (2%). The propensity-score analysis included 963 patients treated with SAPIEN 3 TAVR and 747 with surgical valve replacement. For the primary composite endpoint of mortality, strokes, and moderate or severe aortic regurgitation, TAVR was both non-inferior (p<0.0001) and superior (p<0.0001) to surgical valve replacement. A limitation of this study was the lack of a comparator group. Additionally, this study only addresses the intermediate risk population, wherein most patients were elderly with several coexisting illnesses. Further studies, especially randomized trials of TAVR versus surgery, are needed to examine the value of TAVR in younger, lower-risk, patients without major comorbidities.

In a meta-analysis, Kondur et al. (2016) reported outcomes in patients at low to intermediate risk with aortic stenosis who underwent surgical aortic valve replacement (SAVR) versus TAVR. The primary outcome measures were 30-day mortality, all-cause mortality, stroke, and myocardial infarction (MI). Secondary outcome measures were major vascular complications, moderate or severe paravalvular regurgitation, permanent pacemaker implantation, major bleeding, and acute kidney injury. Three randomized controlled trials and two prospective observational studies were identified and included in the meta-analysis. The total number of participants was 3199 with mean age of 80 years and mean follow-up duration of 1.05 years. Total number of participants treated with TAVR was 1618 (50.6%). TAVR procedures were performed using the self-expanding CoreValve System in some of the studies and the SAPIEN XT in other studies. The authors reported no significant difference between the TAVR and SAVR in terms of survival rate, 30-day mortality, all-cause mortality, stroke, and MI. However, requirement of permanent pacemaker implantation was significantly higher in patients treated with TAVR. In addition, higher incidence of moderate or severe paravalvular regurgitation and major vascular complications were found to be associated with TAVR patient population.

Additional meta-analysis have been reported in patients at low to intermediate risk with aortic stenosis who underwent SAVR versus TAVR (Garg, et al., 2017; Arora, et al., 2016, Gargiulo, et al., 2016). The meta-analysis have similar conclusions to the above meta-analysis. Additionally many of the earlier studies included studied the use of earlier generation valves that are not currently the standard of practice (Arora, et al., 2016).

In a systematic review and meta-analysis, Siemieniuk et al. (2017) compared the effect of transcatheter aortic valve implantation (TAVI) versus surgical replacement of an aortic valve (SAVR) in patients with severe aortic stenosis at low and intermediate risk of perioperative death. The authors reported that the most important limitation is that the relatively short duration of follow-up (median follow-up of two years) leaves uncertainty about one critical outcome: the need for reintervention over the longer term, a major concern with TAVI valves. Studies assessing the long-term patient outcomes following TAVR, compared to SAVR in intermediate and low risk patients are needed.

**Literature Review—Transcatheter Aortic Valve Implantation in Low Risk Patients:**
The Low Risk TAVR (LRT) study is the first U.S. FDA-approved Investigational Device Exemption (IDE) prospective multicenter feasibility trial to test the safety of transfemoral TAVR in 200 patients with symptomatic severe aortic stenosis and low risk for surgical aortic valve replacement (Rogers, et al., 2017). Patients determined to be low risk by the Heart Team will be enrolled to undergo TAVR with a commercially available balloon-expandable or self-expandable device. A propensity score-matched, site-specific cohort of historical surgical aortic valve replacement patients will serve as a control group treated during the site's enrollment period or within the prior three years. Low-risk patients with symptomatic bicuspid aortic stenosis undergoing TAVR will be enrolled into a separate registry arm. All TAVR patients will undergo 4-dimensional contrast-enhanced cardiac computed tomography 4-6 weeks after implantation to assess for subclinical leaflet thrombosis and will be followed up clinically for five years with yearly echocardiography to monitor prosthesis function. Enrollment commenced in 2016 and results are expected in 2018 (Rogers, et al., 2017). (ClinicalTrials.gov number NCT01314313).
Transcatheter Aortic Valve Implantation (TAVI) for Treatment of a Failed Surgical Bioprosthesis (TAV-in-SAV): In recent years, several reports have suggested that the use of transcatheter aortic valve replacement (TAVR) within failed surgically inserted bioprosthetic valves (valve-in-valve [VIV]) is technically feasible. The largest case series published to date is from the Global Valve-in-Valve registry which is the known as the Medtronic CoreValve U.S. Expanded Use Post Approval Study TAV in SAV (Dvir, et al., 2012). This study included 202 patients from 38 cardiac centers with a prior surgical bioprosthetic valve replacement that had failed. Bioprosthesis mode of failure was stenosis (n=85; 42%), regurgitation (n=68; 34%), or combined stenosis and regurgitation (n=49; 24%). Implanted devices included CoreValve (n=124) and Edwards SAPIEN (n=78).

Successful VIV implantation was defined as a procedure having all of the following: successful vascular access, delivery, and deployment of a device; successful retrieval of the delivery system; intended performance of the device with neither severe stenosis (mean aortic gradient >40 mm Hg or peak velocity >4 m/s) nor moderate or severe regurgitation; and the patient being transferred alive out of the catheterization suite. After the procedure, valve maximum/mean gradients were 28.4±14.1/15.9±8.6 mm Hg. The procedure was successful in 93.1% of attempts, and 95% of patients had one degree or less of aortic regurgitation post-procedure. Adverse procedural outcomes included initial device malposition in 15.3% of cases and ostial coronary obstruction in 3.5%. Overall mortality was 8.4% at 30 days and 16.3% at one year. At 30 days follow-up, 84.1% of patients were in NYHA functional Class I or II. One-year follow-up was obtained in 87 patients, with 85.8% survival of treated patients. The authors report that “a randomized controlled trial comparing reoperative SAVR and VIV in patients with failed bioprostheses has never been executed, and because VIV treatment is still infrequent, it will be quite difficult to conduct such a trial. As a result, there are not enough data to justify VIV instead of reoperation in most high-risk patients with failed aortic bioprostheses. Nevertheless, VIV could be an acceptable approach in carefully selected high-risk patients and in those considered as having no option (i.e., those with no other effective treatment option for their illness)”.

Phan et al. (2016) performed a systematic review to compare outcomes of transcatheter valve-in-valve (VIV) implantation for degenerated aortic bioprostheses to redo conventional aortic valve replacement (cAVR). A total of 18 retrospective and prospective studies (n=823) were included. Pooled analysis demonstrated VIV achieved significant improvements in mean gradient (38 mmHg preoperatively to 15.2 mmHg postoperatively, p<0.001) and peak gradient (59.2 to 23.2 mmHg, p=0.0003). These improvements were similar to the outcomes achieved by cAVR. The incidence of moderate paravalvular leaks (PVL) were significantly higher for VIV compared to cAVR (3.3% vs. 0.4%, p=0.022). In terms of morbidity, VIV had a significantly lower incidence of stroke (1.9% vs. 8.8%, p=0.002) and bleeding (6.9% vs. 9.1%, p=0.014) compared to redo cAVR. Perioperative mortality rates were similar for VIV (7.9%) and redo cAVR (6.1%, p=0.35). The authors concluded that transcatheter VIV implantation achieves similar hemodynamic outcomes, with lower risk of strokes and bleeding but higher PVL rates compared to redo cAVR. Additional randomized studies and prospective registries are needed to compare the effectiveness of transcatheter VIV with cAVR, and clarify the rates of PVLs.

Raval et al. (2014) performed a systematic review to evaluate the effectiveness and outcomes of ViV implantation using transcatheter heart valves in aortic, mitral, pulmonary, tricuspid positions. 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. The authors reported that long-term follow-up of treated patients will be necessary to establish the true role of ViV implantation for bioprosthetic degeneration.

Hayes Medical Technology Report

The updated 2015 Hayes, Inc. Medical Technology Directory Report, Transcatheter Surgical Valve Implantation (TAVI) Versus Surgical Aortic Valve Replacement (SAVR) for Aortic Stenosis, summarized the available evidence for TAVI. The Hayes evidence findings state that the evidence base consists of three randomized controlled trials with two follow-up publications, four prospective and/or retrospective cohort studies, and six registry studies that examined TAVI and SAVR in patients with aortic stenosis (AS). Findings suggest that for patients with severe AS at medium to high surgical risk, TAVI and SAVR exhibit comparable efficacy. The rate of procedural success for TAVI appears to be high across studies, although it is difficult to compare with relative SAVR success as at least some TAVI failures convert to SAVR. Safety is generally comparable between the two procedures, with the exception of one complication associated with the TAVI procedure: pacemaker implantation. Pacemaker implantation rates were higher in TAVI-treated patients (9 of 11 studies). This risk may
be significant and should be considered for the use of TAVI in surgery-eligible patients. Definitive patient selection criteria for TAVI in patients with severe AS have not been established. However, sufficient evidence exists to support the use of TAVI in patients with severe AS who are judged by a heart team to be at high or greater surgical risk. There was a paucity of evidence regarding the comparative safety of TAVI versus SAVR, particularly risk of pacemaker implantation with TAVI, in patients with severe AS who are at less-than-high surgical risk (Hayes, 2013a, updated 2015, 2016, 2017).

**Professional Societies/Organizations:** The 2017 focused update to the 2014 American College of Cardiology (ACC) and American Heart Association (AHA) Practice Guideline for the Management of Patients with Valvular Heart Disease has the following recommendations for surgical or transcatheter AVR (TAVR) (Nishimura, et al., 2014, 2017). Guideline recommendations are classified as Class I (Strong), Class IIa (Moderate), Class IIb (Weak), Class III (No Benefit: Moderate) and Class III (Harm: Strong). For each Class the Guideline identified suggested phrases for writing recommendations. The classification system is described as follows: Class (Strength) of Recommendation (COR):

- **Class I (Strong):** Benefit >> Risk; Suggested phrases for writing recommendations:
  - Is recommended
  - Is indicated/useful/effective/beneficial
  - Should be performed/administered/other
  - Comparative Effectiveness Phrases†:
    - Treatment/strategy A is recommended/indicated in preference to treatment B
    - Treatment A should be chosen over treatment B

- **Class IIa (Moderate):** Benefit > Risk; Suggested phrases for writing recommendations:
  - Is reasonable
  - Can be useful/effective/beneficial
  - Comparative Effectiveness Phrases†:
    - Treatment/strategy A is probably recommended/indicated in preference to treatment B
    - It is reasonable to choose treatment A over treatment B

- **Class IIb (Weak):** Benefit ≥ Risk; Suggested phrases for writing recommendations:
  - May/might be reasonable
  - May/might be considered
  - Usefulness/effectiveness is unknown/unclear/uncertain or not well established

- **Class III: No Benefit (Moderate) Benefit=Risk; (Generally Level of evidence (LOE) A or B use only).**
  - Suggested phrases for writing recommendations:
    - Is not recommended
    - Is not indicated/useful/effective/beneficial
    - Should not be performed/administered/other

- **Class III: Harm (Strong):** Risk > Benefit; Suggested phrases for writing recommendations:
  - Potentially harmful
  - Causes harm
  - Associated with excess morbidity/mortality
  - Should not be performed/administered/other

The Level (Quality) of Evidence supporting each recommendation is classified as follows:

- **Level A:**
  - High quality evidence‡ from more than 1 RCT
  - Meta-analyses of high-quality RCTs
  - One or more RCTs corroborated by high-quality registry studies

- **Level B-R: (Randomized)**
  - Moderate-quality evidence‡ from 1 or more RCTs
  - Meta-analyses of moderate-quality RCTs

- **Level B-NR: (Nonrandomized)**
  - Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
• Meta-analyses of such studies
Level C-LD: (Limited Data)
• Randomized studies or nonrandomized observational or registry studies with limitations of design or execution
• Meta-analyses of such studies
• Physiological or mechanistic studies in human subjects
Level C-LD: (Expert Opinion): Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†For comparative-effectiveness recommendations (COR I and IIa; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

The following recommendations for surgical or transcatheter AVR and prosthetic valve stenosis are included in the 2017 focused update to the 2014 guideline:

Class I
• For patients in whom TAVR or high-risk surgical AVR is being considered, a Heart Valve Team consisting of an integrated, multidisciplinary group of healthcare professionals with expertise in valvular heart disease, cardiac imaging, interventional cardiology, cardiac anesthesia, and cardiac surgery should collaborate to provide optimal patient care. (Level of Evidence: C)

Class I
• Surgical AVR is recommended for symptomatic patients with severe AS (Stage D) and asymptomatic patients with severe AS (Stage C) who meet an indication for AVR when surgical risk is low or intermediate. (Level of Evidence: B-NR)

Class I
• TAVR is recommended for symptomatic patients with severe AS (Stage D) and a prohibitive risk for surgical AVR who have predicted post-TAVR survival greater than 12 months. (Level of Evidence: A)

Class I
• Surgical AVR or TAVR is recommended for symptomatic patients with severe AS (Stage D) and high risk for surgical AVR, depending on patient-specific procedural risks, values, and preferences. (Level of Evidence: A)

Class Ila:
• TAVR is a reasonable alternative to surgical AVR for symptomatic patients with severe AS (Stage D) and an intermediate surgical risk, depending on patient-specific procedural risks, values, and preferences. (Level of Evidence: B-R)
• For severely symptomatic patients with bioprosthetic aortic 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 valve-in-valve procedure is reasonable. (Level of Evidence: B-NR)

Class IIb:
• Percutaneous aortic balloon dilation may be considered as a bridge to surgical AVR or TAVR for symptomatic patients with severed AS. (Level of Evidence: C)

Class III: No Benefit
• TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS. (Level of Evidence: B)

An ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement (TAVR) (Holmes et al., 2012) was published with involvement of twelve professional societies to examine the current state of the evidence, facilitate integration of this technology as one of the available therapeutic options for patients with aortic valvular stenosis, and enable responsible adoption and diffusion of this promising technology. The authors note that the document is focused on published data; but there is a single completed randomized trial, although others are in progress or planned. Much of the data is therefore based upon information from studies and registries, which are frequently retrospective and include self-reported clinical events rather than adjudicated events.

The expert consensus document states that TAVR offers new and potentially transformational technology for patients with severe aortic valvular stenosis who are either extremely high-risk candidates or inoperable for surgical aortic valve replacement (AVR) or who are inoperable due to associated comorbidities. In the future, this technology may be utilized in lower risk surgical candidates.

The consensus document summarizes current recommendations for treatment of patients with aortic stenosis, including surgical aortic valve replacement, transcatheter aortic valve replacement, balloon aortic valvuloplasty, and medical therapy (refer to Appendix A, below). The document provides the following observations and recommendations regarding transcatheter aortic valve replacement:

• Complex Technology: Although the technique and equipment continue to evolve, TAVR is a complex procedure with many interlocking steps that require meticulous attention to achieve optimal results and minimize complications.

• Team-Based Approach: A foundational requirement of TAVR is a team-based approach to patient care. Given the high-risk profile of patients, who often have multiple comorbidities, as well as the technical complexity of the procedure involved, this team-based care will need to include multiple contributors at different stages in the process but will be mainly centered around the primary cardiologist, the cardiovascular surgeon, and the interventional cardiologist. Patients and families must be included in the care team. Other team members will include cardiac anesthesiologists, heart failure specialists, structural heart disease physicians, imaging specialists and the nursing care team, among others.

• Patient Selection: In adults with severe, symptomatic, calcific stenosis of a trileaflet aortic valve who have aortic and vascular anatomy suitable for transcatheter aortic valve replacement (TAVR) and a predicted survival >12 months:
  - TAVR is recommended in patients with prohibitive surgical risk.
  - TAVR is a reasonable alternative to surgical aortic valve replacement (AVR) in patients at high surgical risk

Prohibitive surgical risk is defined as:
• An estimated 50% or greater risk of mortality or irreversible morbidity at 30 days (as assessed by one cardiologist and two cardiothoracic surgeons), or other factors such as frailty, prior radiation therapy, porcelain aorta, and severe hepatic or pulmonary disease.

Suitable aortic and vascular anatomy is defined as:
• Both aortic annulus size and valve plane to coronary ostium height suitable for placement of an available TAVR.
• Adequate vascular access for passage of the TAVR system (femoral iliac, subclavian, axillary) or suitability for an apical implantation approach.

TAVR is not currently recommended because of limited available information in adults who have:
• An acceptable surgical risk for conventional surgical aortic valve replacement
• Known bicuspid aortic valve
• Failing bioprosthetic aortic valve
• Severe mitral annular calcification or severe mitral regurgitation
• Moderate aortic stenosis
• Other (e.g., severe aortic regurgitation and subaortic stenosis)

In the above groups, additional scientific data will need to be collected to ascertain risk/benefit ratio prior to integration into routine clinical care.

Summary—Transcatheter Aortic Valve Implantation: Transcatheter aortic valve implantation (TAVI) also referred to as transcatheter aortic valve replacement (TAVR) has been proposed as a less invasive alternative to conventional surgical valve replacement. Conventional valve replacement requires general anesthesia, a sternotomy, and heart-lung bypass. A significant percentage of patients with severe aortic stenosis are not considered suitable candidates for surgical aortic valve replacement due to the presence of significant comorbidities. Although evidence published to date is limited, and long-term outcomes have not been fully defined, TAVI may be a reasonable alternative to open heart surgery in carefully selected high-risk patients with severe symptomatic aortic stenosis who meet the FDA-specified indications for use.

At this time there is insufficient evidence in the peer-reviewed scientific evidence to determine the safety and effectiveness of TAVR for the treatment of patients at intermediate or low risk for open surgical repair. There is a paucity of evidence regarding the comparative safety of TAVI versus SAVR, particularly risk of pacemaker implantation with TAVI, in patients with severe aortic stenosis who are at less than high surgical risk.

Evidence in the peer-reviewed literature related to the use of TAVI for valve-in-valve replacement after failed TAVI or degenerated bioprosthetic valve consists primarily of a registry study and small case series. There is insufficient evidence in the published medical literature to demonstrate the safety and efficacy of this procedure compared with surgical repair.

Pulmonary Valve
In the healthy heart, deoxygenated blood flows from the right ventricle through the right ventricular outflow tract (RVOT), an extension of the ventricular cavity, which connects to the pulmonary artery, from where it enters the lungs. The pulmonary valve lies between the right ventricle and the pulmonary artery. It opens and closes with each heart beat and prevents a backflow of blood. Defects in the RVOT and pulmonary valve impede blood flow from the right ventricle to the lungs

Congenital heart defects are the most common cause of RVOT and pulmonary valve dysfunction. The most common congenital heart defects affecting the RVOT and pulmonary valve include: tetralogy of Fallot, pulmonary atresia, transposition of the great arteries, and double outlet right ventricle.

Percutaneous pulmonary valve implantation (PPVI), also referred to as transcatheter or catheter-based pulmonary valve implantation or replacement, is a minimally invasive heart surgery in patients with right ventricular outflow tract (RVOT) defects. The procedure involves the deployment and placement of a pulmonary valve prosthesis via a catheter inserted into a vein. The purpose of PPVI is to delay the need for surgical repair of a dysfunctional RVOT. PPVI is proposed to offer minimal invasiveness and avoids cardiopulmonary bypass. The technique is intended to reduce the number of open heart surgeries with their associated risks and complications (Hayes, 2013b).

Presently there are two PPVI systems that are available: the Medtronic Melody® Transcatheter Pulmonary Valve (Medtronic, Inc., Santa Ana, CA) and the Edwards SAPIEN™ XT Transcatheter Heart Valve and Accessories [Edwards Lifesciences, LLC, Irvine, CA].

The Melody device consists of a segment of bovine jugular vein with a thinned down venous wall containing a native, central competent venous valve. This bovine valve is attached to a platinum/iridium stent with a length of 28 mm and diameter of 18 mm that can be crimped to a size of 6 mm and re-expanded up to 22 mm.
The Edwards SAPIEN XT Transcatheter Heart Valve is comprised of a balloon-expandable, radiopaque, cobalt-chromium frame, trileaflet bovine pericardial tissue valve, and polyethylene terephthalate fabric skirt. The NovaFlex+ delivery system is used for delivery of the Edwards SAPIEN XT.

Transcatheter pulmonary valve (TPV) placement was first reported in 2000. Beginning in January 2007, the Melody® TPV (Medtronic, Inc., Santa Ana, CA) was implanted in 150 patients at five US centers under an Investigational Device Exemption (IDE) protocol for treatment of right ventricular outflow tract (RVOT) dysfunction. In January 2010, enrollment in the US Melody Valve IDE trial was completed, and the Melody valve was approved for placement in dysfunctional RVOT conduits as a palliative measure aimed at delaying surgical intervention (McElhinney, et al., 2011). The trial was initially designed to follow patients for five years after implantation or until explantation, but was modified in 2011 to allow follow-up out to 10 years in patients who provided supplemental written informed consent (Cheatham, et al., 2015).

In January 2015 the Melody TPV received Pre-Market Approval (PMA) from the U.S. Food and Drug Administration (FDA) approval based on clinical evidence from three clinical studies that followed patients implanted with Melody TPV (i.e., the Melody U.S. IDE Study, the Melody U.S. Post Approval Study [PAS] and the European and Canadian Post-Market Surveillance Study [PMSS]).

In February 2016 the SAPIEN XT Transcatheter Heart Valve received Pre-Market Approval (PMA) from the U.S. Food and Drug Administration (FDA) approval based on clinical evidence from the CONgenital Multicenter trial of Pulmonic vAlve regurgitation Studying the SAPIEN InterventIONal (COMPASSION) THV trial.

U.S. Food and Drug Administration (FDA)—Medtronic Melody® Transcatheter Pulmonary Valve (Medtronic, Inc., Santa Ana, CA): The Medtronic Melody® Transcatheter Pulmonary Valve (Model PB10) and Medtronic Ensemble® Transcatheter Valve Delivery System (NU10) received FDA approval through the Humanitarian Device Exemption (HDE) program on January 25, 2010.

The Melody™ Transcatheter Pulmonary Valve, models PB1016 and PB1018 Ensemble™ Transcatheter Valve Delivery System, models NU1018, NU1020, and NU1022 received FDA approval through the PMA process on January 27, 2015 (P140017). According to the PMA approval order, the Melody Transcatheter Pulmonary Valve 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) RVOT conduit that was equal to or greater than 16 mm in diameter when originally implanted and
- Dysfunctional Right Ventricular Outflow Tract (RVOT) conduits with a clinical indication for intervention, and either:
  - regurgitation: ≥ moderate regurgitation, and/or
  - stenosis: mean RVOT gradient ≥ 35 mmHg

Enrollment in the pre-market Investigational Device Exemption (IDE) study was limited to patients who met the following inclusion criteria:

- age ≥ 5 years of old
- weight ≥ 30 kg
- existence of a full (circumferential) RVOT conduit ≥ 16 mm in diameter when originally implanted, or a stented bioprosthesis with a rigid circumferential sewing ring in the RVOT that has an internal diameter ≥ 18 mm and ≤ 22 mm when originally implanted
- Any of the following by transthoracic echocardiography
  - For patients in NYHA Classification II, III, or IV:
    - Moderate (3+) or severe (4+) pulmonary regurgitation, or
    - Mean RVOT gradient ≥ 35 mmHg
  - For patients in NYHA Classification I:
    - Severe (4+) pulmonary regurgitation with RV dilatation (Z-score for tricuspid annular diameter ≥ 2.0) or dysfunction (RV fractional area change < 40%), or
Patients were not permitted to enroll in the pre-market IDE study if they met any of the following exclusion criteria:

- active endocarditis
- a major or progressive non-cardiac disease (e.g. liver failure, renal failure, cancer) that results in a life expectancy of less than one year
- patient or guardian unwilling or unable to provide written informed consent or comply with follow-up requirements
- obstruction of the central veins (including the superior and inferior vena cava, bilateral iliac veins) such that the delivery system cannot be advanced to the heart via transvenous approach from either femoral vein or internal jugular vein
- positive urine or serum pregnancy test 24 hours prior to procedure in female patients of child bearing potential
- known intravenous drug abuse

**Edwards SAPIEN™ XT Transcatheter Heart Valve and Accessories [Edwards Lifesciences, LLC, Irvine, CA]:** The SAPIEN XT Transcatheter Heart Valve and Accessories received FDA approval through the PMA process on February 29, 2016 (P130009/S037). According to the PMA approval order, this device is indicated for use in pediatric and adult patients with a dysfunctional, non-compliant Right Ventricular Outflow Tract (RVOT) conduit with a clinical indication for intervention and pulmonary regurgitation ≥ moderate and/or mean RVOT gradient ≥ 35 mmHg.

The FDA SSED states that Edwards Lifesciences performed a clinical study to establish a reasonable assurance of safety and effectiveness of pulmonic implantation with the Edwards SAPIEN THV in patients with dysfunctional RVOT conduits in the United States under Investigational Device Exemption (IDE) #G060242 (entitled the COgenital Multicenter trial of Pulmonic vAlve regurgitation Studying the SAPIEN InterventIONal THV, "COMPASSION" trial). Data from this clinical study were the basis for the PMA approval decision.

The 2016 FDA PMA approval states that Edwards agreed to conduct a study to evaluate long-term safety and effectiveness of the SAPIEN XT THV in the pulmonic position for the intended patient population (especially pediatric) when used as indicated with all valve sizes. It is a single-arm, prospective, multicenter post approval study using a performance goal based on the original COMPASSION trial. The study patients are pediatric and adult patients with a dysfunctional, non-compliant right ventricular outflow tract (RVOT) conduit with a clinical indication for intervention and pulmonary regurgitation ≥ moderate and/or mean RVOT gradient ≥ 35 mmHg. The eligibility criteria will be consistent with the final FDA-approved IFU and labeling. A sample size of 162 subjects is required for the hypothesis test on the primary effectiveness endpoint with at least 80% of the power. A total of 191 patients will be enrolled at up to 10 sites in the US to account for loss to follow-up. The patients will be followed at hospital discharge, 30 days, 1 year and annually thereafter through 5 years.

**Literature Review—Transcatheter Pulmonary Valve (TPV) Implantation**

**Melody U.S. IDE Studies:** Cheatham et al. (2015) evaluated the midterm hemodynamic and clinical outcomes in the U.S. Melody Valve IDE trial patients (n=148), who were all at least four years out from Melody valve implantation. The nonrandomized IDE trial prospectively enrolled pediatric and adult patients (median age, 19 years) with right ventricular outflow tract conduit obstruction or regurgitation. The patients received and were discharged with a TPV were followed up annually according to a standardized protocol. During a median follow-up of 4.5 years (range, 0.4-7 years), 32 patients underwent right ventricular outflow tract 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 TPV explanted as an initial or second reintervention. Five-year freedom from reintervention and explantation was 76±4% and 92±3%, respectively. A conduit prestent and lower discharge right ventricular outflow tract gradient were associated with longer freedom from reintervention. In the 113 patients who were alive and reintervention free, the follow-up gradient (median, 4.5 years after implantation) was unchanged from early post-TPV replacement, and all but 1 patient had mild or less pulmonary regurgitation. Almost all patients were in New York Heart Association class I.
or II. More severely impaired baseline spirometry was associated with a lower likelihood of improvement in exercise function after TPV replacement. The authors reported that TPV replacement with the Melody valve provided good hemodynamic and clinical outcomes up to 7 years after implantation. Primary valve failure was rare. The main cause of TPV dysfunction was stenosis related to stent fracture, which was uncommon once prestenting became more widely adopted.

One of the clinical and regulatory concerns with the Melody valve has been fracture of the balloon-expandable stent in which the bovine jugular venous valve is housed. In early reports from Europe, survival free from Melody valve stent fracture (MSF) was 85% at 1 year and 75% at 2 years after implant. A similar trend was observed in preliminary analyses of the U.S. Melody Valve IDE cohort. McElhinney et al. (2011) assessed risk factors for Melody stent fracture (MSF), valve dysfunction, and reintervention after TPV placement in the complete IDE cohort after all patients had reached the 1-year follow-up interval (n=150). Existing conduit stents from a prior catheterization were present in 37 patients (25%, fractured in 12); 1 or more new prestents were placed at the TPV implant catheterization in 51 patients. During follow-up (median, 30 months), MSF was diagnosed in 39 patients. Freedom from a diagnosis of MSF was 77±4% at 14 months (after the 1-year evaluation window) and 60±9% at 39 months (3-year window). On multivariable analysis, implant within an existing stent, new prestent, or bioprosthetic valve (combined variable) was associated with longer freedom from MSF (p<0.001), whereas TPV compression (p=0.01) and apposition to the anterior chest wall (p=0.02) were associated with shorter freedom from MSF. Freedom from RVOT reintervention was 86±4% at 27 months. Among patients with a MSF, freedom from RVOT reintervention after MSF diagnosis was 49±10% at 2 years. Factors associated with reintervention were similar to those for MSF. The authors reported that MSF was common after TPV implant and was more likely in patients with severely obstructed RVOT conduits and when the TPV was directly behind the anterior chest wall and/or clearly compressed. A TPV implant site protected by a prestent or bioprosthetic valve was associated with lower risk of MSF and reintervention.

McElhinney et al. (2010) evaluated short and medium-term outcomes in the expanded Melody U.S. Trial (n=136). Implantation was attempted in 124 patients, and was achieved successfully in all except one. Placement was not attempted in the other 12 patients due to the risk of coronary artery compression (n=6) or other clinical or protocol contraindications. There was one death from intracranial hemorrhage after coronary artery dissection, and one valve was explanted after conduit rupture. The median peak RVOT gradient was 37 mm Hg prior to implantation and 12 mm Hg immediately following implantation. Pulmonary regurgitation (PR) was moderate or severe in 92 patients prior to implantation, and no patient had greater than mild PR immediately after implantation or during follow-up (≥ one year in 65 patients). Freedom from stent fracture was 77.8% ± 4.3% at 14 months, and freedom from Melody valve dysfunction or reintervention was 93.5 ± 2.4% at one year. A higher RVOT gradient at discharge and younger age were associated with shorter freedom from dysfunction.

The Melody U.S. Clinical Trial (n=34) was designed to evaluate the safety, procedural success, and short-term effectiveness of the Melody transcatheter pulmonary valve in patients with dysfunctional right ventricular outflow tract conduits. Early results were published by Zahn et al. (2009). Patients underwent catheterization for intended Melody valve implantation at three centers between January and September, 2007. The mean age was 19.4 ± 7.7 years. Doppler mean gradient was 28.8 ± 10.1 mm Hg, and 94% of patients had moderate or severe pulmonary regurgitation (PR). Implantation was successful in 29 of 30 attempts, and not attempted in four patients. Complications included one conduit rupture requiring urgent surgery and device removal, one distal pulmonary artery guidewire perforation, and one instance of wide complex tachycardia. Peak systolic conduit gradient fell from 37.2 ± 16.3 mm Hg to 17.3 ± 7.3 mm Hg. None of the patients had more than mild PR. At 6-months, conduit Doppler mean gradient was 22.4± 8.1 mm Hg, and pulmonary regurgitation fraction as measured by magnetic resonance imaging was significantly improved (3.3 ± 3.6% vs. 27.6 ± 13.3%, p<0.0001). Stent fracture occurred in 8 of 29 implants. Three of these patients were subsequently treated with a second Melody valve for recurrent stenosis during follow-up. The authors concluded that implantation of the Melody valve for RVOT conduit dysfunction can be performed by experienced operators and appears safe, and has encouraging acute and short-term outcomes. Longer follow-up and a larger patient experience are needed to determine the ultimate role of this therapy in the treatment of conduit dysfunction.

Melody U.S. Post Approval Study: In a multicenter prospective nonrandomized study, Armstrong et al. (2014) evaluated the short-term effectiveness of the Melody TPV. This study sought to confirm if the short-term hemodynamic effectiveness of the Melody TPV achieved by real-world providers is equivalent to the historical
results established in the initial five-center Investigational Device Exemption trial. Patients with dysfunctional RVOT conduits were entered in this study at 10 centers. The primary endpoint was acceptable hemodynamic function at six 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 six 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 two patients required reoperation for conduit replacement. The rate of freedom from TPV dysfunction was 96.9% at 1 year.

**SAPIEN COMPASSION Study:** The ongoing COMPASSION study (Clinicaltrials.gov number NCT00676689) was considered in the PMA approval process (FDA, 2016). Per the FDA Summary of Effectiveness and Safety Data (SSED), this prospective, non-randomized, seven center study (n=69) assessed the safety and effectiveness of pulmonic implantation of the SAPIEN THV. The SAPIEN THV is the first generation valve of the SAPIEN device line and is no longer available for distribution. Patient inclusion criteria: weight ≥ 35 kilograms; in situ conduit size of 20-26 mm in diameter; moderate or severe pulmonary regurgitation defined as ≥ 3+ pulmonary regurgitation (PR) by transthoracic echocardiogram (TTE) or RVOT conduit obstruction with a mean gradient of ≥ 35 mmHg by TTE; symptomatic as evidenced by cardiopulmonary exercise testing; catheterization was determined to be feasible by the treating physician. All patients were scheduled to return for follow-up examinations at day 1 post-procedure, discharge, 30 days, 6 months, 12 months, and annually thereafter for 5 years postoperatively. Primary outcome measure was freedom from device- or procedure-related death and/or reintervention at one year. The secondary endpoints included:

1) Freedom from Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 6 months. MACCE was defined as all-cause mortality, myocardial infarction, reintervention, vascular injury resulting in the need for an unplanned vascular intervention, stroke and pulmonary embolism.

2) Functional improvement at six months as defined by:
   a. Improved valve hemodynamics as demonstrated via TTE:
      i. Decrease in pulmonary regurgitation to mild or less for regurgitant lesions
      ii. Decrease in mean pulmonary gradient to less than 30mmHg for stenotic lesions
      iii. Improvement in both i) and ii) above for mixed lesions
   b. Improvement of ≥ 1 NYHA functional class from baseline for patients with NYHA functional class ≥ 2 at baseline.
   c. Freedom from recurrent pulmonary stenosis.

Freedom from device- or procedure-related death and/or reintervention at 1 year met the pre-specified performance goal of 75%. At 5 years, the freedom from device- or procedure-related death and/or reintervention was 77.1%. There were no device- or procedure-related patient deaths at 5 years. Freedom from surgical pulmonic valve repair was 98.3% at 1 year and 91.8% at 5 years. Freedom from transcatheter pulmonic valve implantation was 97.1% at 1 year and 85.8% at 5 years. Freedom from balloon valvuloplasty was 100% at 1 year and 93.7% at 5 years. Freedom from other types of reintervention was 100% at 1 year and 97.9% at 5 years. Two patients experienced a device migration (2/79, 2.5%) early in the study. The instructions for use were modified; no other device migrations occurred in the study after this modification. Serious Adverse Events (SAE) for RVOT conduit ruptures occurred in 5/79 (6.3%) patients. These 5 ruptures were related to balloon valvuloplasty or placement of a pre-stent and no ruptures occurred during placement of the SAPIEN THV. Functional improvement at 6 months reported a decrease in pulmonary regurgitation to mild or less in 96.2% of patients; improved pulmonary stenosis mean gradient was 93.8%; functional improvement in NYHA was 92.2%; and freedom from recurrent pulmonary stenosis was 100%. Improvement in conduit mean gradient decreased from 21.1±14.3 mmHg at baseline to 10.1±7.2 mmHg at 30 days 10.0 ± 7.3 mmHg at 1 year and 12.8±7.8 mmHg at 5 years. An improvement in conduit peak gradient was demonstrated, as it decreased from 37.2±25.5 mmHg at baseline to 18.7±15.0 mmHg at 30 days, 17.4 ± 12.1 mmHg at 1 year and 21.6±14.5 mmHg at 5 years. Moderate/severe pulmonary regurgitation decreased from 90% at baseline to 2% at 30 days, 4 % at 1 year and 0% at 5 years. There was a trend showing patient functional improvement over time, as 22% of the patients were in NYHA class 1 at baseline, 84% at 1 year and 94% at 5 years.
Chowdhury et al. (2013) conducted a prospective, multicenter study (COMPASSION study) to evaluate echocardiographic changes at 1 and 6 months after SAPIEN valve implantation in the pulmonary position (n=33). Pulmonary valve function and the right ventricle after SAPIEN TPV placement were evaluated. Inclusion criteria: weight ≥35 kg; conduit size ≥16 mm and ≤24 mm; moderate or severe PR; symptoms as evidenced by cardiopulmonary exercise testing. PPVI significantly improved peak and mean conduit stenosis gradient; RV end-diastolic area; RV end-systolic area; indexed RV end-diastolic area; tricuspid regurgitation (TR) peak gradient; indexed TR jet area (>0.01 for all measures). The benefit was maintained for 6 months. Proportion of patients with grade ≥2 PR was reduced from 94% at baseline to 12% at 6 mos (p<0.01). Complications were not reported. Limitations of this study include small sample size and short-term follow-up.

Kenny et al. (2011) conducted a phase 1 U.S. Food and Drug Administration–approved clinical trial (COMPASSION study) to evaluate the safety and effectiveness of the Edwards SAPIEN transcatheter heart valve in the pulmonary position in patients with moderate to severe pulmonary regurgitation with or without stenosis. This prospective, multicenter uncontrolled study included 36 patients from 4 centers (3 in the United States and 1 in Europe). Follow-up was 6 months. The study included patients with dysfunctional right ventricle (RV)-pulmonary artery (PA) conduit; body weight ≥35 kg; in situ conduit diameter ≥16 mm and ≤24 mm. Patients had varied clinical histories. Primary and secondary outcome measures are outlined in the above study. Device success was achieved in 31 of 36 patients (86.1%). Hemodynamic measures, conduit peak and mean gradient, estimated RV pressure, pulmonary regurgitant fraction (%), RV end diastolic volume (mL/m2), pulmonary regurgitation severity, cardiopulmonary exercise testing, NYHA functional class improved from baseline to 6 months. Freedom from reintervention was 97% with 1 patient undergoing elective placement of a second valve due to conduit-induced distortion of the initial implant. Complications included PPV migration (9.1%); pulmonary hemorrhage (6.1%); ventricular fibrillation (3%); stent embolization to RV (3%). This study was limited by small sample size and lack of long-term follow-up.

**Additional Studies:**

Butera et al. (2013) conducted a prospective, multicenter web-based registry study of percutaneous pulmonary valve implantation (PPVI) with the Melody valve. The registry was of the Italian Society of Pediatric Cardiology. 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 occurred in almost 20% of patients during follow-up. The authors concluded that longer follow-up and larger series are needed.

Vezmar et al. (2010) conducted a case series to evaluate the physiological and clinical consequences of percutaneous pulmonary valve implantation (PPVI) in patients with chronic right ventricular outflow tract (RVOT) obstruction and volume overload (n=28). Of 28 patients, 16 had the Melody valve implanted within a bioprosthetic valve. The procedure resulted in acute improvement in symptoms, hemodynamic status and objective findings of exercise performance. There were no acute device-related complications, with stent fractures were noted in 10.8% of patients. Early follow-up demonstrated persistent improvement in ventricular parameters, PR, and objective exercise capacity.

Eiken et al. (2011) published results of 102 consecutive percutaneous pulmonary valve implantations, using the Melody valve, performed at two centers in Germany between 2006 and 2010. The median patient age was 21.5 years. Sixty-one patients had undergone surgical correction of a Tetralogy of Fallot/pulmonary atresia with ventricular septal defect, and 14 had a common arterial trunk; the remaining patients had been treated surgically for transposition of the great arteries (n=9) or aortic stenosis (n=8), or had a variety of other cardiac lesions (n=10). The majority of conduits (79) used during previous surgery were homografts. The median peak systolic RVOT gradient between the right ventricle and the pulmonary artery decreased immediately following the procedure from 37 mmHg (29–46 mmHg) to 14 mmHg (9–17 mmHg, p< 0.001). Pulmonary regurgitation assessed by MRI was reduced from a median of 16% (5–26%) to 1% (0–2%, p<0.001). The median end-diastolic RV-volume index also decreased significantly (p=0.001). One patient died due to compression of the left coronary artery. At a median follow-up of 357 days (99–388 days), the mean doppler gradient in the RVOT decreased from a pre-procedure median of 36 mmHg (26–44) to a median of 15 mmHg (12–20) at the latest follow-up (p<0.0001). The authors concluded that PPVI can be performed by an experienced structural heart disease interventionalist in patients with RVOT dysfunction. Medium and long term follow up needs to be assessed to document sustained benefit, however. It remains to be proved whether the improvements in
hemodynamics persist, and the goal to reduce the number of cardiothoracic operations during the lifetime of the patient can be achieved.

**Non-FDA-approved uses of Transcatheter Pulmonary Valve (TPV) Implantation:** There are numerous potential off-label uses of TPV Implantation that have been reported in the literature such as use in native and postsurgical, nonconduit RVOT. These include use of FDA-approved devices for non-FDA-approved indications and use of devices that are not FDA-approved. Generally these studies are small non-comparative studies lacking long-term follow-up (Cools, et al., 2015; Meadows, et al., 2014; Demkow, et al., 2014; Boshoff, et al., 2013; Odemis, et al., 2013).

**Professional Societies/Organizations**

The ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease does not include recommendations for transcatheter pulmonary valve implantation (Warnes, et al., 2008).

**Hayes Medical Technology Report**
An updated 2016 Hayes, Inc. Medical Technology Directory Report, Percutaneous Pulmonary Valve Implantation for Right Ventricular Outflow Tract Defects, reports that two percutaneous pulmonary valve implantation (PPVI) systems are available: the Medtronic Melody pulmonary valve and the Edwards SAPIEN valve. The Melody valve is the most researched percutaneous pulmonary valve system. The Edwards SAPIEN valve is used less frequently as a percutaneous pulmonary valve. The Hayes Directory Report states that the body of evidence is large in size and of low quality, consisting of observational studies. The available observational studies found generally consistent short-term benefits of PPVI for RVOT, with some results dependent on etiology and pathology of the pulmonary valve defect, operator experience, and procedure protocol. Most of the hemodynamic measures improved consistently across 22 observational studies (n=31-155). Only 6 observational studies (n=33-155) evaluated pulmonary regurgitation, but they reported significant improvement from baseline; 60%-100% of patients had no or only mild disease following PPVI; however, long-term pulmonary regurgitation severity remains unknown. Results from 11 observational studies were less consistent, with some showing significant improvements from baseline and others showing small improvements only. The PPVI procedure itself was technically successful in most cases, six studies reported procedure success rates ranging from 82.5%-100%; but reintervention was required in approximately 25%-33% of patients at 5-year follow-up. Overall, PPVI was relatively safe, compared with open chest surgery; however, it has caused severe, potentially life-threatening complications, including stent fracture (0% to 32%); compression or injury of the left coronary artery during the procedure (0.7% to 0.98%); endocarditis (0% to 10%), which may lead to bloodstream infections (9.5%). Seven deaths were definitively or possibly related to PPVI. There is a learning curve associated with PPVI, and experience with this technique improves outcomes and reduces the risk for complications (Hayes, 2013b; updated 2016; 2017).

**Summary—Transcatheter Pulmonary Valve Implantation:** Transcatheter pulmonary valve implantation has been explored as an alternative to conventional valve surgery for the treatment of pulmonary regurgitation and right ventricular outflow tract (RVOT) dysfunction. These conditions often occur in patients with previously repaired pulmonary valves. Pulmonary valve surgery requires cardiopulmonary bypass, and involves insertion of a pulmonary conduit, with or without a valve, to re-establish blood flow to the pulmonary artery. Conduits require frequent replacement due to patient growth and conduit degeneration. Although the published evidence is limited, transcatheter pulmonary valve implantation appears to be a reasonable alternative in carefully selected patients. This procedure may provide improved hemodynamic function and extend the longevity of the existing conduit, and may defer the need for conduit replacement, resulting in a reduction in the number of open heart surgeries required over a lifetime.

**Mitral Valve**
Mitral regurgitation (MR) is a diverse disease that results from dysfunction of any of the portions of the complex mitral valve apparatus, including the chords, leaflets, annulus, and left ventricle. MR is classified on the basis of two broad categories of dysfunction, namely primary (organic or degenerative) disease, which primarily affects
the leaflets (e.g., fibromuscular dysplasia, mitral valve prolapse, rheumatic disease), and secondary (ischemic or functional) diseases, which spare the leaflets (e.g., diseases of the atrium and ventricle, including ischemic dysfunction and dilated cardiomyopathy) (Herrmann, 2014).

Open mitral valve surgery is generally recommended for patients with significant symptomatic MR and those who have evidence of left ventricular dysfunction or enlargement. Although mitral valve regurgitation may recur within the first six months after surgical repair, the grade of MR generally remains stable beyond the first year of follow-up. Transcatheter treatments have been developed to treat valvular disease as an alternative to open surgical treatment.

Many different devices have been created for percutaneous MV repair which are in various stages of development. The only devices that have been evaluated in at least one clinical trial are the Carillon Mitral Contour System (Cardiac Dimensions, Inc., Kirkland, WA), which is an investigational device in the U.S., and the FDA-approved MitraClip Mitral Valve Repair System (Armstrong, et al., 2017; Hayes, 2014).

The MitraClip system consists of implant catheters and the MitraClip device, a permanent implant that attaches to the mitral valve leaflets. The procedure results in a double opening of the mitral valve that allows greater closure and reduces mitral regurgitation. Although the MitraClip has been used to treat both primary and secondary MR, it is currently U.S. FDA-approved for commercial use only in patients with 3 to 4+ primary (degenerative) MR. A multidisciplinary dedicated heart team approach (including primary [general] cardiologists, interventional cardiologists, cardiac surgeons, imaging specialists, valve and heart failure specialists, and cardiac anesthesiologists) is recommended for the evaluation and care of potential candidates for transcatheter mitral valve repair (Armstrong, et al., 2017).

Although the MitraClip is currently the only U.S. FDA-approved device for transcatheter MV repair, a number of other investigational devices are in various stages of development. Investigational transcatheter-based approaches include indirect annuloplasty, direct or left ventricular annuloplasty, hybrid surgical, chordal replacement, and left ventricular remodeling (Armstrong, et al., 2017; Herrmann, 2014).

Percutaneous MV repair for chronic severe secondary (functional) MR provides a less invasive alternative to surgery but is not approved for clinical use in the United States. The COAPT Trial is a clinical trial designed to study the safety and effectiveness of the MitraClip device in heart failure patients who have functional MR and are not appropriate for mitral valve surgery (ClinicalTrials.gov number: NCT01626079).

U.S. FDA–MitraClip Clip Delivery System (MitraClip CDS) (Abbott Vascular, Menlo Park, CA): The MitraClip CDS received FDA approval through the PMA process on October 24, 2013. It 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. The device is contraindicated in patients who cannot tolerate procedural anticoagulation or post procedural antiplatelet regimen, and those with active endocarditis of the mitral valve, rheumatic mitral valve disease, or evidence of intracardiac, inferior vena cava or femoral venous thrombus (FDA, 2013).

Literature Review: Percutaneous Mitral Valve Repair:
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). EVEREST II consists of a randomized arm and a high-risk registry arm (EVEREST II High Risk Registry [HRR] Study and EVEREST II REALISM) (Clinicaltrials.gov number NCT00209274).

EVEREST II Randomized Arm
Feldman et al (2015) reported five-year results of the EVEREST II study. Patients were randomized to percutaneous repair with the MitraClip device (n=184) or conventional mitral valve surgery (n=95) in a 2:1 ratio. Eligible patients had moderate-to-severe (3+) or (4+) chronic MR and were either symptomatic with left
ventricular ejection fraction (LVEF) >25% and LV end-systolic diameter ≤ 55 mm or asymptomatic with one or more of the following: LVEF 25% to 60%, LV end-systolic diameter ≥ 40 mm, new-onset atrial fibrillation, or pulmonary hypertension (pulmonary artery systolic pressure >50 mm Hg at rest or >60 mm Hg with exercise). The study compared treatment groups using the following endpoints through 5 years within the all-treated cohort: 1) freedom from death, surgery for MV dysfunction, and 3+ and 4+ MR; 2) freedom from death; 3) freedom from surgery for MV dysfunction; and 4) freedom from death and surgery for MV dysfunction. At 5 years, the rate of the composite endpoint of freedom from death, surgery, or 3+ or 4+ MR in the as-treated population was 44.2% versus 64.3% in the percutaneous repair and surgical groups, respectively (p=0.01). The difference was driven by increased rates of 3+ or 4+ MR (12.3% vs. 1.8%; p=0.02) and surgery (27.9% vs. 8.9%; p=0.003) with percutaneous repair. After percutaneous repair, 78% of surgeries occurred within the first 6 months. Beyond 6 months, rates of surgery and moderate-to-severe MR were comparable between groups. Five-year mortality/death rates were 20.8% and 26.8% (p=0.4) for percutaneous repair and surgery, respectively.

Four-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation were published by Mauri et al., for the EVEREST II Investigators (2013). Patients with grade 3+ or 4+ mitral regurgitation (MR) were randomized to percutaneous repair with the MitraClip device (n=184) or conventional mitral valve surgery (n=95) in a 2:1 ratio. The rate of the composite endpoint of freedom from death, surgery, or grade 3+ or 4+ MR at four years in the intention-to-treat population was 39.8% vs. 53.4% in the percutaneous repair group and surgical groups, respectively (p=0.070). Rates of death were 17.4% in the percutaneous repair group vs. 17.8% in the surgical group (p=0.914), and 3+ or 4+ MR was present in 21.7% in the percutaneous group vs. 24.7% in the surgical group (p=0.745). Surgery for mitral valve dysfunction was required in 29.4% in the percutaneous group vs. 2.2% in the surgical group at one year (p<0.001) and 24.8% vs. 5.5% at four years (p<0.001). The authors concluded that patients treated with percutaneous mitral valve repair more commonly required surgery to treat residual MR, although after the first year there were few surgeries required after either treatment, and there were no differences in the prevalence of moderate-severe and severe MR or mortality at four years.

**EVEREST II High Risk Registry Arm**

The EVEREST II High Risk Study, an arm of the EVEREST II study, was conducted to assess the safety and effectiveness of the MitraClip device in patients with significant MR at high risk of surgical mortality (Whitlow, et al., 2012). Outcomes of 78 patients with severe symptomatic functional or degenerative MR and an estimated surgical mortality rate of 12% or more were retrospectively compared to 58 patients who were screened but not enrolled. The comparator group received standard care over the twelve month period, with 86% managed medically and 14% undergoing mitral valve surgery. The major effectiveness endpoints for the study were freedom from death at 12 months, freedom from death and MR > 2+ at 12 months, and clinical measures of benefit at 12 months in surviving patients, defined as NYHA functional class, LV measurements, SF-36 Health Survey quality of life, and rehospitalizations for CHF. Protocol-predicted surgical mortality in the study group and comparator group was 18.2% and 17.4%, respectively. There were six procedure-related deaths, although there was no significant difference in 30-day mortality between the study group and comparator group (7.7% and 8.3%, respectively). The twelve-month survival rate was 76% in the study group and 55% in the comparator group (p=0.047). Of surviving patients in the study group with matched baseline and 12-month data, 78% had an MR grade of ≤ 2+; of these, a total of 33% had MR ≤ 1+ at 12 months. NYHA class and quality of life improved in the majority of patients.

**Additional Studies:** In a prospective, multi-center study, Glower et al. (2014) evaluated the safety and effectiveness of the MitraClip in patients from both of the EVEREST II high-risk studies who had completed 12 months of follow-up. Of 351 patients enrolled in either the Everest HRR (n=78) or the REALISM HR study (n=273) a total of 327 of 351 patients completed 12 months of follow-up. Seventy percent of patients had functional mitral regurgitation (MR). Following MitraClip implantation at discharge 325 patients (86%) had MR reduced to less than or equal to 2+. At 12 months, 225 patients (84%) had MR less than or equal to 2+. While 16.4% of patients had MR >2+ at one year, the rate of surgery was low at 2.2%. Survival at 12 months was 77.2%. Patients had improvements in quality of life scores and NYHA functional class. Major adverse events at 30 days included death in 4.8%, myocardial infarction in 1.1%, and stroke in 2.6%. Author reported study limitations state that this data was collected in a narrowly defined group of patients based on specific surgical risk factors and specific anatomic suitability for the MitraClip device. Whether the results can be generalized to
even higher-risk patients with life expectancies of <12 months is uncertain. There was no parallel surgical or medical control group in this study.

Maisano et al. (2013) published results from the ACCESS EU, a prospective multicenter nonrandomized post-approval study of MitraClip therapy in Europe. A total of 567 patients with severe MR were treated with MitraClip therapy at 14 European sites. Compared to patients in EVEREST II, patients in this study were older, presented with multiple comorbidities, and were determined to be at high surgical risk (similar to those enrolled in the EVEREST II high risk study, above). A total of 19 patients died within 30 days after the procedure. The Kaplan Meier survival at one year was 81.8%. There were no device embolizations. Thirty six patients (6.3%) required MV surgery within 12 months of the procedure. The severity of MR improved at twelve months compared to baseline (p<0.001), with 78.9% of patients free from MR severity > 2. At 12 months, 71.4% of patients were in NYHA Class I or II.

Philip et al.(2014) reported results of a systematic review of studies evaluating MitraClip or surgical mitral valve (MV) repair or replacement for severe symptomatic mitral regurgitation (MR) in patients at high surgical risk (logistic EuroSCORE >18 or >10). The review included 21 observational studies which used MitraClip (n=3198 patients) and surgical MV repair (n=490) or MV replacement (n=2775). MitraClip patients had a mean Society of Thoracic Surgeons Score (STS) score of 14 and a mean EuroSCORE of 23. Acute procedural success did not differ significantly between groups. However, the 30-day pooled technical failure rate was 3.2% for MitraClip patients, compared with 0.6% for surgical repair/replacement patients (p=0.002). In pooled analysis, the 30-day mortality rate was 3% among MitraClip patients and 16% in surgical repair/replacement patients. Of the total sample, 1-year data were available for 1064 MitraClip patients (1-year data for surgical repair patients was limited to 47 patients and was not reported). Overall, among MitraClip patients, the 1 year mortality rate was 13.0%, the 1-year stroke rate was 1.6%, and the need for repeat MV surgery was 1.3%. Over 70% of patients in the MitraClip group had severe, symptomatic MR with baseline NYHA class of III and IV. However, at 6 months and 1 year over 55% had less than moderate MR (<2+) and were in NYHA class II or lower. On average, 5% of the patients continued to have severe MR (>4+) and <20% were in NYHA class III or IV despite MitraClip implantation. The authors reported that “implantation of the MitraClip can be safely and effectively accomplished in patients with severe MR at high risk for surgical mortality. Mitral valve surgery is technically feasible but is associated with a higher rate of short term adverse events that impacts mortality. Findings from this review should inform clinical decision makers about the adverse event rates associated with mitral valve surgery and MitraClip in these high-risk patient subsets”.

Takagi et al. (2017) reported results of comparative studies of MitraClip versus surgical repair for mitral regurgitation (MR) in a systematic review and meta-analysis. Eligible studies were randomized controlled or observational comparative studies of MitraClip versus surgical repair enrolling patients with MR and reporting early (30-day or in-hospital) or late (≥6-month including early) all-cause mortality. A total of seven studies (n=1015), six observational (non-randomized) comparative studies and only one RCT, comparing MitraClip with surgical repair with MR were included in this systematic review and meta-analysis. The authors reported no statistically significant difference in early and late-mortality between the two groups and significantly higher incidence (4.8-fold) of recurrent MR in the MitraClip than surgical repair group.

Professional Societies/Organizations:
The 2017 focused update to the AHA/ACC Practice Guideline for the Management of Patients with Valvular Heart Disease maintains the following class IIb recommendation related to the use of transcatheter MV repair for MR:

- 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. (Level of Evidence: B)
The Guideline states that “A RCT of percutaneous mitral valve repair using the MitraClip device versus surgical mitral repair was conducted in the United States. The clip was found to be safe but less effective than surgical repair because residual MR was more prevalent in the percutaneous group. However, the clip reduced severity of MR, improved symptoms, and led to reverse LV remodeling” (Nishimura, et al., 2014, 2017).

The ACC, American Association for Thoracic Surgery, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons released a position statement on transcatheter therapies for MR in 2014. This statement outlines critical components for successful transcatheter MR therapies and recommends ongoing research and inclusion of all patients treated with transcatheter MR therapies in a disease registry (O’Gara, et al., 2014). There has been no update to this guideline since 2014.

Hayes Medical Technology Report
A 2014 Hayes, Inc. Medical Technology Directory Report, Percutaneous Mitral Valve Repair summarized the clinical evidence stating that “the available studies suggest that the percutaneous mitral valve (MV) repair using MitraClip is not as effective as conventional surgery for patients who can undergo conventional surgery. Percutaneous MV repair with MitraClip may be more effective than usual treatment for patients who are not candidates for conventional surgery. There is insufficient evidence to evaluate the Carillon procedure for percutaneous MV repair”. Evidence from one large randomized controlled trial (RCT) found that patient survival and reduction in MV regurgitation were similar for the MitraClip procedure versus conventional open surgery at four years follow-up but MitraClip implantation was associated with a statistically significant increase in the need for additional surgery. Most of the reviewed studies of the MitraClip procedure reported deaths that occurred before hospital discharge or in the 30 days after treatment. Mortality during this time frame ranged from 0% to 8% of patients. Limited nonrandomized comparison studies and several uncontrolled studies provide weak evidence that the MitraClip may be beneficial in high-risk patients who are not candidates for conventional surgery. Additional studies are needed to determine the long-term risks versus benefits of MitraClip implantation in these high-risk patients. In patients who are suitable candidates for conventional open mitral valve (MV) repair surgery, the only available randomized controlled trial (RCT) of the MitraClip procedure found that it was less beneficial than conventional MV surgery. Some of the available studies have shown that the MitraClip procedure can be performed in patients who are not suitable candidates for conventional surgery due to poor health. However, the MitraClip procedure has not been rigorously compared with optimal medical management in these high-risk patients. Multiple ongoing RCTs identified in the ClinicalTrials.gov database are designed to evaluate MitraClip implantation for this indication (Hayes, 2014, reviewed 2015, 2016).

Summary: Percutaneous Mitral Valve Repair: Percutaneous mitral valve repair is an emerging technology. A large RCT with five years of follow-up found that patient survival and reduction in MV regurgitation were similar for the MitraClip procedure versus conventional open surgery. However, additional MV surgery was needed for 28% of MitraClip group patients versus 9% of conventional surgery group patients, a statistically significant difference that seems to outweigh the benefits of avoidance of open heart surgery in this patient population. Appropriate patient selection criteria in terms of MR etiology for MitraClip therapy (functional MR vs. degenerative MR) has not been well-established. The evidence is insufficient to determine the effects of the technology. Although this approach may become an option for patients at 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 high risk for traditional surgical repair there is currently insufficient evidence in the published medical literature to demonstrate the safety and efficacy of this procedure.

Tricuspid Valve
Primary tricuspid valve disease is rare. The underlying etiology can be of either congenital or of acquired nature. Surgical treatment is often reserved for advanced stages of tricuspid disease when dysfunction, particularly in patients with congestive heart failure, has led to symptomatic right heart failure. Patients undergoing tricuspid repair or replacement procedures tend to be at higher risk with poorer outcome. A transcatheter approach for tricuspid valve repair or replacement is being investigated. Patient selection criteria for percutaneous tricuspid valve replacement are based on limited data. Presently there are no FDA-approved devices to be delivered in the tricuspid position (Wagner, et al., 2015; 2016).
The American Board of Internal Medicine’s (ABIM) Foundation Choosing Wisely® Initiative (2014): No relevant statements.

Use Outside the U.S.
The Edwards SAPIEN Transcatheter Aortic Heart Valve received CE mark certification in 2007, permitting commercial distribution in Europe. The device is also included in Health Canada’s Medical Device Active License listing. According to the FDA summary, the device is approved for distribution in the 27 member states under the European Union, Croatia, Iran, Israel, Jordan, Kuwait, Monaco, Norway, Russia, Saudi Arabia, Singapore, South Africa, Switzerland, Thailand and Turkey.

The Edwards SAPIEN Pulmonic Transcatheter Heart Valve received CE mark certification in 2010, permitting commercial distribution in the European Union for placement in the pulmonary position.

The Edwards SAPIEN Transcatheter Aortic Heart Valve received CE mark certification permitting commercial distribution in Europe in 2006. The Melody system is also included in Health Canada’s Medical Device Active License listing.

The Edwards SAPIEN Pulmonic Transcatheter Heart Valve received CE mark certification in 2010, permitting commercial distribution in the European Union for placement in the pulmonary position.

According to the FDA summary, the current Medtronic CoreValve System is commercially available in over 50 countries.

CoreValve (Medtronic) is approved in Europe for use in intermediate-risk patients.

Several additional devices have received CE mark approval and are available outside the U.S., including but not limited to the following:

- Direct Flow Medical transcatheter valve
- JenaValve™ Transapical TAVI system (JenaValve Inc., Munich Germany)
- Engager™ Transcatheter Valve (Medtronic, Minneapolis MN)
- Lotus Valve System (Boston Scientific, Malborough MA)
- Portico™ Transcatheter Aortic Valve Implantation System (St. Jude Medical, St. Paul, MN)
- ACURATE TA™ (Symetris, Switzerland)

European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS): The ESC/EACTS 2012 Guidelines on the Management of Valvular Heart Disease state that based on current data, TAVI is recommended in patients with severe symptomatic aortic stenosis who are, according to the heart team, considered unsuitable for conventional surgery because of severe comorbidities. The guideline further states that among high-risk patients who are still candidates for AVR, the decision for TAVI should be individualized, in consideration of the respective advantages/disadvantages of both techniques. At the present stage, TAVI should not be performed in patients at intermediate risk for surgery and trials are required in this population.” These guidelines do not address transcatheter mitral valve or pulmonary valve repair (Vahanian, et al., 2012).

National Institute for Health and Clinical Excellence (NICE) (United Kingdom)
NICE Interventional Procedure Guidance on transcatheter aortic valve implantation for aortic stenosis, updated in July 2017 includes the following recommendations:

- Current evidence on the safety and efficacy of transcatheter aortic valve implantation (TAVI) 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.
- Details of all patients should be entered into the UK TAVI registry. Adverse events should be reported to the Medicines and Healthcare products Regulatory Agency.
- During the consent process patients should be told about all treatment options and their advantages and disadvantages.
- 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 TAVI device most suitable for them.

- TAVI is a technically challenging procedure that should only be done in specialized centers and only by clinicians and teams with special training and experience in complex endovascular interventions. Units doing this procedure should have both cardiac and vascular surgical support for the emergency treatment of complications and subsequent patient care.

NICE Interventional Procedure Guidance on percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction, updated in January 2013, includes the following recommendations:

- The evidence on percutaneous pulmonary valve implantation (PPVI) for right ventricular outflow tract (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. Therefore, this procedure may be used with normal arrangements for clinical governance, consent and audit.

- The procedure should be performed only in specialist units and with arrangements in place for cardiac surgical support in the event of complications.

- Patient selection should be carried out by a multidisciplinary team including a cardiologist with a special interest in congenital heart disease, an interventional cardiologist and a cardiothoracic surgeon with a special interest in congenital heart disease.

- This is a technically challenging procedure that should be performed only by clinicians with training and experience in interventional cardiology and congenital heart disease.

NICE Interventional Procedure Guidance on percutaneous mitral valve leaflet repair for mitral regurgitation states that evidence on the safety and efficacy of percutaneous mitral valve leaflet repair for mitral regurgitation is currently inadequate in quality and quantity (NICE, 2009).

NICE Interventional Procedure Guidance on transcatheter valve-in-valve implantation for aortic bioprosthetic valve dysfunction 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).

NICE Interventional Procedure Guidance on transapical transcatheter valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis 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).

**Coding/Billing Information**

**Note:** 1) This list of codes may not be all-inclusive.
2) Deleted codes and codes which are not effective at the time the service is rendered may not be eligible for reimbursement.
### Transcatheter Aortic Valve Implantation

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>33361</td>
<td>Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach</td>
</tr>
<tr>
<td>33362</td>
<td>Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open femoral artery approach</td>
</tr>
<tr>
<td>33363</td>
<td>Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open axillary artery approach</td>
</tr>
<tr>
<td>33364</td>
<td>Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open iliac artery approach</td>
</tr>
<tr>
<td>33365</td>
<td>Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transaortic approach (eg, median sternotomy, mediastinotomy)</td>
</tr>
<tr>
<td>33366</td>
<td>Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transapical exposure (eg, left thoracotomy)</td>
</tr>
<tr>
<td>33367</td>
<td>Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with percutaneous peripheral arterial and venous cannulation (eg, femoral vessels) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>33368</td>
<td>Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with open peripheral arterial and venous cannulation (eg, femoral, iliac, axillary vessels) (List separately in addition to code for primary procedure)</td>
</tr>
<tr>
<td>33369</td>
<td>Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; cardiopulmonary bypass support with central arterial and venous cannulation (eg, aorta, right atrium, pulmonary artery) (List separately in addition to code for primary procedure)</td>
</tr>
</tbody>
</table>

### Transcatheter Pulmonary Valve Implantation

Considered Medically Necessary when criteria in the applicable policy statements listed above are met:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>33477</td>
<td>Transcatheter pulmonary valve implantation, percutaneous approach, including pre-stenting of the valve delivery site, when performed</td>
</tr>
</tbody>
</table>

### Percutaneous Mitral Valve Repair

Considered Experimental/Investigational/Unproven:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>33418</td>
<td>Transcatheter mitral valve repair; percutaneous approach, including transseptal puncture when performed; initial prosthesis</td>
</tr>
<tr>
<td>33419</td>
<td>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)</td>
</tr>
<tr>
<td>0345T</td>
<td>Transcatheter mitral valve repair percutaneous approach via the coronary sinus</td>
</tr>
</tbody>
</table>
Percutaneous Tricuspid Valve Repair or Replacement

Considered Experimental/Investigational/Unproven:

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>33999</td>
<td>Unlisted cardiac surgery</td>
</tr>
</tbody>
</table>


References


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**Appendix A: Current Treatment Recommendations for Patients With Aortic Stenosis**

(ACCF/AATS/SCAI/STS Expert Consensus Document on Transcatheter Aortic Valve Replacement (TAVR); Holmes et al., 2012)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Complications</th>
</tr>
</thead>
</table>
| **Surgical Aortic Valve Replacement** | • Symptomatic severe AS (Class I, LOE: B)  
• Severe AS undergoing CABG, aortic surgery or other valve surgery (Class I, LOE: C)  
• Symptomatic moderate AS undergoing CABG, aortic surgery or other valve surgery (Class IIa, LOE: C)  
• Asymptomatic severe AS with hypotensive response to exercise (Class IIb; LOE: C)  
• Asymptomatic extremely severe AS (AVA <0.6 cm², mean gradient >50 mm) | • Mortality (3%)  
• Stroke (2%)  
• Prolonged ventilation (11%)  
• Thromboembolism and bleeding  
• Prosthetic dysfunction  
• Perioperative complications are higher when surgical AVR is combined with CABG |
| **Transcatheter Aortic Valve Replacement** | • TAVR is recommended in patients with severe, symptomatic, calcific stenosis of a trileaflet aortic valve who have aortic and vascular anatomy suitable for TAVR and a | Mortality (3% to 5%)  
• Stroke (6% to 7%)  
• Access complications (17%)  
• Pacemaker insertion |
predicted survival >12 months, and who have a prohibitive surgical risk as defined by an estimated 50% or greater 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.

- TAVR is a reasonable alternative to surgical AVR in patients at high surgical risk (PARTNER Trial Criteria: STS ≥ 8%*)

| Medical Therapy | • No specific therapy for asymptomatic AS
• Medical therapy not indicated for symptomatic severe AS risk factors as indicated
• Statins not indicated for preventing progression of AS
• Diuretics, vasodilators and positive inotropes should be avoided in patients awaiting surgery because of risk of destabilization |

| Medical Therapy | • 2% to 9% (SAPIEN)
• 19% to 43% (CoreValve)
• Bleeding
• Prosthetic dysfunction
• Paravalvular AR
• Acute kidney injury
• Other
• Coronary occlusion
• Valve embolization
• Aortic rupture

| Medical Therapy | • Hemodynamic instability |

Key:
Class I: Conditions for which there is evidence for and/or general agreement that the procedure or treatment is beneficial, useful, and effective;
Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment
Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy

*The original PARTNER protocol specified inclusion criteria as a minimum STS-predicted risk of mortality of ≥ 10. During the trial enrollment phase, the minimum STS-predicted risk of mortality was changed to ≥ 8. In both instances, two surgeons had to document that the true predicted risk of mortality was ≥ 15.

AR indicates aortic regurgitation; AS, aortic stenosis; AVR, aortic valve replacement; CABG, coronary artery bypass graft; LOE, level of evidence; STS, Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement.

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