Medical Coverage Policy

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Transcatheter Heart Valve Procedures

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Nonpharmacological Treatments of Atrial Fibrillation

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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 and cerebral protection devices.

Coverage Policy

Transcatheter Aortic Valve Implantation (Native Valve)

Transcatheter aortic valve implantation using an Edwards Sapien™ (Edwards Lifesciences, LLC, Irvine, CA) or Medtronic CoreValve™ Evolut™ (Medtronic CoreValve LLC, Santa Rosa, CA) U.S. Food and Drug Administration (FDA) approved device is considered medically necessary when ALL of the following criteria are met:

- severe symptomatic calcified native aortic valve stenosis (i.e., aortic valve area ≤ 1.0 cm^2 or aortic valve area index ≤ 0.6 $cm2/m^2$, a mean aortic valve gradient of ≥ 40mm Hg, or a peak aortic-jet velocity of ≥ 4.0 m/s)

- ejection fraction > 20%
- documentation of a heart team discussion including a cardiac surgeon, interventional cardiologist, and non-invasive cardiologist and shared decision making with the individual for whom the implantation is being proposed

Transcatheter Aortic Valve-in-Valve Implantation

Valve-in-valve transcatheter aortic valve implantation using a U.S. Food and Drug Administration (FDA) approved device (i.e., Edwards SAPIEN 3 Transcatheter Heart Valve System, Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System, Edwards SAPIEN XT™ Transcatheter Heart Valve [Edwards Lifesciences, LLC, Irvine, CA], CoreValve System [Medtronic CoreValve LLC, Santa Rosa, CA]) is considered medically necessary when the following device-specific criteria are met:

- symptomatic heart disease due to failing (stenosed, insufficient, or combined) of a surgical or transcatheter bioprosthetic aortic valve
- determination by a heart team, including a cardiac surgeon that the individual is at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality greater than or equal to 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator)

NOTE: See above criteria for the use of these valves for native valve stenosis

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

Transcatheter Pulmonary Valve Implantation

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

- **Harmony™ Transcatheter Pulmonary Valve (TPV) System (Medtronic, Inc., Santa Rosa, CA) for BOTH of the following:**
  - severe pulmonary regurgitation (i.e., severe pulmonary regurgitation as determined by echocardiography and/or pulmonary regurgitant fraction ≥ 30% as determined by cardiac magnetic resonance imaging)
  - individual with a native or surgically-repaired RVOT and clinically indicated for surgical pulmonary valve replacement

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

Percutaneous Mitral Valve Repair

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

- **MitraClip NT Clip Delivery System (CDS) and MitraClip NTR/XTR (Abbott Vascular, Menlo Park, CA) for EITHER of the following:**

  - symptomatic mitral regurgitation (MR) with BOTH of the following:
    - with (MR ≥ 3+) due to primary abnormality of the mitral apparatus (degenerative MR)
    - 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 MR

  OR

  - secondary MR with ALL of the following:
    - with MR ≥ Grade III per American Society of Echocardiography criteria
    - with a left ventricular ejection fraction (LVEF) ≥ 20% and ≤ 50% and left ventricular end systolic dimension (LVESD) ≤ 70 mm
    - MR severity persist despite maximally tolerated guideline-directed medical therapy as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease

Percutaneous mitral valve repair or for any other indication is considered experimental, investigational or unproven.

Percutaneous Transcatheter Mitral Valve-in-Valve Implantation

Percutaneous transcatheter mitral valve-in-valve implantation using a U.S. Food and Drug Administration (FDA) approved device (i.e., Edwards SAPIEN 3 Transcatheter Heart Valve System and Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System) is considered medically necessary when the following device-specific criteria are met:

- symptomatic heart disease due to failing (stenosed, insufficient, or combined) of a surgical bioprosthetic mitral valve
- determination by a heart team, including a cardiac surgeon, that the individual is at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality greater than or equal to 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator)

Experimental, Investigational or Unproven:

The following transcatheter heart valve devices and/or procedures are considered experimental, investigational or unproven:

- transcatheter mitral valve implantation or replacement for native mitral valve pathology (i.e. Tendyne system, Abbott Vascular, Menlo Park, CA)
- percutaneous tricuspid valve repair or replacement
- cerebral protection devices (e.g., Sentinel™ Cerebral Protection System)
- devices for reconfiguration of (RVOT) used in transcatheter heart valve procedures (i.e., Alterra Adaptive Prestent, Edwards Life Sciences, Irvine, CA)

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 (Herrmann, et al., 2019; American Heart Association (AHA), 2016).

Several techniques for TAVI have been described in the literature. Currently, 85-90% of all TAVR valves are implanted by a transfemoral approach (Grover, 2017). For patients in whom a transfemoral approach is not feasible, a number of other alternative access routes are used. The original transapical delivery and direct transaortic route are now seldom used for TAVR. The more preferred alternative access approach currently is a subclavian approach, usually the left. Other alternative access approaches include transcaval, transcarotid, and transmediastinal (Herrmann, et al., 2019).

TAVI has become established as a treatment option for elderly, inoperable and high-risk patients with severe aortic stenosis. 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. Most patients who are currently recommended for surgery are at low or intermediate risk. It has been reported that approximatively 80% of patients with aortic stenosis have a low surgical risk. The expansion of the use of TAVR requires rigorous clinical-trial validation with long-term follow-up (Overtchouk, et al., 2019; Leon, et al., 2016).

The currently available TAVR valves approved by the U.S. Food and Drug Administration (FDA) include the balloon-expandable Edwards Sapien XT™ and Sapien 3 (Edwards Lifesciences, Irvine, CA) and self-expandable Medtronic Evolt R and Evolut PRO systems (Medtronic, Inc., Santa Rosa, CA). The choice of valve depends on anatomic reasons and operator preference and experience (Sanchez, et al., 2020). These two transcatheter 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.

The complications associated with TAVR have been somewhat addressed by improvements in devices, technique, delivery, and patient selection. These complications include paravalvular leak, stroke, valve thrombosis and need for a new, permanent pacemaker. The incidence of clinically evident stroke both in randomized trials when examined by a neurologist and in clinical registries ranges from 2-9%. The incidence of moderate to severe paravalvular leak was significantly problematic in the initial trials of TAVR. Improvements in valve design and increased availability of additional valve sizes have decreased the incidence of moderate to severe paravalvular leak to the range of 3-6%, although mild paravalvular regurgitation occurs in up to one third of patients. The requirement for a new, permanent pacemaker in many patients continues to be an issue with TAVR. The incidence ranges from approximately 10-30%, with most current studies closer to the lower end of this range. Patients with preexisting conduction system abnormalities are particularly prone to develop increased conduction system block after TAVR and thus require a new, permanent pacemaker. Another concern associated with TAVR is valve leaflet thickening and thrombosis. The subsequent expanded use of imaging modalities in surveillance studies revealed an incidence of approximately 7-10%. Randomized studies to five years and single-center experience up to 10 years have not yet shown a major reason for concern regarding valve durability (Mack, et al., 2015; Daubert, et al., 2016). The studies are subject to survivorship bias, and with

small numbers of patients alive at five years or longer after the procedure, the ultimate issue of durability with surgical valves remains undetermined (Herrmann, et al., 2019).

U.S. Food and Drug Administration (FDA)–Edwards SAPIEN™ Transcatheter Heart Valve (Edwards Lifesciences, 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 June 16, 2014, the Edwards SAPIEN XT™ Transcatheter Heart Valve model 9300TFX, 23, 26, and 29 mm, and accessories received FDA PMA approval (P130009). This next-generation, lower profile system includes a 29 mm valve size for patients with a larger native annulus. The device is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area ≤ 1.0 cm^2,or aortic valve area index ≤ 0.6 cm^2, /m^2, a mean aortic valve gradient of ≥ 40 mm/Hg, or a peak aortic-jet velocity of ≥ 4.0 m/s), and with native anatomy appropriate for the 23, 26, or 29 mm valve system, who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).

In a PMA supplement approved 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, and accessories to include 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 PMA supplements approved on August 18, 2016 (P130009/S057 and P140031/010), the FDA expanded the indications for the Edwards SAPIEN XT™ Transcatheter Heart Valve, model 9300TFX, 23, 26, and 29 mm, and accessories and the SAPIEN 3 Transcatheter Heart Valve and accessories model 9600TFX to include 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). Data from 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.

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., predicted risk of surgical mortality ≥ 8% at 30 days, based on the STS risk score and other clinical co-morbidities unmeasured by the STS risk calculator). The FDA Summary of Safety and Effectiveness Data reports in the summary of primary clinical data that the applicant performed an analysis of the real-world off-label use 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.

In a PMA supplement approved on August 16, 2019 (P140031/S085), the FDA approved the Edwards SAPIEN 3 Transcatheter Heart Valve System and Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System to include patients at low risk for surgical aortic valve replacement. The devices are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy. Data from the Placement of Aortic Transcatheter Valves (PARTNER) 3 Trial (Mack, et al., 2019) was the basis for the PMA approval decision (NCT02675114).

In PMA supplement approved on September 9, 2020 (P140031/S112), the FDA approved Edwards SAPIEN 3 Transcatheter Heart Valve System and Edwards SAPIEN 3 Ultra Transcatheter Heart Valve System for patients with symptomatic heart disease due to failing (stenosed, insufficient, or combined) of a surgical or transcatheter bioprosthetic aortic valve or a surgical bioprosthetic 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., predicted risk of surgical mortality greater than or equal to 8% 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 applicant performed an analysis of the real-world off-label use 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 the safety and effectiveness of the Edwards SAPIEN 3 THV System in patients receiving transcatheter heart valve-in-transcatheter heart valve treatment. The data from the TVT Registry were the basis of the PMA approval decision.

In a PMA supplement approved May 13, 2021 (P140031/S125), the FDA approved the SAPIEN 3 and SAPIEN 3 Ultra Transcatheter Heart Valve System, expanding the indications to include patients with a failing native mitral valve with a previously implanted annuloplasty ring. This device is indicated for patients with symptomatic heart disease due to failing (stenosed, insufficient, or combined) of a surgical or transcatheter bioprosthetic aortic valve, a surgical bioprosthetic mitral valve, or a native mitral valve with an annuloplasty ring who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

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 cm^2 or aortic valve area index ≤ 0.6 cm^2/m^2, a mean aortic valve gradient of ≥ 40mm 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.

In a PMA supplement approved on August 16, 2019 (P130021/058), the FDA expanded FDA approval of the Medtronic CoreValve™ Evolut™ R System and Medtronic CoreValve™ Evolut™ Pro System to include patients at low risk for surgical aortic valve replacement. The devices are indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis who are judged by a heart team, including a cardiac surgeon, to be appropriate for the transcatheter heart valve replacement therapy. Data from the Evolut Surgical Replacement and Transcatheter Valve Implantation in Low Risk Patients Trial (Popma, et al., 2019) was the basis for the PMA approval decision (NCT NCT02701283).

In a PMA supplement approved on September 19, 2019 (P130021/059), the FDA approved modifications to the CoreValve Evolt PRO System. The device, as modified, will be marketed under the trade name Evolut PRO+ System.

LOTUS Edge™ Valve System (Boston Scientific Corporation, Marlborough, MA): The LOTUS Edge Valve System received FDA approval through the PMA process on April 23, 2019 (P180029). The LOTUS Edge Valve System is indicated for relief of aortic stenosis in patients with symptomatic heart disease due to severe native calcific aortic stenosis (aortic valve area [AVA] of ≤ 1.0 cm^2 or index of ≤ 0.6 cm2 /m^2) who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of

surgical mortality ≥ 8% at 30 days, based on the Society of Thoracic Surgeons (STS) risk score and other clinical comorbidities unmeasured by the STS risk calculator). The FDA approval was based on the REPRISE III prospective, multicenter, randomized controlled trial.

January 11, 2021 Boston Scientific Corporation announced it has initiated a global, voluntary recall of all unused inventory of the LOTUS Edge™ Aortic Valve System due to complexities associated with the product delivery system. The voluntary recall is related solely to the delivery system, as the valve continues to achieve positive and clinically effective performance post-implant. There is no safety issue for patients who currently have an implanted LOTUS Edge valve.

Literature Review–Transcatheter Aortic Valve Implantation in High Risk Patients:
TAVR is well established for the treatment of high-risk and inoperable patients with symptomatic severe aortic stenosis. A robust evidence base has compared transcatheter aortic valve replacement (TAVR) to the standard of care for aortic stenosis. The series of Placement of AoRTic TraNscathetER Valves (PARTNER) trials began with PARTNER 1B (n=358), which demonstrated superiority of TAVR to medical therapy in inoperable patients, with an absolute survival advantage of 23% at five years (Leon, et al., 2010). The PARTNER 1A (n=699) and CoreValve (n=795) trials randomized high–surgical risk patients between TAVR and surgical aortic valve replacement (SAVR) (Smith, et al., 2011; Adams, et al., 2014). Both trials were noninferiority trials and showed either no difference or improved survival with TAVR at one year. Patients in PARTNER 1A have been followed to five years with no survival difference seen (Sanchez, et al., 2020;Reardon, et al., 2019; Herrmann, et al., 2019; Pibarot, et al., 2019; Mack, et al., 2015; Kapadia, et al., 2015).

Literature Review–Transcatheter Aortic Valve Implantation in Intermediate Risk Patients:
Two multicenter randomized controlled studies have compared TAVR to surgical aortic valve replacement (SAVR) in symptomatic patients at intermediate surgical risk. The PARTNER 2A trial (Leon, et al., 2016) randomized 2032 patients to the balloon-expandable Sapien valve versus SAVR, and the SURTAVI trial (Reardon, et al., 2017) randomized 1660 patients to a self-expanding TAVR (CoreValve or Evolut-R) versus SAVR. The results of both trials demonstrated noninferiority of TAVR to SAVR for the composite endpoint of death and stroke at two years. In a large registry of symptomatic, intermediate-risk patients who underwent TAVR using the balloon-expandable Sapien 3 system (Thourani, et al., 2016), survival was markedly superior to the surgical arm of the PARTNER 2A study (Herrmann et al., 2019).

Literature Review–Transcatheter Aortic Valve Implantation in Low Risk Patients:
Two recent randomized clinical trials (RCTs) reported favorable short-term results with TAVR in low-risk patients (Popma, et al., 2019; Mack, et al., 2019). The Evolut Low Risk Trial (Popma, et al., 2019) reported the estimated two year incidence of the primary endpoint, a composite of death or disabling stroke, was 5.3% in the TAVI group and 6.7% in the SAVR group showing non-inferiority of TAVI and SAVR, but no superiority for either mortality or stroke at one year. The PARTNER 3 Trial (Mack, et al., 2019) The PARTNER 3 low risk study showed superiority of TAVI for stroke and the composite primary endpoint of death, stroke and rehospitalization at one year. The Nordic Aortic Valve Intervention Trial (NOTION) (Thyregod, et al., 2019) randomized patients to receive TAVR or SAVR, and 82% of the patients were at low risk for surgical operations (i.e., Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM] score less than 4%). Similar outcomes were achieved in both TAVR and SAVR treatment arms at five years. A 2018 prospective study by Wakesman et al. reported that transfemoral TAVR, using mainly a third-generation balloon-expandable TAVR device, was associated with no deaths at 30 days compared with 1.7% in a historical, propensity-matched SAVR cohort. The risk/benefit profile for periprocedural complications in low risk patients is similar to the overall TAVR population (i.e., reduction in acute kidney injury and bleeding on the one hand and an increase in pacemaker implantation and vascular complications) (Overtchouk, et al., 2019). Long-term follow-up data on outcomes and valve durability is needed.

Evolut Surgical Replacement and Transcatheter Valve Implantation in Low Risk Patients: In the Evolut Low Risk randomized controlled noninferiority trial, Popma et al. (2019) reported the safety and efficacy of transcatheter aortic valve implantation (TAVI) in patients with aortic stenosis with low surgical risk. The as-treated cohort included 1403 patients. Patients were randomly assigned to TAVI with one of three Medtronic self-expanding valves (i.e., CoreValve, Evolut R, or Evolut Pro) (n=725) or surgical aortic valve replacement (n=678). Eligible patients had severe aortic-valve stenosis with suitable anatomy for TAVR or surgery and no more than a predicted 3% risk of death by 30 days of surgery, as assessed by a local heart team. The patients' mean age

was 74. Patients were evaluated at one, six, 12, 18 and 24 months after the procedure. At the pre-specified interim analysis, 12-month follow-up was available for 432 patients in the TAVR group and 352 in the surgery group; 24-month follow-up was available for 72 patients in the TAVR group and 65 patients in the surgery group. The median follow-up time in each group was 12.2 months. The estimated incidence of the primary endpoint, a composite of death or disabling stroke at two years, was 5.3% in the TAVI group and 6.7% in the surgery group meeting the noninferiority threshold. At 24 months, death from any cause was 4.5% for the TAVR group and 4.5% for the SAVR group and the incidence of disabling stroke was 1.1% for TAVR and 3.5% for SAVR. At 30 days, the TAVI group had significantly lower incidences of disabling stroke (0.5% vs. 1.7%), bleeding complications (2.4% vs. 7.5%), acute kidney injury (0.9% vs. 2.8%), and atrial fibrillation (7.7% vs. 35.4%) but higher rates of moderate or severe aortic regurgitation (3.5% vs. 0.5%) and permanent pacemaker implantation (17.4% vs. 6.1%). Mortality rates were not significantly different (0.5% vs. 1.3%). Incidences of stroke, prosthetic-valve thrombosis, endocarditis, and reintervention were similar in the two groups at one year. At one year, hospitalizations for heart failure were significantly less frequent in the TAVI group (3.2% vs. 6.5%) and prosthetic aortic valve gradients were significantly lower (8.6 mmHg vs. 11.2 mmHg) than in the surgery group. Mortality rates at one year were similar in the two groups (2.4% vs. 3.0%). A limitation of this study is this short-term interim analysis occurred when 850 patients had reached 12 months of follow-up. Complete 24 month follow-up of the entire cohort had not been reached. The long-term clinical and echocardiographic follow-up is planned through ten years. This trial showed non-inferiority of TAVI and SAVR regarding the composite primary endpoint of death and stroke but no superiority for either mortality or stroke (ClinicalTrials.gov number, NCT02701283).

Placement of Aortic Transcatheter Valves (PARTNER) 3-Low Risk: In the PARTNER 3 randomized controlled trial (n=950), Mack et al. (2019) reported the safety and efficacy of transcatheter aortic valve implantation (TAVI) in patients with aortic stenosis with low surgical risk. Patients were randomly assigned to TAVI with the balloon-expandable Sapien 3 system (n=496) or surgical aortic valve replacement (n=454). The patients' mean age was 73. The mean Society of Thoracic Surgeons risk score was 1.9%. Inclusion criteria included eligibility for transfemoral access for the TAVI procedure and severe calcific aortic stenosis. Patients were excluded if they had clinical frailty, bicuspid aortic valves, or other anatomical features that increased the risk of complications associated with either TAVR or surgery. The estimated incidence of the primary endpoint, a composite of death, stroke, or rehospitalization at one year after the procedure, was significantly lower in the TAVI group than in the surgical group (8.5% vs. 15.1%) meeting both noninferiority and superiority criteria. At 30 days, TAVI resulted in lower rates of stroke (0.6% vs. 2.4%) and new-onset atrial fibrillation (5% vs. 39.5%). There were no significant differences in the frequency of permanent pacemaker insertions (6.6% vs. 4.1%) or moderate or severe paravalvular regurgitation (0.8% vs. 0.0%). Mortality rates were not significantly different (0.4% vs. 1.1%). At one year, prosthetic valve mean gradients (13.7% vs. 11.6%) and frequency of moderate or severe paravalvular regurgitation (0.6% vs. 0.5%) were similar in the TAVI and surgery groups. Mortality rates were similar in the two groups (1.0% vs. 2.5%). This study is limited by short-term one year outcomes. Long-term follow-up is needed to compare outcomes between TAVI and surgical aortic valve replacement (ClinicalTrials.gov number, NCT02675114).

Waksman et al. (2018) reported results from the multi-center Low Risk TAVR (Feasibility of Transcatheter Aortic Valve Replacement in Low-Risk Patients with Symptomatic, Severe Aortic Stenosis) trial. This is the first U.S. FDA-approved Investigational Device Exemption trial to enroll in the United States. This trial is a prospective, unblinded comparison to historical controls from the Society of Thoracic Surgeons (STS) database. The authors enrolled 200 low-risk patients with symptomatic severe aortic stenosis to undergo TAVR. The authors compared outcomes with an inverse probability weighting–adjusted control cohort of 719 patients who underwent SAVR at the same institutions using the STS database. Patients were confirmed to be low risk based on an STS-PROM score ≤3% and absence of comorbidity that would increase surgical risk. Severe aortic stenosis was defined as a mean aortic valve gradient ≥40 mm Hg or Vmax ≥4 m/s and calculated aortic valve area ≤1.0 cm^2 or aortic valve area index ≤0.6 cm^2/m^2. Only patients who were symptomatic with dyspnea (New York Heart Association [NYHA] functional class II or higher), angina pectoris, or cardiac syncope were included. Patients with unrevascularized coronary artery disease or requiring intervention for another heart valve were excluded. Patients with bicuspid aortic stenosis were excluded and enrolled in a separate registry arm of the trial that is not part of this analysis. The primary endpoint was all cause mortality at 30 days. At 30 days, there was zero all-cause mortality in the TAVR group versus 1.7% mortality in the SAVR group. There was zero in-hospital stroke rate in the TAVR group versus 0.6% stroke in the SAVR group. Permanent pacemaker implantation rates were

similar between TAVR and SAVR (5.0% vs. 4.5%). The rates of new-onset atrial fibrillation (3.0%) and length of stay (2.0±1.1 days) were low in the TAVR group. One patient (0.5%) in the TAVR group had >mild paravalvular leak at 30 days. Fourteen percent of TAVR patients had evidence of subclinical leaflet thrombosis at 30 days (Waksman, et al., 2018). At one year follow-up for TAVR, mortality was 3.0%, stroke rate was 2.1%, and permanent pacemaker implantation rate was 7.3%. Two (1.0%) subjects underwent surgical reintervention for endocarditis. Of the 14% of TAVR subjects who had evidence of hypoattenuated leaflet thickening at 30 days, there was no impact on valve hemodynamics at one year, but the stroke rate was numerically higher (3.8% vs. 1.9%). The STS database does not capture any data beyond 30 days, so it is not possible to perform a comparison of TAVR versus SAVR outcomes beyond 30 days (Waksman, et al., 2019). This study is limited by short-term follow-up and study design. Long-term follow-up is needed to evaluate durability of TAVR devices in low-risk patients with symptomatic, severe aortic stenosis (ClinicalTrials.gov number NCT02628899).

Nordic Aortic Valve Intervention (NOTION) trial: Thyregod et al. (2019) reported findings from the NOTION multicenter, nonblinded, superiority trial comparing TAVR with SAVR in patients ≥70 years old with isolated severe aortic valve stenosis. Clinical and echocardiographic outcomes are reported after five years. Patients were enrolled at three Nordic centers and randomized 1:1 (n=280) to TAVR using the self-expanding CoreValve prosthesis (n=145) or SAVR using any stented bioprostheses (n=135). There were no significant baseline differences between patients in the intention-to-treat groups. Inclusion criteria included isolated severe aortic valve stenosis. The majority of patients had a STS-PROM score below 4% and were considered as surgical low-risk patients. The mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 3.0%±1.7%. The major exclusion criteria included need for acute treatment, severe coronary artery disease, severe nonaortic valvular disease, prior heart surgery, recent stroke or myocardial infarction (MI), or severe lung or renal disease. The primary composite outcome was the rate of all-cause mortality, stroke, or myocardial infarction. The baseline characteristics were similar. The primary composite outcome of all-cause mortality, stroke, or MI at both 30 days and one year was not statistically different between TAVR and SAVR groups and remained not different between groups at five years with 38.0% for TAVR and 36.3% for SAVR. TAVR patients had larger prosthetic valve area (1.7 cm^2 vs 1.2 cm^2) with a lower mean transprosthetic gradient (8.2 mm Hg vs 13.7 mm Hg), both unchanged over time. More TAVR patients had moderate/severe total aortic regurgitation (8.2% vs 0.0%) and a new pacemaker (43.7% vs 8.7%). Four patients had prosthetic reintervention and no difference was found for functional outcomes. Although the NOTION trial indicates that TAVR could be a safe treatment alternative in patients with isolated severe aortic valve stenosis and at lower surgical risk, larger scale clinical trials and long-term follow-up are needed to confirm these findings (ClinicalTrials.gov number NCT01057173).

Kolte, et al. (2019) conducted a meta-analysis including four randomized controlled trials (RCTs) (n=2887) of TAVR versus surgical aortic valve replacement (SAVR) in patients who are at low surgical risk (1497 to TAVR and 1390 to SAVR). Follow-up was one year. The primary outcome was all-cause death at one year. At one year, compared with SAVR, TAVR was associated with significantly lower risk of: all-cause death (2.1% vs. 3.5%;p=0.03) and cardiovascular death (1.6% vs. 2.9%;p=0.02). Rates of new/worsening atrial fibrillation, life-threatening/disabling bleeding, and acute kidney injury stage 2/3 were lower, although permanent pacemaker implantation and moderate/severe paravalvular leak were higher after TAVR versus SAVR. There were no significant differences between TAVR versus SAVR for major vascular complications, endocarditis, aortic valve re-intervention, and New York Heart Association functional class ≥II. These one year follow-up findings are complementary to the recent pivotal RCTs suggesting that TAVR may be the preferred option over SAVR in low-risk patients with severe AS who are candidates for bioprosthetic AVR. Long-term follow-up data on outcomes and valve durability is needed.

Bekeredjian et al. (2019) reported the study endpoint of in-hospital, 30-day, and 1-year survival in a prospective registry analysis comparing TAVI patients with SAVR patients in a low surgical risk cohort. The study included patients with Society of Thoracic Surgeons Score of <4%. A total of 20549 low surgical risk patients, comprising 14487 surgical patients and 6062 TAVI patients were included in the study. Transcatheter aortic valve implantation patients showed a significantly higher in-hospital and 30-day survival than SAVR patients (in hospital survival TAVI vs. SAVR: 98.5% vs. 97.3%; p=0.003; 30-day survival TAVI vs. SAVR: 98.1% vs. 97.1%; p=0.014). At one year, survival rates did not differ significantly (survival TAVI vs. SAVR: 90.0% vs. 91.2%; p=0.158). This study is limited by its non-randomized design, being a large, prospective, and all-comers registry.

Witberg et al. (2018) conducted a systematic review and meta-analysis of RCTs and observational studies with propensity score matching (PSM) of TAVR versus surgical aortic valve replacement (SAVR) in patients who are at low surgical risk. The primary outcome was all-cause mortality. The secondary outcomes included stroke, myocardial infarction, bleeding, and various procedural complications. Six studies, two RCTs (n=350) and four observational PSM studies (n=3134), totaling 3484 patients were included. Three of the studies specifically included patients who were only at low surgical risk, while the other three studies included patients at low–intermediate surgical risk, but their mean value was in the low risk category. Follow-up ranged from three months to three years (median 2 years). The short-term 30 day mortality was similar with TAVR or SAVR (2.2% for TAVR and 2.6% for SAVR). TAVR was associated with an increased risk for intermediate-term two year mortality (17.2% for TAVR and 12.7% for SAVR). In terms of periprocedural complications, TAVR was associated with reduced risk for bleeding and renal failure and an increase in vascular complications and pacemaker implantation. Although there is no difference in short-term mortality between TAVR/SAVR, TAVR was associated with an increased risk for intermediate, median 2 years, term mortality. The risk/benefit profile for periprocedural complications in low risk patients is similar to the overall TAVR population (i.e., reduction in acute kidney injury and bleeding on the one hand and an increase in pacemaker implantation and vascular complications). This meta-analysis did not include data from the Partner 3 and Medtronic Transcatheter Aortic Valve Replacement in Low Risk Patients RCTs.

In a meta-analysis, Vipparthy et al. (2020) reported on outcomes of TAVI versus surgical aortic valve replacement in patients who are at low risk for surgery. Twelve studies (five randomized controlled trials and seven observational studies) totaling 27,956 patients were included. Studies comparing TAVI and SAVR included patients with severe aortic stenosis and low surgical risk defined by a STS score of ≤4% and logistic Euroscore of ≤10% and randomized controlled trials or observational study (prospective or retrospective). Follow-up ranged from three months to five years. Short-term all-cause mortality, short-term, and one-year cardiac mortality were significantly lower in the TAVI group. One-year all-cause mortality, short-term, and one-year stroke and myocardial infarction were similar in both groups. Rate of acute kidney injury and new-onset atrial fibrillation were lower in the TAVI group, whereas permanent pacemaker implantation and major vascular complications were higher in the TAVI group. Subgroup analysis of randomized controlled trials showed significantly lower one-year all-cause mortality in the TAVI group. The authors concluded that in severe aortic stenosis patients at low surgical risk, TAVI when compared with surgical aortic valve replacement, demonstrated a lower rate of short-term all-cause mortality, short-term, and one-year cardiac mortality and similar in terms of one-year all-cause mortality.

In a meta-analysis, Arora et al. (2017) compared the 30-day risk of clinical outcomes between TAVR and SAVR in the lower surgical risk population. Studies were included if the overall mean Society of Thoracic Surgeons Score was < 4% (or equivalent Euroscore). A total of four studies, including one clinical trial and three propensity-matched cohort studies met the inclusion criteria (n=2252). The authors reported that TAVR patients had lower risk of 30 day mortality and strokes but lacked the power to obtain statistical significance. TAVR patients were also less likely to have bleeding complications acute kidney injury, and were more likely to have vascular complications, paravalvular regurgitation and need for pacemaker implantations. Among lower risk patients, TAVR and SAVR appear to be comparable in short term outcomes. Additional long-term studies comparing TAVR and SAVR in low risk patients are needed.

The September 2018 Hayes Medical Technology Directory Comparative Effectiveness Review Transcatheter Aortic Valve Implantation (TAVI) and Surgical Aortic Valve Replacement (SAVR) for Aortic Stenosis in Low Risk Patients reports on the use of primary TAVI to treat severe calcific aortic stenosis (AS) in patients at low or intermediate surgical risk for complications with open SAVR, and who have not undergone prior SAVR or TAVI. To accommodate a large body of literature, a Review of Reviews methodology was adopted for this report. A systematic search identified one systematic review (SR) by Witberg et al. (2018) which included two randomized controlled trials (RCTs) and four propensity score-matched observational studies [PMOS]) comparing TAVI with SAVR in low-risk patients and one SR in intermediate-risk patients by Lazkani et al. (2018) which included four RCTs, one case-controlled study and six cohort studies. One subsequently published propensity score-matched observational study in intermediate-risk patients was also identified (Thourani, et al., 2016). The authors concluded that “For treatment of severe calcific AS in patients with intermediate surgical risk for complications during open valve replacement, TAVI may be a suitable alternative to SAVR in patients for whom a dedicated heart team determines it is appropriate in consideration of presurgical assessment as described in clinical

practice guidelines. Moderate-quality evidence indicates mortality, stroke, and myocardial infarction are not significantly different in intermediate-risk patients treated with TAVI or SAVR at follow-up of at least two years. Further, evidence indicates that the incidence of acute kidney injury and atrial fibrillation are lower after TAVI than after SAVR. However, new pacemaker implantation, vascular complications, and aortic insufficiency are higher after TAVI than after SAVR. Additional well-designed RCTs that provide data regarding the long-term durability and safety of TAVI are needed. For treatment of patients with severe calcific AS in patients with low surgical risk for complications during open surgical valve replacement, the available evidence of moderate quality indicates a higher incidence of mortality after TAVI than SAVR at one to three years follow-up" (Hayes, 2018; annual review 2019; 2020).

Valve-in-Valve (VIV) Transcatheter Aortic Valve Implantation for Treatment of a Failed Surgical Bioprosthesis

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. Karla et al. (2020) evaluated data from The Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database concluding that the number of patients undergoing surgical aortic valve replacement for a degenerated bioprosthesis is decreasing in United States, particularly among older and high-risk patients. These trends may reflect the adoption of ViV TAVR for a degenerated bioprosthesis after its FDA approval in 2015.

Deeb et al. (2017) evaluated the safety and effectiveness of self-expanding transcatheter aortic valve replacement (TAVR) in patients with surgical valve failure (SVF). The CoreValve U.S. Expanded Use Study was a prospective, nonrandomized study that enrolled 233 patients with symptomatic SVF who were deemed unsuitable for reoperation. Patients were treated with self-expanding TAVR and evaluated for 30-day and one year outcomes after the procedure. SVF occurred through stenosis (56.4%), regurgitation (22.0%), or a combination (21.6%). A total of 227 patients underwent attempted TAVR and successful TAVR was achieved in 225 (99.1%) patients. Patients were elderly (76.7±10.8 years), had a Society of Thoracic Surgeons Predicted Risk of Mortality score of 9.0± 6.7%, and were severely symptomatic (86.8% New York Heart Association functional class III or IV). The all-cause mortality rate was 2.2% at 30 days and 14.6% at one year; major stroke rate was 0.4% at 30 days and 1.8% at one year. Moderate aortic regurgitation occurred in 3.5% of patients at 30 days and 7.4% of patients at one year, with no severe aortic regurgitation. The rate of new permanent pacemaker implantation was 8.1% at 30 days and 11.0% at one year. The mean valve gradient was 17.0± 8.8 mm Hg at 30 days and 16.6± 8.9 mm Hg at one year. Factors significantly associated with higher discharge mean aortic gradients were surgical valve size, stenosis as modality of SVF, and presence of surgical valve prosthesis patient mismatch (all $p< 0.001$). This study was not a randomized trial, and no comparisons were pre-specified. Due to a relatively low number of patients in the study, subgroup analyses were somewhat limited. Longer-term follow-up is needed to determine the impact of the higher residual mean value gradients.

Dauerman et al. (2019) reported three years outcomes data of the CoreValve U.S. Expanded Use Study above. From March 2013 to May 2015, 226 patients deemed extreme risk (STS-PROM [Society of Thoracic Surgeons Predicted Risk of Mortality] 9.0±7%) had attempted valve-in-valve TAVR. All-cause mortality or major stroke was 28.6%, and 93% of patients were in New York Heart Association I or II heart failure at three years. Valve performance was maintained over three years with low valve reintervention rates (4.4%), an improvement in effective orifice area over time and a 2.7% rate of severe structural valve deterioration. Preexisting severe prosthesis-patient mismatch was not associated with 3-year mortality but was associated with significantly less improvement in quality of life at 3-year follow-up ($p=0.01$).

A large case series was published by Dvir et al. (2012) 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. 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)".

Using Valve-in-Valve International Data (VIVID) registry data, Dvir et al. (2014) determined the survival of patients after transcatheter ViV implantation inside failed surgical bioprosthetic valves. Correlates for survival were evaluated using a multinational registry that included 459 patients with degenerated bioprosthetic valves undergoing ViV implantation. Modes of bioprosthesis failure were stenosis (n=181), regurgitation (n=139) and combined (n=139). The stenosis group had a higher percentage of small valves (37% vs 20.9% and 26.6% in the regurgitation and combined groups, respectively). Within one month following ViV implantation, 35 (7.6%) patients died, eight (1.7%) had major stroke and 313 (92.6%) of surviving patients had good functional status (NYHA class I/II). The overall one year survival rate was 83.2%; 62 death events; 228 survivors). Patients in the stenosis group had worse one year survival (76.6%; 34 deaths; 86 survivors) in comparison with the regurgitation group (91.2%; 10 deaths; 76 survivors) and the combined group (83.9%; 18 deaths; 66 survivors). Similarly, patients with small valves had worse one year survival (74.8%; 27 deaths; 57 survivors) versus with intermediate-sized valves (81.8%; 26 deaths; 92 survivors) and with large valves (93.3%; 7 deaths; 73 survivors). Factors associated with mortality within one year included having small surgical bioprosthesis (≤21 mm) and baseline stenosis (vs regurgitation).

The PARTNER II Trial: Placement of Aortic Transcatheter Valves II - PARTNER II - Nested Registry 3/Valve-in-Valve [PII NR3/ViV]: Webb et al. (2017) evaluated 30-day and one year outcomes in high-risk patients undergoing ViV TAVR using the SAPIEN XT valve. Patients with symptomatic degeneration of surgical aortic bioprostheses at high risk (≥50% major morbidity or mortality) for reoperative surgery were prospectively enrolled in the multicenter PARTNER II ViV trial and continued access registries. ViV procedures were performed in 365 patients (96 initial registry, 269 continued access patients). Mean age was 78.9 ± 10.2 years, and mean Society of Thoracic Surgeons (STS) score was 9.1 ± 4.7%. At 30 days, all-cause mortality was 2.7%, stroke was 2.7%, major vascular complication was 4.1%, conversion to surgery was 0.6%, coronary occlusion was 0.8% and new pacemaker insertion was 1.9%. One year all-cause mortality was 12.4%. Mortality fell from the initial registry to the subsequent continued access registry, both at 30 days (8.2% vs. 0.7%, respectively) and at one year (19.7% vs. 9.8%, respectively). At one year, mean gradient was 17.6 mmHg, and effective orifice area was 1.16 cm2, with greater than mild paravalvular regurgitation of 1.9%. Left ventricular ejection fraction increased (50.6% to 54.2%), and mass index decreased (135.7 to 117.6 g/m2), with reductions in both mitral (34.9% vs. 12.7%) and tricuspid (31.8% vs. 21.2%) moderate or severe regurgitation. Follow-up at three years was complete in 337 patients (92.3%), while 28 patients (7.7%) were either withdrawn from the study or were lost to follow-up at three years (Webb, et al., 2019). At three years, the overall estimate of all-cause mortality was 32.7%. Repeat aortic valve re-replacement was required in 1.9% of the patients. There were 158 patients with evaluable echocardiograms at 3-year follow-up. Mean transaortic gradient was 35.0 mm Hg at baseline, decreasing to 17.8 mm Hg at 30-day follow-up and 16.6 mm Hg at 3-year follow-up. Baseline effective orifice area was 0.93 cm^2, increasing to 1.13 and 1.15 cm^2 at 30 days and 3 years, respectively. Moderate to severe aortic regurgitation was reduced from 45.1% at pre-TAVR baseline to 2.5% at 3 years. Moderate or severe mitral and tricuspid regurgitation also decreased (33.7% vs. 8.6% and 29.7% vs. 18.8%, respectively). Baseline left ventricular ejection fraction was 50.7%, increasing to 54.7% at three years, while left ventricular mass index was 136.4 g/m^2, decreasing to 109.1 g/m^2 at three years. New York Heart Association functional class improved, with 90.4% in class III or IV at baseline and 14.1% at three years. Kansas City Cardiomyopathy Questionnaire overall score increased (43.1 to 73.1). Study limitations include lack of randomization and the available THV sizes (23 and 26 mm) did not allow inclusion of patients with the smallest or largest of surgical bioprostheses. Clinical and hemodynamic outcomes may vary with different THV devices.

In a retrospective study, Woitek et al. (2020) reported the early safety, clinical efficacy, and all-cause one-year-mortality of transfemoral transcatheter aortic valve prosthesis (VinV-TFAVI) and redo surgery for failing aortic bioprostheses (re-SAVR). Patients receiving either VinV-TFAVI (n=147) or re-SAVR (n=111) for a degenerated aortic bioprosthesis were included in this study. All-cause 1-year mortality was the primary outcome measure. Early safety and clinical efficacy were evaluated at 30 days. Baseline characteristics differed significantly between both groups including age, Society of Thoracic Surgeons – Predicted Risk of Mortality, and incidence of relevant comorbidities. Re-stenosis was the predominant mode of failure in 45.9% of re-SAVR and 63.1% of VinV-TFAVI patients. The rate of "early safety" endpoints was lower with VinV-TFAVI (17.7% vs. 64.9%), the rate of clinical efficacy endpoints was better with re-SAVR (53.1% vs. 32.4%). All-cause 1-year-mortality (VinV-TFAVI 8.8% vs re-SAVR 9.9%) was not different. Treatment strategy was not associated with 1-year-mortality. The incidence of prosthesis-patient mismatch was higher in VinV-TFAVI compared to re-SAVR. The reported limitations state that the degenerated valves were heterogeneous, and as many as 27 different valve types were used for the primary aortic valve replacement in the study population. The discrepancy in baseline characteristics makes comparisons among groups difficult. Although this study reports the largest cohort available to date, the number of patients is small, making conclusions difficult to draw, especially concerning rare events. Only mid-term outcomes were reported in this study. There might be differences concerning the durability of the replaced valves or the survival over a longer period. The authors concluded that VinV-TFAVI represents a viable alternative for patients with degenerated aortic bioprosthesis who are at increased risk for a surgical reoperation. For patients at low risk for reoperation, a better clinical efficacy and acceptable safety may favor re-SAVR.

In a retrospective observational study, Tam et al. (2020) compared early and late outcomes between redo surgical aortic valve replacement (AVR) and valve-in-valve (ViV) transcatheter AVR. Clinical and administrative databases were linked to obtain patients undergoing ViV and redo surgical AVR (RS) for failed previous biological prostheses. A total of 558 patients undergoing intervention for failed biological prostheses between March 31, 2008, and September 30, 2017, at 11 Ontario institutions (ViV, n=214; RS, n=344) were included. Patients who underwent ViV were older and had more comorbidities. Propensity matching on 27 variables yielded similar groups for comparison (n=131 pairs). Mean time from initial AVR to RS or ViV was 8.6 ± 4.4 years and 11.3 ± 4.5 years, respectively. Thirty-day mortality was significantly lower with ViV compared with RS. The rates of permanent pacemaker implantation and blood transfusions were also lower with ViV, as was length of stay. Survival at five years was higher with ViV (76.8% vs. 66.8%). This study is limited by its design. The risk profile of the ViV TAVR cohort was considerably different from that of redo SAVR patients. The cohort was elderly and higher risk thus limiting the findings to a younger and lower risk patient population. The authors concluded that in patients with a failed biological prostheses and suitable anatomy, ViV TAVR may be the treatment strategy of choice over redo SAVR, with overall lower rates of early morbidity and mortality, shorter length of hospital stay, and improved late survival at five years. Further follow-up is required to determine the durability and late clinical performance of ViV TAVR.

Malik et al. (2020) reported in-hospital outcomes in patients who underwent ViV-TAVI and compared a propensity matched cohort of such patients to redo-SAVR in a nationally representative cohort of patients from the US National Inpatient Sample database. The primary outcomes were in-hospital adverse events composite outcome (comprising of mortality, myocardial infarction, stroke, or acute kidney injury) and all-cause mortality. Over five years, there has been a considerable increase in both interventions for prosthetic aortic valve failure, with significantly higher utilization of ViV-TAVI compared to redo-SAVR. Out of the 3,305 hospitalizations for prosthetic aortic valve failure, 1,420 in matched pairs underwent either ViV-TAVI (n=710) or redo-SAVR (n=710). ViV-TAVI was associated with lower in-hospital composite adverse outcomes (14.1% vs 25.4%, p=0.018), and numerically lower but statistically insignificant mortality (<1.0% vs 5.2%; p=0.06). ViV-TAVI was associated with a decreased length of hospitalization (mean 6.6 vs 9.7 days; p<0.01). In the matched cohort, postoperative bleeding and transfusions were significantly lower for ViV-TAVI compared with redo-SAVR (17.6% vs 31.0% and 12% vs 31% respectively, p<0.01 for both). Sepsis, acute kidney injury, permanent pacemaker implantation, and vascular complications, although numerically better, did not differ between the two strategies. The authors reported that this analysis from a large administrative database suggests that ViV-TAVI seems to be associated with better survival in patients requiring repeat aortic valve surgery especially in patients who are older and have higher co-morbidities. Further prospective and long-term studies are needed to confirm the long-term superiority of ViV-TAVI.

In a retrospective study, Deharo et al. (2020) reported the outcomes of VIV TAVR versus redo SAVR based on the French administrative hospital-discharge database. Propensity score matching was used for the analysis of outcomes. A total of 4,327 patients were found in the database. After matching on baseline characteristics, 717 patients were analyzed in each arm. At 30 days, VIV TAVR was associated with lower rates of the composite of all-cause mortality, all-cause stroke, myocardial infarction, and major or life-threatening bleeding. During follow-up (median 516 days), the combined endpoint of cardiovascular death, all-cause stroke, myocardial infarction, or rehospitalization for heart failure was not different between the two groups. Rehospitalization for heart failure and pacemaker implantation were more frequently reported in the VIV TAVR group. A time-dependent interaction between all-cause and cardiovascular mortality following VIV TAVR was reported. VIV TAVR was observed to be associated with better short-term outcomes than redo SAVR. Major cardiovascular outcomes were not different between the two treatments during long-term follow-up. The authors state that in this nationwide propensity-matched analysis, all-cause and cardiovascular mortality was lower within 30 days after VIV TAVR than after reoperative SAVR, but long-term rehospitalization for heart failure was less frequent in those undergoing reoperative SAVR.

Takagi et al. (2019) performed a meta-analysis of comparative studies to determine whether valve-in-valve transcatheter aortic valve implantation (VIV-TAVI) is associated with better survival than redo surgical aortic valve replacement (SAVR) in patients with degenerated aortic valve bioprostheses. Six reports of retrospective comparative studies enrolling a total of 498 patients were identified. Pooled analyses of baseline characteristics demonstrated no statistically significant differences in the proportion of women, patients with diabetes mellitus, patients with coronary artery disease, and patients with baseline New York Heart Association functional class of ≥III; baseline ejection fraction; and predicted mortality between the VIV-TAVI and redo SAVR groups. Patients in the VIV-TAVI group, however, were significantly older and had undergone prior coronary artery bypass grafting more frequently than those in the redo SAVR group. There was no statistically significant differences in early (30 days or in hospital) (p=0.83) and midterm (180 days–3 years) all-cause mortalities (p=0.21) between the VIV-TAVI and redo SAVR groups. The authors reported that in patients with degenerated aortic valve bioprostheses, especially elderly or high-risk patients, VIV-TAVI could be a safe, feasible alternative to redo SAVR. The reported limitation of this meta-analysis state that only data was included from retrospective observational comparative studies with a lack of randomized data. The differences in baseline characteristics in the present analysis emphasize the need for prospective randomized trials. This study is limited by the retrospective, observational nature of the study and its potential biases.

Gozdek et al. (2018) performed a systematic review and meta-analysis to directly compare redo surgical aortic valve replacement (re-sAVR) with valve-in-valve transcatheter aortic valve implantation (ViV TAVI) for patients with failed degenerated aortic bioprostheses. Multiple databases were screened for all available reports comparing ViV TAVI with re-sAVR in patients with failing degenerated aortic bioprostheses. The primary outcome was all-cause mortality determined from the longest available survival data. Five observational studies (n=342) were included in the meta-analysis; patients in the ViV TAVI group were older and had a higher baseline risk compared to those in the re-sAVR group. Although there was no statistical difference in procedural mortality, 30-day mortality and cardiovascular mortality at a mean follow-up period of 18 months, cumulative survival analysis favored surgery with borderline statistical significance (p=0.039). ViV TAVI was associated with a significantly lower rate of permanent pacemaker implantations (p= 0.002) and shorter intensive care unit (p<0.001) and hospital stays (p=0.020). In contrast, re-sAVR offered superior echocardiographic outcomes: lower incidence of patient–prosthesis mismatch (p=0.008), fewer paravalvular leaks (p=0.023) and lower mean postoperative aortic valve gradients in the prespecified analysis (p=0.017). The authors reported that the ViV TAVI approach is a safe and feasible alternative to re-sAVR that may offer an effective, less invasive treatment for patients with failed surgical aortic valve bioprostheses who are inoperable or at high risk. Re-sAVR should remain the standard of care, particularly in the low-risk population, because it offers superior hemodynamic outcomes with low mortality rates.

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.

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 TAVI may be a reasonable alternative to open heart surgery in carefully selected, low, intermediate or high-risk patients with severe symptomatic aortic stenosis who meet the FDA-specified indications for use.

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 registry studies and retrospective studies. There is evidence in the published medical literature to demonstrate the safety and efficacy of this procedure compared with surgical repair for a subset of patients who are at high or greater risk for open aortic surgical therapy.

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
- Mean RVOT gradient ≥ 40 mmHg

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

On February 24, 2017, approval of the Melody® system was expanded to include patients with a dysfunctional surgical bioprosthetic valve (valve-in-valve). Per the FDA Summary of Effectiveness and Safety Data (SSED), the clinical data supporting the PMA supplemental approval decision were pooled from the following three (3) sources: Melody Transcatheter Pulmonary Valve (TPV) Long-term Follow-up Post Approval Study (PAS) n=8 patients; Melody TPV New Enrollment PAS n=17 patients and Real-World Data n=100 patients.

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 Summary of Effectiveness and Safety Data (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 COngenital 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.

Harmony™ Transcatheter Pulmonary Valve (TPV) System (Medtronic, Inc., Santa Rosa, CA)
Harmony™ Transcatheter Pulmonary Valve (TPV) System (Medtronic, Inc., Santa Rosa, CA) received FDA approval through the premarket approval application (PMA) process March 2021 (P200046). This device is indicated for use in the management of pediatric and adult patients with severe pulmonary regurgitation (i.e., severe pulmonary regurgitation as determined by echocardiography and/or pulmonary regurgitant fraction ≥ 30%

as determined by cardiac magnetic resonance imaging) who have a native or surgically-repaired right ventricular outflow tract and are clinically indicated for surgical pulmonary valve replacement.

The FDA approval includes an Annual Report that must include, separately for each model number (if applicable), the number of devices sold and distributed during the reporting period, including those distributed to distributors. The distribution data will serve as a denominator and provide necessary context for FDA to ascertain the frequency and prevalence of adverse events, as FDA evaluates the continued safety and effectiveness of the device. In addition to the Annual Report requirements, following data is requried in post-approval study (PAS) reports for each PAS listed below.

- Continued Follow-up of the Harmony TPV IDE Cohort: This study will be conducted in accordance with the protocol, entitled, “Clinical Investigation Plan Addendum – Post Approval (PAS) Phase” (Version 1.0), dated March 22, 2021. The study will consist of 82 patients enrolled in the IDE study (including the Continued Access Protocol investigation). The objective of the study is to characterize the clinical outcomes annually, unless otherwise specified, through 10 years post implant. The safety and effectiveness endpoints include device success, freedom from TPV dysfunction, freedom from all-cause mortality, serious device-related adverse events, characterization of right ventricular remodeling (6 months, 2 years, 5 years and 10 years), quality of life score (SF36), and reoperation.

- Harmony TPV New Enrollment Study: This study will be conducted in accordance with the protocol, entitled, “Harmony Post-Approval Study Clinical Investigation Plan” (Version 1.0), dated March 22, 2021. The study will enroll 150 patients at up to 30 sites that did not participate in the Harmony TPV IDE Study. The objective of the study is to characterize the real-world performance of the Harmony TPV through 10 years post implant. The safety and effectiveness endpoints include proportion of patients without valve intervention and with acceptable hemodynamic function at 6 months, procedure success at 30 days, as well as freedom from all-cause mortality, freedom from reoperation, freedom from catheter reintervention, freedom from TPV dysfunction, and serious procedure- and device-related adverse events at 6 months and annually through 10 years.

- A PAS Progress Report for the “Continued Follow-up of the Harmony TPV IDE Cohort” PAS study must be submitted annually.

Harmony TPV device is contraindicated for patients with an infection in the heart or elsewhere; patients who cannot tolerate blood thinning medicines; or patients who have sensitivity to Nitinol (titanium or nickel).

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 one 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 seven 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 one year and 75% at two 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 one year follow-up interval (n=150). Existing conduit stents from a prior catheterization were present in 37 patients (25%, fractured in 12); one 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 one year evaluation window) and 60±9% at 39 months (three-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 experiences 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, six months, 12 months, and annually thereafter for five 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 six 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 one year met the pre-specified performance goal of 75%. At five 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 five years. Freedom from surgical pulmonic valve repair was 98.3% at one year and 91.8% at five years. Freedom from transcatheter pulmonic valve implantation was 97.1% at one year and 85.8% at five years. Freedom from balloon valvuloplasty was 100% at one year and 93.7% at five years. Freedom from other types of reintervention was 100% at one year and 97.9% at five 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 five 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 one year and 12.8±7.8 mmHg at five 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 one year and 21.6±14.5 mmHg at five years. Moderate/severe pulmonic regurgitation decreased from 90% at baseline to 2% at 30 days, 4 % at one year and 0% at five 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 one year and 94% at five years.

Chowdhury et al. (2013) conducted a prospective, multicenter study (COMPASSION study) to evaluate echocardiographic changes at one and six 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 endsystolic area; indexed RV end-diastolic area; tricuspid regurgitation (TR) peak gradient; indexed TR jet area ($p<0.01$ for all measures). The benefit was maintained for six months. Proportion of

patients with grade ≥2 PR was reduced from 94% at baseline to 12% at six 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 (THV) 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 four centers (three in the United States and one in Europe). Follow-up was six 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 six months. Freedom from reintervention was 97% with one 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, and14 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.

Harmony Transcatheter Pulmonary Valve (TPV) System
Bergersen et al. (2017) conducted a multicenter, feasibility study to obtain in vivo data to confirm assumptions on Harmony transcatheter pulmonary valve device loading conditions and to assess procedural feasibility, safety, and valve performance. The study included 21 patients approved for implant and underwent catheterization; and

20 were implanted. Catheterized patients had a median age of 25 years, were predominantly diagnosed with tetralogy of Fallot (95%), had severe pulmonary regurgitation (95%), and had trivial or mild stenosis. The device was delivered in the desired location in 19 of 20 (95%) patients. Proximal migration occurred in one patient during delivery system removal. Two devices were surgically explanted. Premature ventricular contractions related to the procedure were reported in three patients; two were resolved without treatment. One patient had ventricular arrhythmias that required treatment and later were resolved. At one month, echocardiography revealed none or trivial pulmonary regurgitation in all and a mean right ventricular outflow tract gradient of 16 ± 8 mm Hg (range 6 to 31 mm Hg). The authors concluded that in this early feasibility study of the Harmony transcatheter pulmonary valve device, there was high procedural success and safety, and favorable acute device performance.

Benson et al. (2020) reported on a native TPV EFS (Early Feasibility Study) prospective, multicenter, nonrandomized feasibility study with a report of three-year outcomes. The study included 20 implanted (Harmony TPV) patients, with 17 completing three year follow-up (maximum: 4.1 years). There were no deaths and two early explants. One patient did not complete the three year visit. In patients with available three year echocardiographic data, one had a mild paravalvular leak and the rest had none/trace; one patient had mild pulmonary valve regurgitation and the remainder had none/trace. The three year mean right ventricular outflow tract echocardiographic gradient was 15.7±5.5 mm Hg. Radiographically, no late frame fractures or erosions were identified. At two years, two patients presented with an increased echocardiographic outflow gradient (one mixed lesion with moderate/severe pulmonary valve regurgitation). Computed tomography scans identified neointimal tissue ingrowth within the stent frame in both patients, and they were treated successfully with a transcatheter valve-in-valve procedure (Melody TPV). Additional follow-up computed tomography scans performed at 3.2±0.5 years after implant were obtained in 16 patients and revealed luminal tissue thickening at the inflow and outflow portion of the frame with no significant alteration of the valve housing. The authors concluded that three year results from the Native TPV EFS revealed stable Harmony TPV device position, good valve function in most, and the absence of moderate/severe paravalvular leak and significant late frame fractures and that two patients developed significant neointimal proliferation requiring valve-in-valve treatment, while all others had no clinically significant right ventricular outflow tract obstruction.

Non-FDA approved Devices and off-label use of FDA approved devices
There are potential off-label uses of transcatheter pulmonary valve (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. Ruiz et al. (2019) address the issues that need to be resolved for the use of TPV implantation in nRVOT include establishing appropriate pre-procedural imaging criteria for patient and valve selection to perform TPV implantation in nRVOT; evaluation of feasibility and safety of larger transcatheter valves in nRVOT; assessment of long-term outcomes and durability with transcatheter valves in nRVOT and regulatory approval of TVP implantation in nRVOT.

Devices that are being investigated include the Alterra Adaptive Prestent™ (Edwards Life Sciences, Irvine, CA) which is a size reducer and docking station for the 29-mm SAPIEN S3 valve in the RVOT (Balzer, 2019; Ruiz, et al., 2019; Cabalka, et al., 2018; Martin, et al., 2018; Zahn, et al., 2018; Bergersen, et al., 2017; Cools, et al., 2015; Malekzadeh-Milani, et al., 2014; Meadows, et al., 2014; Demkow, et al., 2014; Boshoff, et al., 2013; Odemis, et al., 2013). The Alterra Adaptive Prestent is a self-expanding, partially covered stent designed to internally reconfigure RVOT, which is purported to make them suitable for implantation of a commercially available balloon expandable heart valve, the SAPIEN 3. The device was designed to internally remodel a wide variety of RVOT morphologies, to create a suitable “landing zone” for implantation of a standard balloon expandable transcatheter heart valve (THV) in an attempt to treat a broader range of patients (Zahn, et al., 2018). The device has not received FDA approval and is considered experimental, investigational or unproven.

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 six 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 five-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 (0-32%); compression or injury of the left coronary artery during the procedure (0.7-0.98%); endocarditis (0-10%), which may lead to blood stream 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; 2018; 2020).

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. The mitral valve allows blood to flow from the left atrium to the left ventricle. Mitral valve regurgitation (MR) happens when the valve doesn't close properly, allowing blood to flow back into the atrium from the ventricle during systole. The heart has to work harder, resulting in an enlarged left ventricle. If not treated, this can lead to problems including heart failure.

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). There are instances in which both primary and secondary MR are present. Identification of the cause and type (primary or secondary) of MR is required for appropriate management of MR and associated conditions (Herrmann, et al., 2019, Gaasch, 2020; Nishimura, et al., 2017).

There is a limited role for medical management in patients with chronic primary MR, since mitral valve intervention is required to address the primary process. Surgical treatment is considered for patients with functional disability and for patients with no symptoms or only mild symptoms but with progressively deteriorating left ventricle (LV) function or progressively increasing LV dimensions, as documented by noninvasive studies. Without surgical treatment, the prognosis for patients with MR and heart failure is poor, so mitral valve repair or replacement is recommended for symptomatic patients (Thomas, et al., 2019; Gaasch, 2020).

The best therapy for chronic secondary MR is not clear because MR is only one component of the disease, with clinical outcomes also related to severe LV systolic dysfunction, coronary disease, idiopathic myocardial disease, or other diseases affecting the heart muscle. Thus, restoration of mitral valve competence is not curative. First-line therapy for secondary MR is management of heart failure with reduced ejection fraction including pharmacologic therapy as well as cardiac resynchronization therapy, as indicated. Treatment of secondary MR includes assessment and management of concurrent conditions, particularly coronary artery disease (CAD). Standard recommendations for coronary revascularization apply. This includes surgical revascularization for

patients with ischemic cardiomyopathy (LVEF ≤35%) with CAD amenable to revascularization. Mitral valve intervention (transcatheter mitral valve repair or mitral valve surgery) is proposed in selected patients with secondary MR with criteria including the severity of MR, symptoms on optimal medical therapy, and presence of a concurrent indication for cardiac surgery (coronary artery bypass graft surgery [CABG] or aortic valve surgery) (Gaasch, 2020; Nishimura, et al., 2017).

Many patients who have mitral valve regurgitation are poor candidates for open surgery, cardiopulmonary bypass, and cardiac arrest, due to comorbidities, frailty, or scarring from prior surgeries. People with degenerative or functional MR are usually older (typically over 70 years) and frail, with multiple comorbidities. This increases the perioperative risks of morbidity and mortality for open heart surgery. Percutaneous MV repair may improve the health of these patients without exposing them to the risks of open surgery (NICE, 2019; Hayes, 2018).

Percutaneous/Transcatheter Mitral Valve Repair (PMVR): Many different devices have been created for PMVR which are in various stages of development (e.g., NeoChord DS1000 System, NeoChord, Minneapolis, MN; Mitra-Spacer™, Cardiosolutions, West Bridgewater, Mass; MitraFlex, TransCardiac Therapeutics, Atlanta, Ga (Krishnaswamy, et al. 2020; Herrmann, et al., 2019). 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 (Herrmann, et al., 2019; Hayes, 2018; Armstrong, et al., 2020).

Investigational transcatheter-based approaches for mitral valve repair/replacement include indirect annuloplasty, direct or left ventricular annuloplasty, hybrid surgical, chordal replacement, and left ventricular remodeling (Armstrong, et al., 2020; Herrmann, 2019).

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. The MitraClip has been used to treat both primary and secondary 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., 2020).

Transcatheter MVR with the MitraClip device is performed in the cardiac catheterization laboratory using a combination of fluoroscopic and transesophageal echocardiographic (TEE) guidance. The procedure is usually performed under general anesthesia. Antithrombotic therapy is recommended at the time of and following the procedure. Access is obtained via the femoral vein, and a transseptal puncture is performed to cross the interatrial septum into the left atrium. The MitraClip steerable catheter is then advanced into the left atrium, and echocardiographic guidance is utilized to align the MitraClip device with the regurgitant valve leaflets and into the left ventricle. The MitraClip is then drawn back with the clip arms open in order to grasp the leaflets at the site of regurgitation. The arms are then closed, and Doppler echocardiography is used to determine the reduction in MR. If the reduction in MR is not adequate, the clip arms can be reopened and the placement adjusted prior to final device deployment. It has been reported that in approximately 40 percent of cases, an additional MitraClip may be implanted in order to adequately reduce MR. Real-time two- and three-dimensional transesophageal echocardiography guides the positioning of the trans-septal puncture during the procedure, placement of the mitral clip, and assessment of the mitral valve morphology and regurgitation severity following the clip placement (Armstrong, et al., 2020).

Transcatheter MVR is associated with an overall complication rate of 15-19% at 30 days. Early (30-day) complication rates are primarily due to need for periprocedural blood transfusion, while late events are primarily related to underlying heart failure or patient comorbidities. Complications include access site bleeding, partial clip detachment, and rarely device embolization or development of mitral stenosis (Armstrong, et al., 2020).

U.S. FDA– MitraClip NT Clip Delivery System (CDS) and MitraClip NTR/XTR CDS (Abbott Vascular, Menlo Park, CA): The MitraClip CDS received FDA approval through the PMA process on October 24, 2013 (P100009). 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 MR. 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).

The MitraClip CDS has since been phased out and is no longer in commercial distribution. The MitraClip NT CDS and MitraClip NTR/XTR CDS are design iterations of the MitraClip CDS. The former was approved under P100009/S015 on May 10, 2016; the latter was approved under P100009/S025 on May 23, 2018 (FDA, 2019).

On March 14, 2019 the MitraClip NT CDS and MitraClip NTR/XTR CDS received supplemental FDA PMA approval (P100009/S028) expanding the indication to include secondary MR. The devices, when used with maximally tolerated guideline-directed medical therapy (GDMT), are indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria) in patients with a left ventricular ejection fraction (LVEF) ≥ 20% and ≤ 50%, and a left ventricular end systolic dimension (LVESD) ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease (FDA, 2019).

The MitraClip NT CDS and MitraClip NTR/XTR CDS are contraindicated in patients with the following conditions:

- patients who cannot tolerate procedural anticoagulation or post procedural anti-platelet regimen
- active endocarditis of the mitral valve
- rheumatic mitral valve disease
- evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus

Data from the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) Trial (Stone, et al., 2018) was the basis for the PMA approval decision (NCT01626079).

Literature Review: Percutaneous Mitral Valve Repair

COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) Trial: Stone et al. (2018) reported if patients with heart failure who have secondary mitral regurgitation (MR) due to left ventricular dysfunction have improved health outcomes with transcatheter mitral-valve repair. Patients were randomized to transcatheter mitral valve repair plus medical therapy (n=302) or medical therapy alone (n=312). Eligible patients included those with ischemic or nonischemic cardiomyopathy with a left ventricular ejection fraction of 20-50%; moderate to severe (grade 3+) or severe (grade 4+) secondary MR confirmed by echocardiography before enrolment; symptomatic (New York Heart Association [NYHA] functional class II, III, or IVa [ambulatory]) despite using stable maximal doses of guideline-directed medical therapy and cardiac resynchronization therapy (if appropriate), which were administered in accordance with guidelines of professional societies; mitral valve surgery was deemed not to be appropriate. Each patient was assessed by a team that consisted of a heart-failure specialist, an interventional cardiologist, and a cardiothoracic surgeon with expertise in mitral valve disease. The primary effectiveness endpoint was all hospitalizations for heart failure within 24 months of follow-up, including recurrent events in patients with more than 1 event. The primary safety endpoint was freedom from device-related complications at 12 months (a prespecified objective performance goal was set at 88%). Median follow-up in device group was 22.7 months (16.5 months in control group). Hospitalizations for heart failure within 24 months was 35.8% per patient-year in the device group as compared with 67.9% per patient-year in the control group ($p<0.001$). Rate of freedom from device-related complications at 12 months was 96.6% ($p<0.001$) for comparison with the performance goal. Death from any cause within 24 months occurred in 29.1% of the patients in the device group as compared with 46.1% in the control group ($p<0.001$). The authors concluded that “among patients with heart failure and moderate-to-severe or severe secondary MR who remained symptomatic despite the use of maximal doses of guideline-directed medical therapy, transcatheter mitral-valve repair resulted in a lower rate of hospitalization for heart failure and lower all-cause mortality within 24 months of follow-up than medical therapy alone. The rate of freedom from device-related complications exceeded a prespecified safety threshold”. A reported limitation of the

study states that long term follow-up, which is to be ongoing thru five years, is necessary to characterize the safety and effectiveness of the device.

Arnold et al. (2019) reported the health status outcomes of patients in the COAPT study. Health status was assessed at baseline and at one, six, 12, and 24 months with the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the SF-36 health status survey. The primary health status endpoint was the KCCQ overall summary score (KCCQ-OS; range 0 to 100; higher=better; minimum clinically important difference=5 points). At baseline, patients had substantially impaired health status. While health status was unchanged over time in the standard care arm, patients randomized to transcatheter mitral-valve repair (TMVr) demonstrated substantial improvement in the KCCQ-OS at one month, with only slight attenuation of this benefit through 24 months. At 24 months, 36.4% of TMVr patients were alive with a moderately large (≥10-point) improvement versus 16.6% of standard care patients ($p< 0.001$). TMVr patients also reported better generic health status at each time point. The authors reported the following study limitations: COAPT was a nonblinded trial which may introduce bias; the true health status of patients who died, had they survived, is not knowable; the durability of the health status benefit of TMVr beyond 24 months is not known, which is an important consideration in patients with underlying cardiomyopathy and comorbidities.

Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation (MITRA-FR) (NCT01920698): Obadia et al. (2018) reported if percutaneous mitral-valve repair (PMVR) improves clinical outcomes in patients who have chronic heart failure with reduced left ventricular ejection fraction and severe secondary mitral-valve regurgitation. Patients were randomized in a 1:1 ratio to undergo PMVR in addition to receiving medical therapy (intervention group; n=152) or to receive medical therapy alone (control group; n=152). Patients were eligible if they had severe secondary MR with a regurgitant volume of >30 ml per beat or an effective regurgitant orifice area of >20 mm^2 as assessed by echocardiography, in accordance with the 2012 guidelines of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery. Patients were also required to have a LVEF between 15% and 40% and to have chronic heart failure symptoms (assessed as NYHA functional class ≥II). Patients were considered to be unsuitable candidates for mitral valve surgery, with a EuroSCORE II value of 6.6 (IQR 3.5 to 11.9) in the PMVR group compared with 5.9 (IQR 3.4 to 10.4) in the control group. Primary outcome measure was composite of death and readmission for heart failure. Secondary outcome measures were echocardiographic parameters, MR grade, NYHA class and quality of life. At 12 months, the rate of the primary outcome was 54.6% (83 of 152 patients) in the intervention group and 51.3% (78 of 152 patients) in the control group (p=0.53). The rate of death from any cause was 24.3% (37 of 152 patients) in the intervention group and 22.4% (34 of 152 patients) in the control group. The rate of unplanned hospitalization for heart failure was 48.7% (74 of 152 patients) in the intervention group and 47.4% (72 of 152 patients) in the control group. Reported limitation is missing follow-up data for the assessment of echocardiography, functional status, natriuretic peptide, and quality of life. At one year at least 48 patients in the intervention group had MR grade of 2+ or higher. The authors concluded that “among patients with severe secondary MR, the rate of death or unplanned hospitalization for heart failure at one year did not differ significantly between patients who underwent percutaneous mitral-valve repair in addition to receiving medical therapy and those who received medical therapy alone”.

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. EVEREST II consists of a prospective randomized arm and a high-risk registry arm (Clinicaltrials.gov number NCT00209274).

EVEREST II Randomized Arm: Feldman et al. (2015; 2011) reported one and five-year results of the EVEREST II study. Patients were randomized to percutaneous mitral valve repair (PMVR) with the MitraClip device (n=184) or conventional mitral valve surgery (n=95) in a 2:1 ratio. Blinding of patients and treating personnel was not possible. A total of 21/279 patients who underwent randomization withdrew consent for treatment (3% in the PMVR group and 16% in the surgery group). 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). Patients with both functional and degenerative MR were included. 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. Of 258 treated patients, 243 (94%) complied with the protocol for the 12-month follow-up. After one year, 37/178 (21%) patients allocated to PMVR went on to receive surgical intervention. The primary outcome at one year demonstrated that conventional surgery was more effective than PMVR for reducing MR. However, improvements in left ventricular (LV) remodeling and clinical outcomes were similar for both approaches and the percutaneous approach demonstrated a greater level of safety than did surgery.

The 5-year analysis of the all-treated cohort included 154 (87%) and 56 (70%) patients in the device and surgical arms, respectively. At 5 years, the rate of the composite endpoint of freedom from death, MV surgery, or reoperation, and 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=0.36) for percutaneous repair and surgery, respectively. Limitations included no blinding of assessment to treatment; some patients with MR grade <3 included in violation of inclusion criteria; 20% patients were excluded, withdrew, or were lost to follow-up. The authors concluded that although mitral valve repair surgery is superior to percutaneous mitral valve intervention using the MitraClip device in reducing the severity of MR, the device reduces symptoms, produces durable reduction of MR, and promotes favorable reverse remodeling of the left ventricle 5 years after intervention.

Four-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation (MR) were published by Mauri et al., for the EVEREST II Investigators (2013). Patients with grade 3+ or 4+ 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 36 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. Reported limitation of this study included comparator group was recruited retrospectively, the patient number is limited, transesophageal echocardiograms were not available for review in all patients, and several of the patients included did not have appropriate anatomic criteria for MitraClip placement. 12-month echocardiographic and functional data were obtained and reported for surviving patients only, and no imputation for deceased patients' data was performed. Thus, the

matched data reported may represent an overestimation of the true benefit provided by MitraClip placement. The authors concluded that data from this study suggest a role for the MitraClip device in treating symptomatic patients with 3 to 4+ MR who are at high risk of mortality with MV surgery. MitraClip device placement in this high-risk group is feasible, effective in reducing symptoms and improving clinical status, and relatively safe in patients who otherwise have no safe option to reduce MR. Favorable LV remodeling demonstrates that the degree of reduction in MR obtained with the MitraClip device is hemodynamically important.

Kar et al. (2018) reported 5-year clinical outcomes to the EVEREST II High Risk Study. At five years, clinical follow-up was achieved in 90% of 78 enrolled patients (46 with functional MR (FMR) and 32 with degenerative MR (DMR)). The rate of post procedural adverse events declined from 30 days to one year follow-up and was stable thereafter through five years. Two patients (2.6%) developed mitral stenosis. Two patients underwent MV surgery, including one due to MS. A total of 42 deaths were reported through five years. Effectiveness measures at five years showed reductions in MR severity to ≤2+ in 75% of patients (p=0.0107), left ventricular (LV) end-diastolic volume (−38.2 mL; 95% CI −55.0 to –21.4; p<0.0001) and LV end-systolic volume (−14.6 mL; 95% CI −27.7 to −1.5; p=0.0303) compared with baseline. The New York Heart Association (NYHA) functional class improved from baseline to five years (p<0.005), and septal-lateral annular dimensions remained stable with no indication of mitral annular dilation through five years. The authors concluded that long term safety and efficacy of MitraClip in high-surgical risk patients was maintatined through five years. The observed mortality was most likely a consequence of the advanced age and comorbidity profile of the enrolled patients, while improvements in NYHA class in surviving patients were durable through long-term follow-up. The EVEREST II HRS is limited by the small study population, enrollment of both patients with functional MR and degenerative MR, and a lack of medical control group.

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). The study included symptomatic patients with grades 3 to 4+ MR with valve morphology meeting the criteria necessary for MV device placement. All 351 patients met protocol entry criteria for high surgical risk: 151 patients (43.0%) had an STS score of at least 12%, and 200 patients (57.0%) had an STS score<12% but had at least 1 of the protocol-defined risk factors, which characterized the patient as high risk. 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. The primary objective of the first phase of the ACCESS-EU study (reported) was to gain information with regard to the use of the MitraClip system in Europe with respect to health economics and clinical care, to define demographic data of patients, and to provide further evidence of the safety and effectiveness of the MitraClip System in a real-world setting. A primary outcome was not specified. 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. The authors concluded that in the real-world, post-approval experience in Europe, patients undergoing the MitraClip therapy are high-risk, elderly patients, mainly affected by functional MR. In this patient population, the MitraClip procedure is effective with low rates of hospital mortality and adverse events.

Systematic Review and Meta-Analysis: In a meta-analysis, Marmagkiolis et al. (2019) evaluated the safety and efficacy of percutaneous mitral valve repair for the management of functional mitral insufficiency. Studies comparing percutaneous mitral valve repair using the MitraClip device against conservative therapy for the management of functional mitral regurgitation were included. Seven studies with 1174 patients in the MitraClip group and 1015 patients in the medical therapy group met inclusion criteria. Two studies (COAPT and MITRA-FR) were RCTs, two were single-center observational studies, and three compared their MitraClip cohort with a propensity-matched patient group. Three studies were performed in North America and the rest were performed in Europe. Outside the United States, the device is more often used to treat functional mitral regurgitation in patients with heart failure. The 12-month mortality in the MitraClip group was 18.4% compared with 25.9% in the medical therapy group ($p < 0.002$). The rate of readmission at 12 months was 29.9% in the MitraClip group compared with 54.1% in the medical therapy group ($p < 0.0001$). The prognostic efficacy of MitraClip repair appears to be more substantial over longer follow-up period over medical therapy alone. The authors concluded that based on the results of this meta-analysis, percutaneous mitral valve repair with MitraClip appears to be superior to medical therapy for symptomatic moderate-to-severe functional mitral insufficiency. Further clinical research is needed to identify the ideal patient subgroups who receive maximum benefit with the MitraClip therapy. Several current and planned studies such as REALISM, EXPAND, MitraClipANZ, PREMISE, and ACCESS-EU are expected to help identify such subgroup.

In a systematic review and meta-analysis, Giannini et al. (2018) reported survival outcomes of MitraClip with those of medical therapy in patients with functional MR. A total of six eligible observational studies including 2121 participants. MitraClip (n=833) or conservative therapy (n=1288) were included. Four studies exclusively enrolled patients with functional MR while the remaining studies included both functional and degenerative MR. Patients enrolled were predominantly male (78%) and characterized by advance age (median age 71 years), high estimated surgical risk (median logistic EuroSCORE 21% and median Society of Thoracic Surgeons score 11%) and a high burden of co-morbidities (i.e. chronic kidney disease 45%, chronic obstructive pulmonary disease 45%, diabetes mellitus 45%, a history of previous myocardial infarction 25%, and percutaneous coronary intervention 49%). Despite optimal medical therapy, all patients were symptomatic for dyspnea, with 95% in New York Heart Association Class III–IV. The mechanism of MR was functional in 93% of patients with 67% of ischemic etiology. The primary outcome was death by any cause. The secondary outcome was freedom from readmission. Median follow-up was 400 days. MitraClip, when compared with medical therapy ($p=0.005$), was associated with significant reduction of death ($p=0.002$) and of readmission due to cardiac disease. At patient-level analysis, including 344 patients, MitraClip confirmed survival benefit over medical therapy for all patients with functional MR and among the most important subgroups. Adverse events included profuse bleeding that required multiple transfusions 13% (9–20%), whereas the incidence of new onset of atrial fibrillation occurred in 1% (0.5–4%). Reported limitations included lack of randomized controlled trials (RCTs) and the study included a wide spectrum of high-risk patients with both functional and degenerative MR. The authors concluded that compared with conservative treatment, MitraClip is associated with a significant survival benefit. This superiority is particularly pronounced among patients with functional MR and across all the main subgroups.

In a systematic review and meta-analysis, De Rosa et al. (2018) reported long-term survival, clinical status, and echocardiographic findings of patients with severe functional mitral regurgitation (FMR) undergoing MitraClip (MC) treatment and to explore the role of baseline features on outcome. A total of 23 studies were included (n=3,253). Only six studies reported the primary endpoint data at two-year follow-up. The in hospital death rate was 2.31%, whereas the mortality rate was 5.37% at 1 month, 11.87% at 6 months, 18.47% at one year and 31.08% at two years. Mitral regurgitation Grade <3+ was observed in 92.76% patients at discharge and in 83.36% patients at follow-up. At follow-up, 76.63% of patients NYHA Class I–II and there were significant improvements in left ventricular (LV) volume, ejection fraction, and pulmonary pressure. Atrial fibrillation had a statistically significant negative effect on one year survival and on the reduction in left ventricular end-diastolic and end-systolic volume. Study limitations included one unpublished study presented at an international congress and only one study had a randomized design. Therefore, the heterogeneity observed for some results, such as the reduction in LVEF at follow-up, may reflect differences between the study cohorts included in the meta-analysis. The authors concluded that in patients with heart failure and severe functional MR, TMVr with MitraClip is safe and results in a durable MR reduction associated with significant clinical and echocardiographic improvement. Despite the need for confirmation by randomized studies, the results of this analysis suggest good performance of MitraClip in terms of all-cause mortality in this particularly high-risk population.

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 (≥six-month including early) all-cause mortality. The MR etiology was mixed including degenerative and functional. A total of seven studies (n=1015), six observational (non-randomized) comparative studies and only one RCT (EVEREST II), comparing MitraClip with surgical repair with MR were included in this systematic review and meta-analysis. The late follow-up duration was from 180 days to five years. 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.

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, one year data were available for 1064 MitraClip patients (one year data for surgical repair patients was limited to 47 patients and was not reported). Overall, among MitraClip patients, the one year mortality rate was 13.0%, the one 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 six 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".

Hayes Medical Technology Report: A 2018 Hayes, Inc. Medical Technology Directory Comparative Effectiveness Review, Percutaneous Mitral Valve Repair summarized the clinical evidence stating that "A single randomized controlled trial (RCT), the EVEREST II RCT found that patients who are candidates for conventional open surgery had some minor short-term benefits such as reduced need for transfusion, but these perioperative benefits did not outweigh the longer-term risks of need for additional surgery and recurrence of MR. One nonrandomized study found no differences in survival outcomes between high-risk patients treated with the MitraClip and those treated with open surgery. In high-risk patients who are not acceptable candidates for surgery, six nonrandomized studies that compared MitraClip implantation with optimal medical management found benefits such as improved scores of heart function and improved survival after the MitraClip procedure; however, RCTs are needed to confirm these promising findings. Two studies compared MitraClip implantation with minimally invasive open surgery and one study compared the Carillon system with usual care, but these nonrandomized studies do not provide sufficient evidence to support conclusions about relative efficacy" (Hayes, 2018: annual review 2019; 2020).

An UpToDate document on management of chronic primary mitral regurgitation recommends percutaneous mitral valve repair for patients with prohibitive surgical risk because of severe comorbidities who are severely symptomatic patients (New York Heart Association class III to IV) despite optimal guideline-directed medical therapy with chronic severe primary MR (stage D) and who have a reasonable life expectancy and favorable anatomy for transcatheter repair (Gaasch, 2019).

An UpToDate document on transcatheter mitral valve repair (TMVR) reports that based on evidence in patients with primary MR, TMVR using the MitraClip device is less effective at reducing MR than mitral surgery, with subsequent surgery for mitral valve dysfunction at one year more common after TMVR. On the other hand, major post procedural adverse events are less frequent with TMVR. Clinical studies have demonstrated reduction in the severity of primary MR, reduced left ventricular and left atrial volumes, and improved exercise capacity and quality of life in patients treated with the MitraClip device (Armstrong, et al., 2020).

An UpToDate document on management and prognosis of chronic secondary mitral regurgitation recommends that for most patients with moderate-to-severe or severe (3+ to 4+) chronic secondary MR with LVEF ≤50 percent and New York Heart Association (NYHA) functional class II, III, or IVa (ambulatory) HF despite optimum evidence-based management (pharmacologic therapy plus cardiac resynchronization therapy, as indicated), suggest referral to a heart valve team to assess the feasibility and potential benefit and risk of transcatheter mitral valve repair (TMVR). For some patients durable TMVR is not feasible or appropriate due to technical issues, life expectancy (with TMVR) is less than one year, or comorbidities limiting the likelihood of improvement in the patient's quality of life. Recommendations for TMVR for secondary MR are evolving as randomized trials were completed after publication of major society guidelines (Gaasch, 2019).

Summary: Percutaneous Mitral Valve Repair: A large RCT with five years of follow-up found that patient survival and reduction in degenerative 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. On the other hand, major post procedural adverse events are less frequent with percutaneous mitral valve repair. This approach has become an option for patients with 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 MR.

Appropriate patient selection criteria in terms of MR etiology for percutaneous mitral valve repair (functional MR) has not been well-established. Two randomized controlled trials assessing the efficacy of TMVR using the MitraClip compared with continued medical therapy alone in patients with secondary MR yielded different results.

Transcatheter Mitral Valve Replacement (MVR): Transcatheter mitral valve replacement (MVR) is being investigated as an alternative for patients with severe mitral valve disease who are poor candidates or have increased risk for conventional mitral valve surgery. Several transcatheter mitral valve replacement (MVR) devices are under development with ongoing clinical trials. One device is the Permavalve™ (MicroInterventional Devices, Inc., Newtown, PA) transcatheter MVR device which is under investigation in the United States.

There are currently no FDA-approved devices for transcatheter MVR through the PMA process.The transcatheter MVR field is at an early stage, and progress will be significantly slower than the development of TAVR due to the complexity of the mitral valve anatomy and pathology. Challenges exist with the currently available technology. Improved and less bulky valve designs and delivery methods may improve technical success. A better understanding of the kind of anticoagulation needed for transcatheter MVR being developed. Optimizing the patient-selection process by using multimodality imaging tools to accurately measure the annulus size and evaluate the risk of LVOT obstruction is essential to minimize complications (Armstrong, et al., 2020; Guerrero, et al., 2017; Regueiro, et al., 2017b; Ramwali, et al., 2016; De Backer, et al., 2014). Evidence in the peer-reviewed literature is limited to case series and registry data with very small numbers of patients. Further studies with a larger number of patients and longer follow-up are needed to determine device durability and the ideal candidates for MVR (Regueiro, et al., 2017a; Guerrero, et al., 2016; Puri, et al., 2016).

June 2021, Tendyne™ transcatheter mitral valve implantation (TMVI) replacement system (Abbott Vascular, Menlo Park, CA) received Breakthrough Device status from the FDA. The breakthrough designation for the Tendyne system, which is in ongoing clinical trials, is for patients who have severe mitral annular calcification and need valve replacement but can't get open-heart surgery. The Breakthrough Devices Program is a voluntary program for certain medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. The goal of the Breakthrough Devices Program is to provide patients and health care providers with timely access to these medical devices while preserving the statutory standards for premarket approval, 510(k) clearance, and De Novo marketing authorization, consistent with the Agency's mission to protect and promote public health.

Mitral Valve-in-Valve (MViV) Implantation

Transcatheter mitral valve-in-valve implantation has been proposed as a treatment for failed surgically implanted mitral valve bioprosthesis. The standard treatment for a failed bioprosthetic valve is repeat open heart surgery to replace the valve. Repeat open heart surgery is associated with a higher risk of morbidity and mortality than primary surgery. Transapical transcatheter mitral valve-in-valve implantation is a less invasive alternative when repeat open heart surgery is considered to have a high risk. It avoids the need for routine cardiopulmonary bypass and can be used to treat failed bioprosthetic mitral valves originally placed during open heart surgery (NICE, 2021).

Literature Review—Mitral Valve-in-Valve Implantation
Whisenant et al. (2020) reported on registry-based prospective cohort study of SAPIEN 3 MViV, patients entered in the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry from June 2015 to July 2019 with objective to assess contemporary outcomes of transcatheter mitral valve-in-valve (MViV) SAPIEN 3 MViV replacement. The primary efficacy end point was one-year mortality. The primary safety end point was procedural technical success as defined by the Mitral Valve Academic Research Consortium criteria. Secondary end points included 30-day mortality, New York Heart Association-defined heart failure, and mitral valve performance. The study included 1,529 patients (mean [SD] age, 73.3 [11.84] years; 904 women [59.1%]) who underwent transseptal or transapical MViV implant at 295 hospitals. Transseptal (TS) MViV involves transesophageal echo-guided TS puncture and over-the-wire delivery of the THV through an expandable 14F or 16F sheath in the femoral vein, and transapical access includes surgical exposure, access, and closure of the left ventricular apex. The mean (SD) Society of Thoracic Surgeons predicted risk of mortality was 11.1% (8.7%). Procedural technical success was achieved for 1480 of 1529 patients (96.8%). All-cause mortality was 5.4% at 30 days and 16.7% at 1 year. Transseptal access was associated with lower one-year all-cause mortality than transapical access (15.8% vs 21.7%; P=.03). Transcatheter MViV led to early, sustained, and clinically meaningful improvements in heart failure (class III/IV New York Heart Association heart failure of 87.1% at baseline vs 9.7% at 1 year). The mean (SD) mitral valve gradient at 1 year was 7 (2.89) mm Hg.

Hu et al. (2018) conducted a systematic review of transcatheter mitral valve-in-valve (TMVIV) and valve-in-ring (TMVIR) implantation for degenerated mitral bioprostheses and failed annuloplasty rings as treatment options for patients deemed unsuitable for repeat surgery. A systematic literature review was conducted to summarize the data regarding the baseline characteristics and clinical outcomes of patients undergoing TMVIV and TMVIR procedures. The inclusion criteria was: patients received either a TMVIV or TMVIR implantation and reported data necessary to assess the baseline characteristics and outcomes. The review included 245 patients (172 patients who underwent TMVIV surgery and 73 patients who underwent TMVIR surgery) were included in the study; 93.5% of patients experienced successful TMVIV or TMVIR implantation. The mortality rates at discharge, 30 days, and 6 months were 5.7%, 8.1%, and 23.4%, respectively. The transapical (TA) access route was used in most procedures (55.2%). The TA and transseptal (TS) access routes resulted in similar outcomes. No significant differences were observed in the short-term outcomes between the patients who developed mitral stenosis versus mitral regurgitation as the mode of failure. The authors note that no standard guidelines exist for the TMVIV and TMVIR procedures and no long-term clinical trials (including randomized trials) have been performed to evaluate these techniques. It was noted that only a few articles reported long-term follow-up data; therefore, evaluation of long-term outcomes was not possible and that all studies included in this study lacked control groups.

Takagi et al. (2018) conducted a meta-analysis of transcatheter mitral valve implantation (TMVI) for deteriorated bioprosthetic valves (valve-in-valve [VIV]-TMVI) and/or failed annuloplasty rings (valve-in-ring [VIR]-TMVI) comparing observed early (30-day) mortality with predicted operative mortality. The study included 17 studies with a total of 1,017 patients undergoing VIV/VIR-TMVI. For each study, data regarding observed 30-day mortality and predicted operative mortality (Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM]) were used to generate risk ratios (RRs) and 95% confidence intervals (CIs). Study-specific estimates were combined using the inverse variance-weighted average of logarithmic RRs in the random-effects model. Onegroup meta-analyses of 30-day/late (including 30-day) mortality rates were also performed in the random-effects model. In all but four studies, the STS-PROM was available and varied from 7.7% to 22.0% (weighted mean, 11.5%). Pooled analyses of all VIV/VIR-TMVI studies demonstrated the 30-day mortality rate of 5.4% (95%CI, 4.0-6.8%), the midterm (1- to 5-year) mortality rate of 13.7% (95%CI, 9.0-18.5%), and significantly lower observed 30-day mortality than predicted operative mortality (RR, 0.67; 95%CI, 0.49-0.91; P = 0.01). It was noted that only two studies included a comparator.

Kamioka et al. (2018) conducted a retrospective review of patients with degenerated mitral bioprostheses who underwent redo surgical mitral valve replacement (SMVR) or TMVR at three U.S. institutions. Clinical and echocardiographic outcomes of patients who had transcatheter mitral valve-in-valve replacement (TMVR) were compared with those of patients who underwent redo SMVR. The study included 62 patients that underwent TMVR and 59 patients that underwent SMVR. Mean age and the Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) scores were significantly higher in patients with TMVR than in those with SMVR (age 74.9 ± 9.4 years vs. 63.7 ± 14.9 years; $p < 0.001$; STS PROM 12.7 ± 8.0% vs. 8.7 ± 10.1%; $p < 0.0001$). Total procedure time, intensive care unit hours, and post-procedure length of stay were all significantly shorter in the TMVR group. There was no difference in mortality at one year between the two groups (TMVR 11.3% vs. SMVR 11.9%; $p = 0.92$). Mean mitral valve pressure gradient and the grade of mitral regurgitation (MR) were similar between the TMVR group and the SMVR group (mitral valve pressure gradient 7.1 ± 2.5 mm Hg vs. 6.5 ± 2.5 mm Hg; $p = 0.42$; MR [≥moderate] 3.8% vs. 5.6%; $p = 1.00$) at 30 days. At one year, the mitral valve pressure gradient was higher in the TMVR group (TMVR 7.2 ± 2.7 vs. SMVR 5.5 ± 1.8; $p = 0.01$), although there was no difference in the grade of MR. The study is limited by the retrospective nature, small number of subjects and the findings should be confirmed by long-term follow-up and larger number of subjects,

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. Edwards Lifesciences was awarded CE Mark approval for the Cardioband transcatheter tricuspid valve system on April 30, 2018 (Overtchuck, et al., 2020; Hayes, 2019; Wagner, et al., 2015; 2016).

Professional Societies/Organizations

American College of Cardiology (ACC)/American Heart Association (AHA): these organizations published updated guidelines for the management of patients with valvular heart disease (Otto, et al., 2020).
The guidelines include the following recommendations:

- Treatment of severe aortic stenosis with either a transcatheter or surgical valve prosthesis should be based primarily on symptoms or reduced ventricular systolic function. Earlier intervention may be considered if indicated by results of exercise testing, biomarkers, rapid progression, or the presence of very severe stenosis.
- Indications for transcatheter aortic valve implantation are expanding as a result of multiple randomized trials of transcatheter aortic valve implantation atrioversus surgical aortic valve replacement. The choice of type of intervention for a patient with severe aortic stenosis should be a shared decision-making process that considers the lifetime risks and benefits associated with type of valve (mechanical versus bioprosthetic) and type of approach (transcatheter versus surgical).
- A mitral transcatheter edge-to-edge repair is of benefit to patients with severely symptomatic primary mitral regurgitation who are at high or prohibitive risk for surgery, as well as to a select subset of patients with secondary mitral regurgitation who remain severely symptomatic despite guideline-directed management and therapy for heart failure.
- Bioprosthetic valve dysfunction may occur because of either degeneration of the valve leaflets or valve thrombosis. Catheter-based treatment for prosthetic valve dysfunction is reasonable in selected patients for bioprosthetic leaflet degeneration or paravalvular leak in the absence of active infection.

Recommendations for choice of surgical aortic valve replacement (SAVR) versus transcatheter aortic valve implantation (TAVI) for Patients for Whom a Bioprosthetic aortic valve replacement (AVR) Is Appropriate:

- For symptomatic and asymptomatic patients with severe AS and any indication for AVR who are <65 years of age or have a life expectancy >20 years, SAVR is recommended.(COR 1 LOE A)
- For symptomatic patients with severe aortic stenosis (AS) who are 65 to 80 years of age and have no anatomic contraindication to transfemoral TAVI, either SAVR or transfemoral TAVI is recommended after shared decision-making about the balance between expected patient longevity and valve durability. (COR 1 LOE A)

- For symptomatic patients with severe AS who are >80 years of age or for younger patients with a life expectancy <10 years and no anatomic contraindication to transfemoral TAVI, transfemoral TAVI is recommended in preference to SAVR.(COR 1 LOE A)
- In asymptomatic patients with severe AS and an left ventricular ejection fraction (LVEF) <50% who are ≤80 years of age and have no anatomic contraindication to transfemoral TAVI, the decision between TAVI and SAVR should follow the same recommendations as for symptomatic patients in Recommendations above (COR1; LOE B-NR)
- For asymptomatic patients with severe AS and an abnormal exercise test, very severe AS, rapid progression, or an elevated BNP (COR 2a indications for AVR), SAVR is recommended in preference to TAVI. (COR1; LOE B-NR)
- For patients with an indication for AVR for whom a bioprosthetic valve is preferred but valve or vascular anatomy or other factors are not suitable for transfemoral TAVI, SAVR is recommended. (COR 1 LOE A)
- For symptomatic patients of any age with severe AS and a high or prohibitive surgical risk, TAVI is recommended if predicted post-TAVI survival is >12 months with an acceptable quality of life .(COR 1 LOE A)

Recommendations for intervention for chronic primary mitral regurgitation (MR):

- In severely symptomatic patients (NYHA class III or IV) with primary severe MR and high or prohibitive surgical risk, transcatheter edge-to-edge repair (TEER) is reasonable if mitral valve anatomy is favorable for the repair procedure and patient life expectancy is at least 1 year (COR 2A LOE B-NR)

Recommendations for intervention for secondary MR

- In patients with chronic severe secondary MR related to LV systolic dysfunction (left ventricular ejection fraction [LVEF] <50%) who have persistent severe symptoms (NYHA class II, III, or IV) while on optimal guideline-directed management and therapy for HF (Stage D), TEER is reasonable in patients with appropriate anatomy as defined on and transesophageal echocardiographic (TEE) and with LVEF between 20% and 50%, LVESD ≤70 mm, and pulmonary artery systolic pressure ≤70 mm Hg (COR 2A LOE B-R)

Recommendations for intervention for prosthetic valve stenosis:

- In patients with symptomatic severe stenosis of a bioprosthetic or mechanical prosthetic valve, repeat surgical intervention is indicated unless surgical risk is high or prohibitive (COR 1; LOE B-NR)
- For severely symptomatic patients with bioprosthetic aortic valve stenosis and high or prohibitive surgical risk, a transcatheter valve-in-valve (ViV) procedure is reasonable when performed at a Comprehensive Valve Center (COR 2A LOE B-NR)

Recommendations for intervention for prosthetic valve regurgitation:

- In patients with prosthetic paravalvular regurgitation with the following: 1) either intractable hemolysis or NYHA class III or IV symptoms and 2) who are at high or prohibitive surgical risk and 3) have anatomic features suitable for catheter-based therapy, percutaneous repair of paravalvular leak is reasonable when performed at a Comprehensive Valve Center. (COR 2A LOE B-NR)
- For patients with severe HF symptoms caused by bioprosthetic valve regurgitation who are at high to prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a Comprehensive Valve Center. (COR 2A LOE B-NR)

Recommendations
Class (Strength) of Recommendation (COR):
Class 1 (Strong)
Class 2a (Moderate
Class 2b (weak)

Level of Evidence (LOE)
Level A
High quality evidence from more than one RCT
Meta-analysis of high quality RCTs

One or more RCTs corroborated b high quality registry studies

Level B-R
Moderate-quality evidence from one or more RCTs
Meta-analyses of moderate-quality RCTs

Level B-NR
Moderate quality from one or more well-designed, well executed nonrandomized studies, observational studies, or registry studies
Meta-analyses of such studies

The guidelines note in the section for Evidence Gaps and Future Directions for Patients With (valvular heart disease) VHD:
Promoting equity:

- Identify and address disparities in outcomes and survival across diverse patient populations
- Develop novel, cost-effective approaches for long-term management in rural settings
- Expand access to therapies for valvular dysfunction

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). This guideline was updated in 2018 (Stout, et al., 2018). The updated guideline addresses percutaneous pulmonary replacement with recommendations for Tetralogy of Fallot (TOF) stating:

- Pulmonary valve replacement (surgical or percutaneous) for relief of symptoms is recommended for patients with repaired TOF and moderate or greater pulmonary regurgitation (PR) with cardiovascular symptoms not otherwise explained (Class or Recommendation I; Level of evidence B-NR)
- Pulmonary valve replacement (surgical or percutaneous) is reasonable for preservation of ventricular size and function in asymptomatic patients with repaired TOF and ventricular enlargement or dysfunction and moderate or greater PR (Class or Recommendation IIa; Level of evidence B-NR)

Transcatheter Cerebral Embolic Protection (TCEP) Devices
Despite the new-generation TAVR devices and increased operator experience, the risk of cerebrovascular events varies from 2.7% to 5.5% at 30 days. Transcatheter cerebral embolic protection (TCEP) is proposed to address the risk of neurological injury during or after TAVR. Several TCEP devices are commercially available outside the U.S. The Sentinel™ Cerebral Protection System (Boston Scientific Corporation, Marlborough, MA) is the first TCEP device to be FDA-approved. The Sentinel Cerebral Protection System (CPS) is a single-use device that filters and collects debris released during TAVR in order to prevent the debris from migrating to the brain. The device contains two independent filters within a single-delivery catheter that is delivered via the right radial artery or brachial artery. The larger proximal filter is deployed in the brachiocephalic trunk, and the smaller distal filter is deployed in the left common carotid artery before TAVR (Gasior, 2018; Hayes, 2018).

U.S. Food and Drug Administration (FDA): The Sentinel™ Cerebral Protection System (Boston Scientific Corporation, Maple Grove, MN) received 510(k) premarket FDA approval on 2/19/2020 as a Class II medical device (K192460). It is indicated for use as an embolic protection device to capture and remove thrombus/debris while performing transcatheter aortic valve replacement procedures. The diameters of the arteries at the site of filter placement should be between 9 – 15 mm for the brachiocephalic and 6.5 – 10 mm in the left common carotid.

The TriGUARD 3™ Cerebral Embolic Protection Devic (Keystone Heart, Tampa FL) has not yet received FDA approval and is not commercially available in the U.S.

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

and an UpToDate report do not indicate the use of the Sentinel cerebral protection system or embolic protection devices in association with transcatheter aortic valve replacement to be generally accepted/established or standard of care (Hermann, et al., 2019; Dalby, et al., 2020; Veluz, et al., 2017; Kodali, et al., 2016).

Kapadia et al. (2017) conducted a prospective randomized multicenter controlled trial (SENTINEL RCT) evaluating the safety and efficacy of transcatheter cerebral embolic protection (TCEP) during TAVR. Nineteen centers randomized 363 patients undergoing TAVR to a safety arm (n=123), device imaging (n=121), and control imaging (n=119). The primary safety endpoint consisted of major adverse cardiac and cerebrovascular events (MACCE) at 30 days, and the primary efficacy endpoint was reduction in new lesion volume in protected brain territories on magnetic resonance imaging scans at two to seven days. Patients underwent neurocognitive assessments, and the debris captured was analyzed. The rate of MACCE (7.3%) was noninferior to the performance goal (18.3%, p noninferior <0.001) and not statistically different from that of the control group (9.9%; p=0.41). New lesion volume was 178.0 mm^3 in control subjects and 102.8 mm^3 in the device arm (p=0.33). A post hoc multivariable analysis identified pre-existing lesion volume and valve type as predictors of new lesion volume. Strokes at 30 days were 9.1% in control subjects and 5.6% in patients with devices (p=0.25) Neurocognitive function was similar in control subjects and patients with devices, but there was a correlation between lesion volume and neurocognitive decline (p=0.0022). Debris found within filters in 99% of patients included thrombus, calcification, valve tissue, artery wall, and foreign material. The dual-filter embolism protection device was safely deployed and effective in collecting particulate embolic debris from patients undergoing TAVR, but reduction in cerebral ischemic lesion volume as assessed by MRI was not statistically significan. There were numerous limitations to this study. Follow-up MRI studies were not obtained in 25% of patients from the imaging cohort because of patient noncompliance and the need for new pacemakers post-TAVR. The sample size was too small to assess clinical outcomes and too small to evaluate follow-up MRI findings or neurocognitive outcomes. The use of quantitative MRI analysis as a surrogate endpoint must be further clarified, including stricter time windows for follow-up studies and larger sample sizes. There needs to be a requirement of baseline MRI studies to account for previous lesion volume.

Van Mieghem et al. (2016) conducted a RCT (MISTRAL-C) to assess whether use of the filter-based Sentinel™ Cerebral Protection System (CPS) during transcatheter aortic valve implantation (TAVI) can affect the early incidence of new brain lesions, as assessed by diffusion-weighted magnetic resonance imaging (DW-MRI), and neurocognitive performance. A total of 65 patients were randomized 1:1 to transfemoral TAVI with or without the Sentinel CPS. Patients underwent DW-MRI and extensive neurological examination, including neurocognitive testing one day before and five to seven days after TAVI. Follow-up DW-MRI and neurocognitive testing was completed in 57% and 80%, respectively. New brain lesions were found in 78% of patients with follow-up MRI. Patients with the Sentinel CPS had numerically fewer new lesions and a smaller total lesion volume (95 mm^3 vs. 197 mm^3). Overall, 27% of Sentinel CPS patients and 13% of control patients had no new lesions. Ten or more new brain lesions were found only in the control cohort (in 20% vs. 0% in the Sentinel CPS cohort, p=0.03). Neurocognitive deterioration was present in 4% of patients with Sentinel CPS vs. 27% of patients without (p=0.017). The filters captured debris in all patients with Sentinel CPS protection. This study is limited by the small sample size and underpowered due to a higher than expected MRI drop-out rate. A total of 43% of patients did not complete the follow-up MRI study.

In a prospective study, Seeger et al. (2017) evaluated the impact of cerebral embolic protection on stroke-free survival in 802 patients undergoing TAVR for severe aortic stenosis. The Sentinel cerebral embolic protection device was used in 34.9% (n=280) of consecutive patients. In the remaining group of patients (n=522), TAVR was performed without cerebral embolic protection. Neurological follow-up was done within seven days post-procedure. The primary endpoint was a composite of all-cause mortality or all-stroke within seven days. With use of cerebral embolic protection, the rate of disabling and nondisabling stroke was significantly reduced from 4.6% to 1.4% (p=0.03) in the propensity-matched population (n=560). The primary endpoint occurred significantly less frequently, with 2.1% (n=6 of 280) in the protected group compared with 6.8% (n=19 of 280) in the control group (p=0.01). In patients undergoing TAVR, use of a cerebral embolic protection device demonstrated a significantly higher rate of stroke-free survival compared with unprotected TAVR. This study is limited by lack of randomization.

In the Claret Embolic Protection and TAVI (CLEAN-TAVI) blinded RCT, Haussig et al. (2016) evaluated the effect of a cerebral protection device on the number and volume of cerebral lesions in high risk patients with

severe aortic stenosis undergoing TAVR. One hundred patients were randomly assigned to undergo TAVR with a cerebral protection device (filter group; n=50) or without a cerebral protection device (control group; n=50). Brain MRI was performed at baseline, two days and seven days after TAVR. The primary end point was the numerical difference in new positive post procedure diffusion-weighted magnetic resonance imaging (DWMRI) brain lesions at two days after TAVI in potentially protected territories. The first hierarchical secondary outcome was the difference in volume of new lesions after TAVI in potentially protected territories. The use of a cerebral protection device reduced the frequency of ischemic cerebral lesions in potentially protected regions. The number of new lesions was 4.00 in the filter group and 10.00 in the control group. New lesion volume after TAVR was 242 mm^3 in the filter group and 527 mm^3 in the control group. One patient in the control group died prior to the 30-day visit. Life-threatening hemorrhages occurred in one patient in the filter group and one in the control group. Major vascular complications occurred in five patients in the filter group and six patients in the control group. One patient in the filter group and five in the control group had acute kidney injury, and three patients in the filter group had a thoracotomy. Larger studies, with longer follow-up are needed to assess the effect of cerebral protection device use on neurological and cognitive function after TAVR. Clinicaltrials.gov number NCT01833052.

Lam et al. (2019) performed a systematic review to assess the efficacy for embolic protection device (EPD) use in transcatheter aortic valve implantation (TAVI). There were 14 selected research studies on the impact of EPD on TAVI of which seven had sample size less than 50. The studies encompassed 900 patients who underwent TAVI, in which 557 patients received EPD delivery. An imaging modality, the cerebral diffusion-weighted magnetic resonance imaging (DW-MRI), provided information on the presence, number, and volume of silent ischemic emboli. Clinical outcomes included the occurrence of stroke or transient ischemic attack, as well as other organ involvements, such as myocardial infarction and acute renal injury. Neurocognitive tests were adopted to aid evaluation of clinical outcomes. The authors report that overall, in the systematic review, the use of EPD in TAVI has been shown to reduce the volume of new ischemic lesions on cerebral DW-MRI when compared with performing TAVI alone. However, the deployment of EPD may not improve other aspects of neuroimaging tests, such as the number of ischemic lesion per patient. Also, there were no significant difference in hard clinical end points, such as day 30 stroke incidence and mortality. The authors state that additional research is needed to establish the significant benefits of using EPD in patients before they are adopted in the standard TAVI procedure.

Bagur et al. (2017) performed a systematic review and meta-analysis evaluating the impact of embolic protection devices on cerebrovascular events during TAVR. Sixteen studies involving 1170 patients (865/305 with/without embolic protection devices) were included. Multiple types of embolic protection devices were included. The embolic protection device delivery success rate was reported in all studies and was achieved in 94.5% of patients. Meta-analyses comparing the two methods showed no significant differences between patients undergoing TAVR with or without embolic protection devices with respect to clinically evident stroke and 30-day mortality. Embolic protection during TAVR may be associated with smaller volume of silent ischemic lesions and smaller total volume of silent ischemic lesions. However, it may not reduce the number of new-single, multiple or total number of lesions. There was a high rate of loss to follow-up in most of studies.

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

A 2018 Hayes Emerging Technology Report on the Sentinel Cerebral Protection System (CPS) states that in a review of the abstracts retrieved for their report they found mixed outcomes for the use of the Sentinel CPS in patients undergoing TAVR. Reported outcomes suggested that the requested device was safe and captured

debris; however, the evidence was insufficient to conclude that use of the device prevented neurocognitive deficits.

Professional Societies/Organizations: A search of the National Guideline Clearinghouse did not identify any guidelines discussing the Sentinel CPS or transcatheter cerebral embolic protection in general.

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 Medtronic Melody Transcatheter Pulmonary Valve (TPV) 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 Europe 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, Marlborough MA)
- Portico™ Transcatheter Aortic Valve Implantation System (St. Jude Medical, St. Paul, MN)
- ACURATE TA™ (Symetris, Switzerland)
- TriClip™ Transcatheter Tricuspid Valve Repair System (Abbott, Abbott Park, IL)

European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS): These organizations published updated ESC/EACTS Guidelines on the Management of Valvular Heart Disease (Vahanian, et al., 2021). The guidelines include recommendations for transcatheter aortic valve implantation (TAVI) and mitral valve repair.

The guidelines include the following recommendations:

Recommended mode of intervention in patients with aortic stenosis:

- The choice between surgical and transcatheter intervention must be based upon careful evaluation of clinical, anatomical and procedural factors by the Heart Team, weighing the risks and benefits of each approach for an individual patient. The Heart Team recommendation should be discussed with the patient who can then make an informed treatment choice. (Class I/Level C)
- Surgical aortic valve replacement (SAVR) is recommended in younger patients who are low risk for surgery (<75 years and STS-PROM/EuroSCORE II <4%) or in patients who are operable and unsuitable for transfemoral TAVI. (Class I/Level B)
- Transcatheter aortic valve implantation (TAVI) is recommended in older patients (≥75 years), or in those who are high-risk (STS-PROM/ EuroSCORE II >8%) or unsuitable for surgery. (Class I/Level A)
- SAVR or TAVI are recommended for remaining patients according to individual clinical, anatomical and procedural characteristics. (Class I/Level B)

- Non-transfemoral TAVI may be considered in patients who are inoperable for SAVR and unsuitable for transfemoral TAVI (Class IIb/Level C)

Recommendations on indications for mitral valve intervention in chronic severe secondary mitral regurgitation:

Patients with concomitant coronary artery or other cardiac disease requiring treatment:
- Valve surgery is recommended in patients undergoing coronary artery bypass grafting (CABG) or other cardiac surgery (Class I/Level B)
- In symptomatic patients, who are judged not appropriate for surgery by the Heart Team on the basis of their individual characteristics, percutaneous coronary intervention (PCI) (and/or TAVI) possibly followed by TEER (in case of persisting severe SMR) should be considered (Class IIa/Level C)

Patients without concomitant coronary artery or other cardiac disease requiring treatment
- Transcatheter edge-to-edge repair (TEER) should be considered in selected symptomatic patients, not eligible for surgery and fulfilling criteria suggesting an increased chance of responding to the treatment. (Class IIa/Level B)
- Valve surgery may be considered in symptomatic patients judged appropriate for surgery by the Heart Team (Class IIb/Level C)
- In high-risk symptomatic patients not eligible for surgery and not fulfilling the criteria suggesting an increased chance of responding to TEER, the Heart Team may consider in selected cases a TEER procedure or other transcatheter valve therapy if applicable, after careful evaluation for ventricular assist device or heart transplant (Class IIb/Level C)

Recommendations on indications for intervention in tricuspid valve disease

Indications for intervention in secondary tricuspid regurgitation:
- Transcatheter treatment of symptomatic secondary severe tricuspid regurgitation may be considered in inoperable patients at a Heart Valve Centre with expertise in the treatment of tricuspid valve disease. (Class IIb/Level C)

Recommendations on management of prosthetic valve dysfunction

Bioprosthetic failure:
- Transcatheter, transfemoral valve-in-valve implantation in the aortic position should be considered by the Heart Team depending on anatomic considerations, features of the prosthesis, and in patients who are at high operative risk or inoperable (Class IIb/Level B).
- Transcatheter valve-in-valve implantation in the mitral and tricuspid position may be considered in selected patients at high-risk for surgical reintervention (Class IIb/Level B).

Classes of recommendations

Class I: Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective

Class IIb: Usefulness/efficacy is less well established by evidence/opinion

Levels of Evidence

Level of evidence A: Data derived from multiple randomized clinical trials or meta-analyses.

Level of evidence B: Data derived from a single randomized clinical trial or large non-randomized studies.

Level of evidence C: Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

National Institute for Health and Clinical Excellence (NICE) (United Kingdom)

NICE published Interventional Procedure Guidance for transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis (September 2021). The guidance included the following recommendations:

- Evidence on the safety of transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis is adequate and shows some serious but well-recognized complications. Evidence on its efficacy is limited in quality. So, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research.
- Patient selection should be done by a multidisciplinary team which must include interventional cardiologists experienced in the procedure, cardiac surgeons, an expert in cardiac imaging, and where appropriate, a cardiac anaesthetist and a specialist in medicine for older people. The multidisciplinary team should determine the risk level for each patient and the device most suitable for them.
- The procedure is technically challenging and should only be done in specialised centres, and only by clinical teams with special training and experience in complex endovascular cardiac interventions, including regular experience in transcatheter valve implantation procedures. Centres doing these procedures should have cardiac surgical support for emergency treatment of complications and subsequent patient care.
- NICE encourages further research into transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis. Studies should include details on patient selection, type and size of valve used, functional outcomes (New York Heart Association functional class, mitral valve regurgitation), quality of life, patient-reported outcome measures, survival and complications. Studies should report long-term follow up of clinical outcomes and valve durability. NICE may update this guidance on publication of further evidence.

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.

Updated NICE Interventional Procedure (IP) Guidance on percutaneous mitral valve leaflet repair for mitral regurgitation recommends that:

- Current evidence on the safety and efficacy of percutaneous mitral valve leaflet repair for mitral regurgitation is adequate to support the use of this procedure, in patients for whom open surgery is contraindicated following risk assessment, provided that standard arrangements are in place for clinical governance, consent and audit.
- Patient selection should be done by a multidisciplinary structural heart team, typically including an interventional cardiologist, an expert in transesophageal echocardiography, an expert in heart failure, a cardiac anesthetist, a cardiac surgeon and a specialist nurse.
- Percutaneous mitral valve leaflet repair for mitral regurgitation should only be done in specialized centers with access to both cardiac surgical and vascular surgical support in case emergency treatment of complications is needed.
- This procedure should only be done by clinicians with specialist training and supervision by an experienced mentor for at least the first 20 procedures.
- Clinicians should enter details about all patients having percutaneous mitral valve leaflet repair for mitral regurgitation onto the National Institute for Cardiovascular Outcomes Research database.

This NICE IP overview is based on over 10,000 patients. The studies consist of 3 randomized controlled trials (RCTs), 4 single-arm observational studies, 3 systematic reviews, 3 comparative observational studies, and 3 case reports (NICE, 2019).

Updated NICE Interventional Procedure Guidance on valve-in-valve TAVI 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. The committee comments state that the longer-term evidence for valve-in-valve transcatheter aortic valve implantation (ViV-TAVI) is from earlier-generation TAVI devices and the technology is evolving. Longer-term evidence is needed and this should be taken into account by the multidisciplinary team. (NICE, 2019).

Medicare Coverage Determinations

	Contractor	Policy Name/Number	Revision Effective Date
NCD	National	Transcatheter Mitral Valve Replacement/20.33	8/7/2014
NCD	National	Transcatheter Aortic Valve Replacement (TAVR)/20.32	6/21/2019
LCD		No LCDs found	

Note: Please review the current Medicare Policy for the most up-to-date information.

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.

Aortic Valve Implantation

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

CPT®* Codes	Description
33361	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; percutaneous femoral artery approach
33362	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open femoral artery approach
33363	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open axillary artery approach
33364	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; open iliac artery approach
33365	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transaortic approach (eg, median sternotomy, mediastinotomy)
33366	Transcatheter aortic valve replacement (TAVR/TAVI) with prosthetic valve; transapical exposure (eg, left thoracotomy)
33367	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)
33368	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)
33369	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)

Pulmonary Valve Implantation

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

CPT®* Codes	Description
33477	Transcatheter pulmonary valve implantation, percutaneous approach, including pre-stenting of the valve delivery site, when performed

Considered Experimental/Investigational/Unproven when used to report devices for reconfiguration of right ventricular outflow tract (RVOT) used in transcatheter heart valve procedures:

CPT®* Codes	Description
33999	Unlisted procedure, cardiac surgery

Percutaneous Mitral Valve Implantation, Repair or Replacement

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

CPT®* Codes	Description
33418	Transcatheter mitral valve repair; percutaneous approach, including transseptal puncture when performed; initial prosthesis
33419	Transcatheter mitral valve repair; percutaneous approach, including transseptal puncture when performed; additional prosthesis(es) during same session (List separately in addition to code for primary procedure)
0483T	Transcatheter mitral valve implantation/replacement (TMVI) with prosthetic valve; percutaneous approach, including transseptal puncture, when performed

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
0345T	Transcatheter mitral valve repair percutaneous approach via the coronary sinus
0484T	Transcatheter mitral valve implantation/replacement (TMVI) with prosthetic valve; transthoracic exposure (eg, thoracotomy, transapical)
0543T	Transapical mitral valve repair, including transthoracic echocardiography, when performed, with placement of artificial chordae tendineae
0544T	Transcatheter mitral valve annulus reconstruction, with implantation of adjustable annulus reconstruction device, percutaneous approach including transseptal puncture

Tricuspid Valve Repair or Replacement

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
0545T	Transcatheter tricuspid valve annulus reconstruction with implantation of adjustable annulus reconstruction device, percutaneous approach
0569T	Transcatheter tricuspid valve repair; percutaneous approach; initial prosthesis
0570T	Transcatheter tricuspid valve repair; percutaneous approach; each additional prosthesis during same session (List separately in addition to code for primary procedure)

Cerebral Protection Device

Considered Experimental/Investigational/Unproven:

CPT®* Codes	Description
33370	Transcatheter placement and subsequent removal of cerebral embolic protection device(s), including arterial access, catheterization, imaging, and radiological supervision and interpretation, percutaneous (List separately in addition to code for primary procedure) (Code effective 01/01/2022)

HCPCS® Code	Description
C1884	Embolization protective system

References

1. Abdel-Wahab M, Mehilli J, Frerker C, Neumann FJ, Kurz T, Tölg R, Zachow D, et al. Comparison of balloon-expandable vs self-expandable valves in patients undergoing transcatheter aortic valve replacement: the CHOICE randomized clinical trial. JAMA. 2014 Apr 16;311(15):1503-14.

2. Adams DH, Popma JJ, Reardon MJ, Yakubov SJ, Coselli JS, Deeb GM, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med. 2014 May 8;370(19):1790-8.

3. Ailawadi G, Lim DS, Mack MJ, Trento A, Kar S, Grayburn PA, et al; EVEREST II Investigators. One-Year Outcomes After MitraClip for Functional Mitral Regurgitation. Circulation. 2019 Jan 2;139(1):37-47.

4. Al-Abcha A, Saleh Y, Boumegouas M, Prasad R, Herzallah K, Baloch ZQ, et al. Meta-Analysis of Valve-in-Valve Transcatheter Aortic Valve Implantation Versus Redo-surgical Aortic Valve Replacement in Failed Bioprosthetic Aortic Valve. Am J Cardiol. 2021 May 1;146:74-81.

5. Alkhouli M, Rihal CS, Zack CJ, Eleid MF, Maor E, Sarraf M, et al. Transcatheter and Surgical Management of Mitral Paravalvular Leak: Long-Term Outcomes. JACC Cardiovasc Interv. 2017 Oct 9;10(19):1946-1956.

6. Alozie A, Paranskaya L, Westphal B, Kaminski A, Sherif M, Sindt M, et al. Clinical outcomes of conventional surgery versus MitraClip® therapy for moderate to severe symptomatic mitral valve regurgitation in the elderly population: an institutional experience. BMC Cardiovasc Disord. 2017 Mar 20;17(1):85.

7. American Heart Association (AHA). Options for Heart Valve Replacement. Last reviewed May 11, 2020. Accessed October 7, 2021. Available at URL address: https://www.heart.org/en/health-topics/heart-valve-problems-and-disease/understanding-your-heart-valve-treatment-options/options-for-heart-valve-replacement

8. Amonn K, Stortecky S, Brinks H, Gahl B, Windecker S, Wenaweser P, Carrel T, Huber C. Quality of life in high-risk patients: comparison of transcatheter aortic valve implantation with surgical aortic valve replacement. Eur J Cardiothorac Surg. 2013 Jan;43(1):34-41; discussion 41-2.

9. Antunes, M. J., Rodríguez-Palomares, J., Prendergast, B., De Bonis, M., Rosenhek, R., Al-Attar, N., et al., & ESC Working Groups of Cardiovascular Surgery and Valvular Heart Disease (2017). Management of tricuspid valve regurgitation: Position statement of the European Society of Cardiology Working Groups of Cardiovascular Surgery and Valvular Heart Disease. European journal of cardio-thoracic surgery: official journal of the European Association for Cardio-thoracic Surgery, 52(6), 1022–1030.

10. Anwer LA, Dearani JA, Daly RC, Stulak JM, Schaff HV, Nguyen A, et al. . Degenerative Mitral Regurgitation After Nonmitral Cardiac Surgery: MitraClip Versus Surgical Reconstruction. Ann Thorac Surg. 2019 Mar;107(3):725-731.

11. Armstrong E, Foster E. Transcatheter mitral valve repair. In: UpToDate, Yeon SB (Ed), UpToDate, Waltham, MA. Last updated: Jan 31, 2020 (Accessed on October 7, 2021.)

12. Armstrong AK, Balzer DT, Cabalka AK, Gray RG, Javois AJ, Moore JW, et al. One-year follow-up of the Melody transcatheter pulmonary valve multicenter post-approval study. JACC Cardiovasc Interv. 2014 Nov;7(11):1254-62.

13. Armstrong AK, Berger F, Jones TK, Moore JW, Benson LN, Cheatham JP, et al. Association between patient age at implant and outcomes after transcatheter pulmonary valve replacement in the multicenter Melody valve trials. Catheter Cardiovasc Interv. 2019 Aug 16.

14. Arnold SV, Chinnakondepalli KM, Spertus JA, Magnuson EA, Baron SJ, Kar S, et al; COAPT Investigators. Health Status After Transcatheter Mitral-Valve Repair in Heart Failure and Secondary Mitral Regurgitation: COAPT Trial. J Am Coll Cardiol. 2019 May 7;73(17):2123-2132.

15. Arora S, Strassle PD, Ramm CJ, Rhodes JA, Vaidya SR, Caranasos TG, Vavalle JP. Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Lower Surgical Risk Scores: A Systematic Review and Meta-Analysis of Early Outcomes. Heart Lung Circ. 2017 Aug;26(8):840-845.

16. Arora S, Misenheimer JA, Jones W, Bahekar A, Caughey M, Ramm CJ, et al. Transcatheter versus surgical aortic valve replacement in intermediate risk patients: a meta-analysis. Cardiovasc Diagn Ther. 2016 Jun;6(3):241-9.

17. Asch FM, Grayburn PA, Siegel RJ, Kar S, Lim DS, Zaroff JG, et al; COAPT Investigators. Transcatheter Mitral Valve Replacement in Patients with Heart Failure and Secondary Mitral Regurgitation: From COAPT Trial. J Am Coll Cardiol. 2019 Sep 19.

18. Bagur R, Solo K, Alghofaili S, Nombela-Franco L, Kwok CS, Hayman S, et al. Cerebral Embolic Protection Devices During Transcatheter Aortic Valve Implantation: Systematic Review and Meta-Analysis. Stroke. 2017 May;48(5):1306-1315.

19. Balzer D. Pulmonary Valve Replacement for Tetralogy of Fallot. Methodist Debakey Cardiovasc J. 2019 Apr-Jun;15(2):122-132.

20. Bansal N, Kobayashi D, Forbes TJ, Du W, Zerin JM, Joshi A, Turner DR. Bilateral branch pulmonary artery valve implantation in repaired tetralogy of fallot. Catheter Cardiovasc Interv. 2018 Apr 1;91(5):911-919.

21. Baron SJ, Arnold SV, Reynolds MR, Wang K, Deeb M, Reardon MJ, et al; US CoreValve Investigators. Durability of quality of life benefits of transcatheter aortic valve replacement: Long-term results from the CoreValve US extreme risk trial. Am Heart J. 2017 Dec;194:39-48.

22. Baron SJ, Magnuson EA, Lu M, Wang K, Chinnakondepalli K, Mack M, et al; PARTNER 3 Investigators. Health Status after Transcatheter vs. Surgical Aortic Valve Replacement in Low-Risk Patients with Aortic Stenosis. J Am Coll Cardiol. 2019 Sep 18.

23. Baumbach A, Mullen M, Brickman AM, Aggarwal SK, Pietras CG, Forrest JK, Et al. Safety and performance of a novel embolic deflection device in patients undergoing transcatheter aortic valve replacement: results from the DEFLECT I study. EuroIntervention. 2015 May;11(1):75-84.

24. Bekeredjian R, Szabo G, Balaban Ü, Bleiziffer S, Bauer T, Ensminger S, et al. Patients at low surgical risk as defined by the Society of Thoracic Surgeons Score undergoing isolated interventional or surgical aortic valve implantation: in-hospital data and 1-year results from the German Aortic Valve Registry (GARY). Eur Heart J. 2019 May 1;40(17):1323-1330.

25. Benson LN, Gillespie MJ, Bergersen L, Cheatham SL, Hor KN, Horlick EM, et al. Three-Year Outcomes From the Harmony Native Outflow Tract Early Feasibility Study. Circ Cardiovasc Interv. 2020 Jan;13(1):e008320.

26. Bergersen L, Benson LN, Gillespie MJ, Cheatham SL, Crean AM, Hor KN, et al. Harmony Feasibility Trial: Acute and Short-Term Outcomes With a Self-Expanding Transcatheter Pulmonary Valve. JACC Cardiovasc Interv. 2017 Sep 11;10(17):1763-1773.

27. Bonow RO, O'Gara PT, Adams DH, Badhwar V, Bavaria JE, Elmariah S, Hung JW, Lindenfeld J, Morris AA, Satpathy R, Whisenant B, Woo YJ. 2020 Focused Update of the 2017 ACC Expert Consensus Decision Pathway on the Management of Mitral Regurgitation: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2020 May 5;75(17):2236-2270.

28. Bonow RO, O'Gara PT, Adams DH, Badhwar V, Bavaria JE, Elmariah S, Hung JW, Lindenfeld J, Morris A, Satpathy R, Whisenant B, Woo YJ. 2019 AATS/ACC/SCAI/STS Expert Consensus Systems of Care Document: Operator and Institutional Recommendations and Requirements for Transcatheter Mitral Valve Intervention: A Joint Report of the American Association for Thoracic Surgery, the American College of Cardiology, the Society for Cardiovascular Angiography and Interventions, and The Society of Thoracic Surgeons. J Am Coll Cardiol. 2020 Jul 7;76(1):96-117.

29. Bonow RO, Brown AS, Gillam LD, Kapadia SR, Kavinsky CJ, Lindman BR, et al. ACC/AATS/AHA/ASE/EACTS/HVS/SCA/SCAI/SCCT/SCMR/STS 2017 Appropriate Use Criteria for the Treatment of Patients With Severe Aortic Stenosis: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, European Association for Cardio-Thoracic Surgery, Heart Valve Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2017 Nov 14;70(20):2566-2598.

30. Boshoff DE, Cools BL, Heying R, Troost E, Kefer J, Budts W, Gewillig M. Off-label use of percutaneous pulmonary valved stents in the right ventricular outflow tract: time to rewrite the label? Catheter Cardiovasc Interv. 2013 May;81(6):987-95.

31. Brecker S, Bax J. Transcatheter aortic valve replacement: Periprocedural and postprocedural management. In: UpToDate, Yeon SB (Ed), UpToDate, Waltham, MA. Last updated: Jul 12, 2021 (Accessed October 7, 2021).

32. Brecker S, Aldea G. Choice of intervention for severe calcific aortic stenosis. In: UpToDate, Yeon SB (Ed), UpToDate, Waltham, MA. last updated: Apr 14, 2020 (Accessed October 7, 2021).

33. Butera G, Milanesi O, Spadoni I, Piazza L, Donti A, Ricci C, et al. Melody transcatheter pulmonary valve implantation. Results from the registry of the Italian Society of Pediatric Cardiology. Catheter Cardiovasc Interv. 2013 Feb;81(2):310-6.

34. Cabalka AK, Asnes JD, Balzer DT, Cheatham JP, Gillespie MJ, Jones TK, et al. Transcatheter pulmonary valve replacement using the melody valve for treatment of dysfunctional surgical bioprostheses: A multicenter study. J Thorac Cardiovasc Surg. 2018 Apr;155(4):1712-1724.e1.

35. Centers for Medicare and Medicaid Services (CMS). National Coverage Determinations (NCDs) alphabetical index. Accessed October 7, 2021). Available at URL address: https://www.cms.gov/medicare-coverage-database/indexes/ncd-alphabetical-index.aspx

36. Chatterjee A, Bajaj NS, McMahon WS, Cribbs MG, White JS, Mukherjee A, Law MA. Transcatheter Pulmonary Valve Implantation: A Comprehensive Systematic Review and Meta-Analyses of Observational Studies. J Am Heart Assoc. 2017 Aug 4;6(8).

37. Cheatham JP, Hellenbrand WE, Zahn EM, Jones TK, Berman DP, Vincent JA, McElhinney DB. Clinical and Hemodynamic Outcomes up to 7 Years After Transcatheter Pulmonary Valve Replacement in the US Melody Valve Investigational Device Exemption Trial. Circulation. 2015 Jun 2;131(22):1960-70.

38. Chowdhury SM, Hijazi ZM, Rhodes J, Kar S, Makkar R, Mullen M, et al. Early echocardiographic changes after percutaneous implantation of the Edwards SAPIEN transcatheter heart valve in the pulmonary position. Echocardiography. 2013 Aug;30(7):786-93.

39. Clavel MA, Webb JG, Pibarot P, Altwegg L, Dumont E, Thompson C, et al. Comparison of the hemodynamic performance of percutaneous and surgical bioprostheses for the treatment of severe aortic stenosis. J Am Coll Cardiol. 2009 May 19;53(20):1883-91.

40. ClinicalTrials.org. COAPT Clinical Trial (COAPT). NCT 01626079. First received: June 20, 2012. Last updated: May 6, 2020. Accessed October 7, 2021. Available at URL address: https://clinicaltrials.gov/ct2/show/results/NCT01626079

41. ClinicalTrials.org. Multicentre Randomized Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR). NCT01920698. First received: Aug 12, 2013. Last updated: July 10, 2018. Accessed October 7, 2021. Available at URL address: https://clinicaltrials.gov/ct2/show/NCT01920698?term=NCT01920698&draw=2&rank=1

42. ClinicalTrials.org. Melody® Transcatheter Pulmonary Valve Post-Approval Study. NCT01186692. First received: August 20, 2010. Last updated: May 1, 2019. Accessed October 7, 2021. Available at URL address: https://clinicaltrials.gov/show/NCT01186692

43. ClinicalTrials.org. Pivotal Study of a Percutaneous Mitral Valve Repair System (EVERESTIIRCT). NCT00209274. First received: September 21, 2005. Last updated: November 7, 2018. Accessed October 7, 2021. Available at URL address: https://clinicaltrials.gov/ct2/show/NCT00209274?term=NCT00209274&rank=1

44. ClinicalTrials.org. THE PARTNER TRIAL: Placement of AoRTic TraNscathetER Valve Trial. NCT00530894. First received: September 14, 2007. Last updated: September 13, 2017. Accessed October 7, 2021. Available at URL address: https://clinicaltrials.gov/ct2/show/results/NCT00530894?term=NCT00530894&rank=1

45. ClinicalTrials.org. COMPASSION: COngenital Multicenter Trial of Pulmonic VAlve Regurgitation Studying the SAPIEN InterventIONal THV. NCT00676689. First received: May 28, 2008. Last updated: February 26, 2020. Accessed October 7, 2021. Available at URL address: https://clinicaltrials.gov/ct2/show/record/NCT00676689?term=NCT00676689&rank=1

46. ClinicalTrials.org. The PARTNER II Trial. Placement of AoRTic TraNscathetER Valve Trial (PARTNER II). NCT01314313. First received March 7, 2011. Last updated August 28, 2020. Accessed October 7, 2021. Available at URL address: https://clinicaltrials.gov/ct2/show/NCT01314313

47. ClinicalTrials.org. Medtronic Evolut Transcatheter Aortic Valve Replacement in Low Risk Patients. NCT01314313. First posted March 8, 2016. Last updated October 14, 2020. Accessed October 7, 2021. Available at URL address: https://clinicaltrials.gov/ct2/show/NCT02701283?term=NCT02701283&draw=2&rank=1

48. ClinicalTrials.org. The Partner 3 Trial. The Safety and Effectiveness of the Sapien 3 Transcatheter Heart Valve in Low Risk Patients with Aortic Stenosis (P3). NCT02675114. First posted February 5, 2016. Last updated May 27, 2020. Accessed October 7, 2021. Available at URL address: https://clinicaltrials.gov/ct2/show/NCT02675114?cond=Transcatheter+Aortic+Valve+Replacement+in+Low+Risk+Patients.&rank=3

49. ClinicalTrials.org. The Medtronic Harmony™ Transcatheter Pulmonary Valve Clinical Study. NCT02979587. First posted December 1, 2016. Last update May 7, 2021. Accessed October 28, 2021. Available at URL address: https://www.clinicaltrials.gov/ct2/show/NCT02979587?term=NCT02979587&rank=1

50. ClinicalTrials.org. PARTNER 3 Trial - Mitral Valve in Valve. NCT03193801. First posted June 21, 2017. Last update posted Sept 5, 2021. Accessed October 28, 2021. Available at URL address: https://clinicaltrials.gov/ct2/show/NCT03193801

51. Cools B, Brown SC, Heying R, Jansen K, Boshoff DE, Budts W, Gewillig M. Percutaneous pulmonary valve implantation for free pulmonary regurgitation following conduit-free surgery of the right ventricular outflow tract. Int J Cardiol. 2015 May 1;186:129-35.

52. Dahle G. Current Devices in TMVI and Their Limitations: Focus on Tendyne. Front Cardiovasc Med. 2020 Dec 23;7:592909.

53. Dalby M, Panoulas.V. Transcatheter aortic valve replacement: complications. In: UpToDate, Yeon SB (Ed), UpToDate, Waltham, MA. last updated: Oct 10, 2019 (Accessed October 7, 2021).

54. Dauerman HL, Deeb GM, O'Hair DP, et al. Durability and Clinical Outcomes of Transcatheter Aortic Valve Replacement for Failed Surgical Bioprostheses. Circ Cardiovasc Interv. 2019;12(10):e008155.

55. De Backer O, Piazza N, Banai S, Lutter G, Maisano F, Herrmann HC, et al. Percutaneous transcatheter mitral valve replacement: an overview of devices in preclinical and early clinical evaluation. Circ Cardiovasc Interv. 2014 Jun;7(3):400-9.

56. Deeb GM, Reardon MJ, Chetcuti S, Patel HJ, Grossman PM, Yakubov SJ, et al; CoreValve US Clinical Investigators. 3-Year Outcomes in High-Risk Patients Who Underwent Surgical or Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2016 Jun 7;67(22):2565-74.

57. Deeb GM, Chetcuti SJ, Reardon MJ, Patel HJ, Grossman PM, Schreiber T, et al. 1-Year Results in Patients Undergoing Transcatheter Aortic Valve Replacement With Failed Surgical Bioprostheses. JACC Cardiovasc Interv. 2017 May 22;10(10):1034-1044.

58. Deharo P, Bisson A, Herbert J, et al. Transcatheter Valve-in-Valve Aortic Valve Replacement as an Alternative to Surgical Re-Replacement. J Am Coll Cardiol. 2020;76(5):489-499.

59. Demkow M, Rużyłło W, Biernacka EK, Kalińczuk Ł, Spiewak M, Kowalski M,et al. Percutaneous Edwards SAPIEN™ valve implantation for significant pulmonary regurgitation after previous surgical repair with a right ventricular outflow patch. Catheter Cardiovasc Interv. 2014 Feb 15;83(3):474-81.

60. De Rosa R, Silverio A, Baldi C, Di Maio M, Prota C, Radano I, et al. Transcatheter Repair of Functional Mitral Regurgitation in Heart Failure Patients-A Meta-Analysis of 23 Studies on MitraClip Implantation. Circ J. 2018 Sep 13.

61. Dvir D, Webb J, Brecker S, Bleiziffer S, Hildick-Smith D, et al. Transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: results from the global valve-in-valve registry. Circulation. 2012 Nov 6;126(19):2335-44.

62. Dvir D, Webb JG, Bleiziffer S, Pasic M, Waksman R, Kodali S, et al.; Valve-in-Valve International Data Registry Investigators. Transcatheter aortic valve implantation in failed bioprosthetic surgical valves. JAMA. 2014 Jul;312(2):162-70.

63. Eiken A, Ewert P, Hager A, Peters B, Fratz S, Kuehne T, et al. Percutaneous pulmonary valve implantation: two-centre experience with more than 100 patients. Eur Heart J. 2011 May;32(10):1260-5.

64. Eicken A. Percutaneous pulmonic valve implantation. In: UpToDate, Yeon SB (Ed), UpToDate, Waltham, MA. last updated: Sep 02, 2020 (Accessed October 7, 2021).

65. Erkapic D, DE Rosa S, Kelava A, Lehmann R, Fichtlscherer S, Hohnloser SH. Risk for Permanent Pacemaker After Transcatheter Aortic Valve Implantation: A Comprehensive Analysis of the Literature. Cardiovasc Electrophysiol. 2011 Nov 3.

66. Falk V, Baumgartner H, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al.; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. Eur J Cardiothorac Surg. 2017 Oct 1;52(4):616-664.

67. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, et al; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med. 2011 Apr 14;364(15):1395-406. doi: 10.1056/NEJMoa1009355. Epub 2011 Apr 4. Erratum in: N Engl J Med. 2011 Jul 14;365(2):189. Glower, Donald G [corrected to Glower, Donald D]. PubMed PMID: 21463154.

68. Feldman T, Kar S, Elmariah S, Smart SC, Trento A, Siegel RJ, et al; EVEREST II Investigators. Randomized Comparison of Percutaneous Repair and Surgery for Mitral Regurgitation: 5-Year Results of EVEREST II. J Am Coll Cardiol. 2015 Dec 29;66(25):2844-54.

69. Fraisse A, Aldebert P, Malekzadeh-Milani S, Thambo JB, Piéchaud JF, Aucoururier P, et al. Melody ® transcatheter pulmonary valve implantation: results from a French registry. Arch Cardiovasc Dis. 2014 Nov;107(11):607-14.

70. Frankenstein L, Kaier K, Katus HA, Bode C, Wengenmayer T, von Zur Mühlen C, et al. Impact of the introduction of percutaneous edge-to-edge mitral valve reconstruction on clinical practice in Germany compared to surgical valve repair. Clin Res Cardiol. 2020 May 27.

71. Fu J, Popal MS, Li Y, Li G, Qi Y, Fang F, et al. Transcatheter versus surgical aortic valve replacement in low and intermediate risk patients with severe aortic stenosis: systematic review and meta-analysis of

randomized controlled trials and propensity score matching observational studies.J Thorac Dis. 2019 May;11(5):1945-1962.

72. Fusari M, Bona V, Muratori M, Salvi L, Salis S, Tamborini G, Biglioli P. Transcatheter vs. surgical aortic valve replacement: a retrospective analysis assessing clinical effectiveness and safety. J Cardiovasc Med (Hagerstown). 2012 Apr;13(4):229-41.

73. Gaasch WH. Management of chronic primary mitral regurgitation. In: UpToDate, Yeon SB (Ed), UpToDate, Waltham, MA. last updated: May 28, 2020 (Accessed October 29, 2021).

74. Gaasch WH. Management and prognosis of chronic secondary mitral regurgitation. In: UpToDate, Yeon SB (Ed), UpToDate, Waltham, MA. last updated: Nov 20, 2019 (Accessed October 29, 2021).

75. Gaasch WH. Indications for valve replacement in aortic stenosis in adults. Last updated April 22, 2019. In: UpToDate, Yeon SB (Ed), UpToDate, Waltham, MA. last updated: Jan 29, 2020 (Accessed October 29, 2021).

76. Garg A, Rao SV, Visveswaran G, Agrawal S, Sharma A, Garg L, et al. Transcatheter Aortic Valve Replacement Versus Surgical Valve Replacement in Low-Intermediate Surgical Risk Patients: A Systematic Review and Meta-Analysis. J Invasive Cardiol. 2017 Jun;29(6):209-216.

77. Gargiulo G, Sannino A, Capodanno D, Barbanti M, Buccheri S, Perrino C,et al. Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement: A Systematic Review and Meta-analysis. Ann Intern Med. 2016 Sep 6;165(5):334-44.

78. Gasior T, Mangner N, Bijoch J, Wojakowski W. Cerebral embolic protection systems for transcatheter aortic valve replacement. J Interv Cardiol. 2018 Dec;31(6):891-898.

79. Giannini C, D'ascenzo F, Fiorelli F, Spontoni P, Swaans MJ, Velazquez EJ, et al. A meta-analysis of MitraClip combined with medical therapy vs. medical therapy alone for treatment of mitral regurgitation in heart failure patients. ESC Heart Fail. 2018 Dec;5(6):1150-1158.

80. Gillespie MJ, Bergersen L, Benson LN, Weng S, Cheatham JP. 5-Year Outcomes From the Harmony Native Outflow Tract Early Feasibility Study. JACC Cardiovasc Interv. 2021 Apr 12;14(7):816-817.

81. Gillespie MJ, Benson LN, Bergersen L, Bacha EA, Cheatham SL, Crean AM, et al.. Patient Selection Process for the Harmony Transcatheter Pulmonary Valve Early Feasibility Study. Am J Cardiol. 2017 Oct 15;120(8):1387-1392.

82. Giugno L, Faccini A, Carminati M. Percutaneous Pulmonary Valve Implantation. Korean Circ J. 2020 Apr;50(4):302-316..

83. Giustino G, Mehran R, Veltkamp R, Faggioni M, Baber U, Dangas GD. Neurological Outcomes With Embolic Protection Devices in Patients Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. JACC Cardiovasc Interv. 2016 Oct 24;9(20):2124-2133.

84. Glower DD, Kar S, Trento A, Lim DS, Bajwa T, Quesada R, et al. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. J Am Coll Cardiol. 2014 Jul 15;64(2):172-81.

85. Gozdek M, Raffa GM, Suwalski P, Kolodziejczak M, Anisimowicz L, Kubica J,et al; SIRIO-TAVI group. Comparative performance of transcatheter aortic valve-in-valve implantation versus conventional surgical redo aortic valve replacement in patients with degenerated aortic valve bioprostheses: systematic review and meta-analysis. Eur J Cardiothorac Surg. 2018 Mar 1;53(3):495-504.

86. Grover FL, Vemulapalli S, Carroll JD, Edwards FH, Mack MJ, Thourani VH, et al; STS/ACC TVT Registry. 2016 Annual Report of The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry. J Am Coll Cardiol. 2017 Mar 14;69(10):1215-1230.

87. Guerrero M, Salinger MH, Levisay JP, Feldman T. Transcatheter Mitral Valve Replacement Therapies. American College of Cardiology. Expert Analysis. April 28, 2017. Accessed October 8, 2021. Available at URL address: https://www.acc.org/latest-in-cardiology/articles/2017/04/28/09/32/transcatheter-mitral-valve-replacement-therapies

88. Guerrero M, Dvir D, Himbert D, Urena M, Eleid M, Wang DD, et al. Transcatheter Mitral Valve Replacement in Native Mitral Valve Disease With Severe Mitral Annular Calcification: Results From the First Multicenter Global Registry. JACC Cardiovasc Interv. 2016 Jul 11;9(13):1361-71.

89. Hamilton GW, Koshy AN, Fulcher J, Tang GHL, Bapat V, Murphy A, et al. Meta-analysis Comparing Valve-In-Valve Transcatheter Aortic Valve Implantation With Self-Expanding Versus Balloon-Expandable Valves. Am J Cardiol. 2020 May 15;125(10):1558-1565.

90. Hascoet S, Dalla Pozza R, Bentham J, Carere RG, Kanaan M, Ewert P, et al. Early outcomes of percutaneous pulmonary valve implantation using the Edwards SAPIEN 3 transcatheter heart valve system. EuroIntervention. 2019 Jan 20;14(13):1378-1385.

91. Haussig S, Mangner N, Dwyer MG, Lehmkuhl L, Lücke C, Woitek F, et al. Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial. JAMA. 2016 Aug 9;316(6):592-601.

92. Hayes, Inc. Hayes Medical Technology Directory Report. Percutaneous Pulmonary Valve Implantation for Right Ventricular Outflow Tract Defects. Lansdale, PA: Hayes, Inc.; published Dec 21, 2013b; Updated January 14, 2016; annual review Jan 2017; December 2018; May 2020.

93. Hayes, Inc. Hayes Medical Technology Directory Report. Comparative Effectiveness Review. Percutaneous Mitral Valve Repair. Lansdale, PA: Hayes, Inc.; published April 2018; annual review April 2019; August 2020.

94. Hayes, Inc. Hayes Medical Technology Directory Report. Comparative Effectiveness Review. Transcatheter Aortic Valve Implantation (TAVI) and Surgical Aortic Valve Replacement (SAVR) for Aortic Stenosis in Lower Risk Patients. Lansdale, PA: Hayes, Inc.; published Sept 27, 2018; annual review August 2020.

95. Hayes, Inc. Emerging Technology Report. Sentinel Cerebral Protection System (CPS). Lansdale, PA: Hayes, Inc.; published January 11, 2018; Archived January 2019.

96. Hayes, Inc. Evidence Analysis Research Brief. Transcatheter Tricuspid Valve Replacement for Tricuspid Valve Disease. Lansdale, PA: Hayes, Inc.; published August 8, 2019. Archived September 2020.

97. Hayes, Inc. Evidence Analysis Research Brief. Transcatheter Mitral Valve Replacement for Mitral Regurgitation. Lansdale, PA: Hayes, Inc.; published August 17, 2020.

98. Herrmann HC. Transcatheter mitral valve repair and replacement. In: Otto CM, Bonow RO. Valvular Heart Disease: A Companion to Braunwald's Heart Disease. 4th Ed. Philadelphia, PA: Saunders; 2014: Ch 22. pg 341-52.

99. Herrmann HC, Mack MJ. Transcatheter therapies for valvular heart disease. In: Bonow: Braunwald's heart disease-a textbook of cardiovascular medicine, 11th ed. Saunders, an imprint of Elsevier, 2019. Ch 72.1464-82.

100. Holmes DR Jr., Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiol. 2012 Jan 30.

101. Holzamer A, Kim WK, Rück A, Sathananthan J, Keller L, Cosma J, et al. Valve-in-Valve Implantation Using the ACURATE Neo in Degenerated Aortic Bioprostheses: An International Multicenter Analysis. JACC Cardiovasc Interv. 2019 Nov 25;12(22):2309-2316.

102. Hu J, Chen Y, Cheng S, Zhang S, Wu K, Wang W, Zhou Y. Transcatheter mitral valve implantation for degenerated mitral bioprostheses or failed surgical annuloplasty rings: A systematic review and meta-analysis. J Card Surg. 2018 Sep;33(9):508-519.

103. Jørgensen TH, Thyregod HGH, Ihlemann N, Nissen H, Petursson P, Kjeldsen BJ, et al. Eight-year outcomes for patients with aortic valve stenosis at low surgical risk randomized to transcatheter vs. surgical aortic valve replacement. Eur Heart J. 2021 Aug 7;42(30):2912-2919.

104. Kalra A, Raza S, Hussain M, Shorbaji K, Delozier S, Deo SV, et al. Aortic Valve Replacement in Bioprosthetic Failure: Insights From The Society of Thoracic Surgeons National Database. Ann Thorac Surg. 2020 Nov;110(5):1637-1642.

105. Kamioka N, Babaliaros V, Morse MA, Frisoli T, Lerakis S, Iturbe JM, et al. Comparison of Clinical and Echocardiographic Outcomes After Surgical Redo Mitral Valve Replacement and Transcatheter Mitral Valve-in-Valve Therapy. JACC Cardiovasc Interv. 2018 Jun 25;11(12):1131-1138.

106. Kapadia SR, Leon MB, Makkar RR, Tuzcu EM, Svensson LG, Kodali S, et al; PARTNER trial investigators. 5-year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomized controlled trial. Lancet. 2015 Jun 20;385(9986):2485-91.

107. Kapadia SR, Kodali S, Makkar R, Mehran R, Lazar RM, Zivadinov R, et al; SENTINEL Trial Investigators. Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2017 Jan 31;69(4):367-377.

108. Kar S, Feldman T, Qasim A, Trento A, Kapadia S, Pedersen W, et al; EVEREST II Investigators. Five-year outcomes of transcatheter reduction of significant mitral regurgitation in high-surgical-risk patients. Heart. 2018 Aug 4. pii: heartjnl-2017-312605.

109. Kenny D, Hijazi ZM, Kar S, Rhodes J, Mullen M, Makkar R, et al. Percutaneous implantation of the Edwards SAPIEN transcatheter heart valve for conduit failure in the pulmonary position: early phase 1 results from an international multicenter clinical trial. J Am Coll Cardiol. 2011 Nov 15;58(21):2248-56.

110. Kenny D, Rhodes JF, Fleming GA, Kar S, Zahn EM, Vincent J, et al. 3-Year Outcomes of the Edwards SAPIEN Transcatheter Heart Valve for Conduit Failure in the Pulmonary Position From the COMPASSION Multicenter Clinical Trial. JACC Cardiovasc Interv. 2018 Oct 8;11(19):1920-1929.

111. Khan SU, Lone AN, Saleem MA, Kaluski E. Transcatheter vs surgical aortic-valve replacement in low-to intermediate-surgical-risk candidates: A meta-analysis and systematic review. Clin Cardiol. 2017 Nov;40(11):974-981.

112. Kodali SK, Williams MR, Smith CR, Svensson LG, Webb JG, Makkar RR, et al.; PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012 May 3;366(18):1686-95.

113. Kodali SK, Doshi D, Leon M. Aortic Valvuloplasty and Transcatheter Aortic Valve Replacement. In: Cardiovascular Intervention: A Companion to Braunwald's Heart Disease, 10th ed. Saunders, an imprint of Elsevier, 2016. Ch 29.451-81.

114. Kolte D, Vlahakes GJ, Palacios IF, Sakhuja R, Passeri JJ, Inglessis I, Elmariah S. Transcatheter Versus Surgical Aortic Valve Replacement in Low-Risk Patients. J Am Coll Cardiol. 2019 Sep 24;74(12):1532-1540.

115. Kondur A, Briasoulis A, Palla M, Penumetcha A, Mallikethi-Reddy S, et al. Meta-Analysis of Transcatheter Aortic Valve Replacement Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis. Am J Cardiol. 2016 Jan 15;117(2):252-7.

116. Kortlandt F, Velu J, Schurer R, Hendriks T, Van den Branden B, Bouma B, et al. Survival After MitraClip Treatment Compared to Surgical and Conservative Treatment for High-Surgical-Risk Patients With Mitral Regurgitation. Circ Cardiovasc Interv. 2018 Jun;11(6):e005985.

117. Krishnaswamy A. Percutaneous mitral valve repair. In: Topol E. Textbook of Interventional Cardiology, Eighth Edition. Philadelphia, PA: Elsevier; 2020: Ch 52. pg 822-37.

118. Lam HT, Kwong JM, Lam PL, Yeung WL, Chan YC. Evidence for Cerebral Embolic Prevention in Transcatheter Aortic Valve Implantation and Thoracic Endovascular Aortic Repair. Ann Vasc Surg. 2019;55:292-306.

119. Lazkani M, Singh N, Howe C, Patel N, Colón MJ, Tasset M, et al. An updated meta-analysis of TAVR in patients at intermediate risk for SAVR. Cardiovasc Revasc Med. 2018 Apr 20. pii: S1553-8389(18)30129-5.

120. Leon MB, Smith CR, Mack MJ, Makkar RR, Svensson LG, Kodali SK, et al; PARTNER 2 Investigators. Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2016 Apr 28;374(17):1609-20.

121. Leon MB, Smith, CR, Mack M, Miller C, Moses JW, Svensson LG, et al., for the PARTNERS Trial Investigators. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010 Oct 21;363(17):1597-607.

122. Lim DS, Reynolds MR, Feldman T, Kar S, Herrmann HC, Wang A et al. Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation after transcatheter mitral valve repair. J Am Coll Cardiol. 2014 Jul 15;64(2):182-92.

123. Linke A, Woitek F, Merx MW, Schiefer C, Möbius-Winkler S, Holzhey D, et al. Valve-in-valve implantation of Medtronic CoreValve prosthesis in patients with failing bioprosthetic aortic valves. Circ Cardiovasc Interv. 2012 Oct;5(5):689-97.

124. Lurz P, Nordmeyer J, Giardini A, Khambadkone S, Muthurangu V, Schievano S. Early versus late functional outcome after successful percutaneous pulmonary valve implantation: are the acute effects of altered right ventricular loading all we can expect? J Am Coll Cardiol. 2011 Feb 8;57(6):724-31.

125. Lurz P, Coats L, Khambadkone S, Nordmeyer J, Boudjemline Y, Schievano S, et al. Percutaneous pulmonary valve implantation: impact of evolving technology and learning curve on clinical outcome. Circulation. 2008 Apr 15;117(15):1964-72.

126. Mack MJ, Leon MB, Smith CR, Miller DC, Moses JW, Tuzcu EM, et al; PARTNER 1 trial investigators. 5-year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet. 2015 Jun 20;385(9986):2477-84.

127. Mack MJ, Leon MB, Thourani VH, Makkar R, Kodali SK, Russo M, et al; PARTNER 3 Investigators. Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients. N Engl J Med. 2019 May 2;380(18):1695-1705.

128. Maisano F, Franzen O, Baldus S, Schäfer U, Hausleiter J, Butter C, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. J Am Coll Cardiol. 2013 Sep 17;62(12):1052-61.

129. Makkar RR, Fontana GP, Jilaihawi H, Kapadia S, Pichard AD, Douglas PS, et al. PARTNER Trial Investigators. Two-year outcomes after transcatheter or surgical aortic-valve replacement. N Engl J Med. 2012 May 3;366(18):1686-95.

130. Malekzadeh-Milani S, Ladouceur M, Cohen S, Iserin L, Boudjemline Y. Results of transcatheter pulmonary valvulation in native or patched right ventricular outflow tracts. Arch Cardiovasc Dis. 2014 Nov;107(11):592-8.

131. Malik AH, Yandrapalli S, Zaid S, Shetty SS, Aronow WS, Ahmad H, Tang GHL. Valve-in-Valve Transcatheter Implantation Versus Redo Surgical Aortic Valve Replacement. Am J Cardiol. 2020 May 1;125(9):1378-1384.

132. Marmagkiolis K, Hakeem A, Ebersole DG, Iliescu C, Ates I, Cilingiroglu M. Clinical outcomes of percutaneous mitral valve repair with MitraClip for the management of functional mitral regurgitation. Catheter Cardiovasc Interv. 2019 Apr 1.

133. Martin MH, Meadows J, McElhinney DB, Goldstein BH, Bergersen L, Qureshi AM, et al. Safety and Feasibility of Melody Transcatheter Pulmonary Valve Replacement in the Native Right Ventricular Outflow Tract: A Multicenter Pediatric Heart Network Scholar Study. JACC Cardiovasc Interv. 2018 Aug 27;11(16):1642-1650.

134. Mauri L, Foster E, Glower DD, Apruzzese P, Massaro JM, Herrmann HC, et al.; EVEREST II Investigators. 4-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. J Am Coll Cardiol. 2013 Jul 23;62(4):317-28.

135. McElhinney DB, Hellenbrand WE, Zahn EM, Jones TK, Cheatham JP, Lock JE, Vincent JA. Short- and medium-term outcomes after transcatheter pulmonary valve placement in the expanded multicenter US melody valve trial. Circulation. 2010 Aug 3;122(5):507-16.

136. McElhinney DB, Cheatham JP, Jones TK, Lock JE, Vincent JA, Zahn EM, Hellenbrand WE. Stent fracture, valve dysfunction, and right ventricular outflow tract reintervention after transcatheter pulmonary valve implantation: patient-related and procedural risk factors in the US Melody Valve Trial. Circ Cardiovasc Interv. 2011 Dec 1;4(6):602-14.

137. McElhinney DB, Benson LN, Eicken A, Kreutzer J, Padera RF, Zahn EM. Infective endocarditis after transcatheter pulmonary valve replacement using the Melody valve: combined results of 3 prospective North American and European studies. Circ Cardiovasc Interv. 2013 Jun;6(3):292-300.

138. Meadows JJ, Moore PM, Berman DP, Cheatham JP, Cheatham SL, Porras D, et al. Use and performance of the Melody Transcatheter Pulmonary Valve in native and postsurgical, nonconduit right ventricular outflow tracts. Circ Cardiovasc Interv. 2014 Jun;7(3):374-80.

139. Medtronic website. CoreValve® Evolut® R System. Accessed October 8, 2021. Available at URL address: https://global.medtronic.com/xg-en/healthcare-professionals/products/cardiovascular/transcatheter-aortic-heart-valves/evolut-r.html

140. Medtronic website. HARMONY™Transcatheter Pulmonary Valve. Accessed October 8, 2021. Available at URL address: https://www.medtronic.com/us-en/healthcare-professionals/products/cardiovascular/transcatheter-pulmonary-valve/harmony.html

141. Micro Interventional Devices, Inc. Permavalve™ mitral valve replacement. Accessed October 8, 2021. Available at URL address: https://www.microinterventional.com/permavalve

142. Minha S, Torguson R, Waksman R. Overview of the 2013 Food and Drug Administration Circulatory System Devices Panel meeting on the MitraClip® Delivery System. Circulation. Aug 20 2013; 128(8):864-868.

143. Moat NE, Ludman P, de Belder MA, Bridgewater B, Cunningham AD, Young CP, Thomas M, Kovac J et al. Long-term outcomes after transcatheter aortic valve implantation in high-risk patients with severe aortic stenosis: the U.K. TAVI (United Kingdom Transcatheter Aortic Valve Implantation) Registry. J Am Coll Cardiol. 2011 Nov 8;58(20):2130-8.

144. Mohananey D, Sankaramangalam K, Kumar A, Jobanputra Y, Villablanca P, Krishnaswamy A, et al. Safety and efficacy of cerebral protection devices in transcatheter aortic valve replacement: A clinical end-points meta-analysis. Cardiovasc Revasc Med. 2018 Oct;19(7 Pt A):785-791.

145. Murdoch DJ, Webb JG. Percutaneous transcatheter valve-in-valve implantation. In: Topol E., Tierstein PS. Textbook of Interventional Cardiology. 8th Ed. Philadelphia, PA: Elsevier; 2020:880-887.e2.

146. Nalluri N, Atti V, Munir AB, Karam B, Patel NJ, Kumar V, et al. Valve in valve transcatheter aortic valve implantation (ViV-TAVI) versus redo-Surgical aortic valve replacement (redo-SAVR): A systematic review and meta-analysis. J Interv Cardiol. 2018 Oct;31(5):661-671.

147. National Institute for Health and Clinical Excellence (NICE). Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis Interventional procedures guidance [IPG706] September 22, 2021. Accessed October 26, 2021. Available at URL address: https://www.nice.org.uk/guidance/ipg706

148. National Institute for Health and Clinical Excellence (NICE). Interventional procedure guidance 653. Valve-in-valve implantation for aortic bioprosthetic valve dysfunction. UK: NICE; 2019 June. Accessed October 8, 2021. Available at URL address: https://www.nice.org.uk/guidance/ipg653

149. National Institute for Health and Clinical Excellence (NICE). Interventional procedure guidance 436. Percutaneous pulmonary valve implantation for right ventricular outflow tract dysfunction. UK: NICE; 2013 January. Accessed October 8, 2021. Available at URL address: https://www.nice.org.uk/guidance/ipg436

150. National Institute for Health and Clinical Excellence (NICE). Interventional procedure guidance 586. Transcatheter aortic valve implantation for aortic stenosis. UK: NICE; 2017 July. Accessed October 8, 2021. Available at URL address: https://www.nice.org.uk/guidance/ipg586

151. National Institute for Health and Clinical Excellence (NICE). Interventional procedure guidance 649. Percutaneous mitral valve leaflet repair for mitral regurgitation. UK: NICE; 2019 May. Accessed October 8, 2021. Available at URL address: https://www.nice.org.uk/guidance/ipg649

152. Neupane S, Singh H, Lämmer J, Othman H, Yamasaki H, Rosman HS, Bossone E, Mehta RH, Eggebrecht H. Meta-Analysis of Transcatheter Valve-in-Valve Implantation Versus Redo Aortic Valve Surgery for Bioprosthetic Aortic Valve Dysfunction. Am J Cardiol. 2018 Jun 15;121(12):1593-1600.

153. Nijhoff F, Abawi M, Agostoni P, Ramjankhan FZ, Doevendans PA, Stella PR. Transcatheter Aortic Valve Implantation With the New Balloon-Expandable Sapien 3 Versus Sapien XT Valve System: A Propensity Score-Matched Single-Center Comparison. Circ Cardiovasc Interv. 2015 Jun;8(6):e002408.

154. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al; 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of

Cardiology/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg. 2014 Jul;148(1):e1-e132.

155. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA,et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017 Jul 11;70(2):252-289.

156. Nishimura RA, O'Gara PT, Bavaria JE, Brindis RG, Carroll JD, Kavinsky CJ, et al. 3rd. 2019 AATS/ACC/ASE/SCAI/STS Expert Consensus Systems of Care Document: A Proposal to Optimize Care for Patients With Valvular Heart Disease: A Joint Report of the American Association for Thoracic Surgery, American College of Cardiology, American Society of Echocardiography, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2019 May 28;73(20):2609-5.

157. Nordmeyer J, Ewert P, Gewillig M, AlJufan M, Carminati M, Kretschmar O, et al. Acute and midterm outcomes of the post-approval MELODY Registry: a multicentre registry of transcatheter pulmonary valve implantation. Eur Heart J. 2019 Jul 14;40(27):2255-2264.

158. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al; MITRA-FR Investigators. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. N Engl J Med. 2018 Dec 13;379(24):2297-2306.

159. Odemis E, Guzeltas A, Saygi M, Ozyilmaz I, Momenah T, Bakir I. Percutaneous pulmonary valve implantation using Edwards SAPIEN transcatheter heart valve in different types of conduits: initial results of a single center experience. Congenit Heart Dis. 2013 Sep-Oct;8(5):411-7.

160. Ondrus T, Bartunek J, Vanderheyden M, Stockman B, Kotrc M, Van Praet F, et al. Minimally invasive mitral valve repair for functional mitral regurgitation in severe heart failure: MitraClip versus minimally invasive surgical approach. Interact Cardiovasc Thorac Surg. 2016 Nov;23(5):784-789.

161. O'Gara PT, Calhoon JH, Moon MR, Tommaso CL; American College of Cardiology; American Association for Thoracic Surgery; Society for Cardiovascular Angiography and Interventions Foundation; Society of Thoracic Surgeons. Transcatheter therapies for mitral regurgitation: a professional society overview from the American College of Cardiology, The American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions Foundation, and The Society of Thoracic Surgeons. J Thorac Cardiovasc Surg. 2014 Mar;147(3):837-49.

162. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021 Feb 2;143(5):e72-e227. doi: 10.1161/CIR.0000000000000923. Epub 2020 Dec 17. Erratum in: Circulation. 2021 Feb 2;143(5):e229. PMID: 33332150.

163. Otto CM, Kumbhani DJ, Alexander KP, Calhoon JH, Desai MY, Kaul S, et al. 2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults With Aortic Stenosis: A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol. 2017 Mar 14;69(10):1313-1346.

164. Otto CM. Management and prognosis of tricuspid regurgitation. In: UpToDate, Yeon SB (Ed), UpToDate, Waltham, MA. last updated: Aug 03, 2020 (Accessed October 8, 2021).

165. Otto CM. Estimating the mortality risk of valvular surgery. In: UpToDate, Yeon SB (Ed), UpToDate, Waltham, MA. last updated: Dec 02, 2018 (Accessed October 8, 2021).

166. Overtchouk P, Prendergast B, Modine T. Why should we extend transcatheter aortic valve implantation to low-risk patients? A comprehensive review. Arch Cardiovasc Dis. 2019 May;112(5):354-362.

167. Parma R, Zembala MO, Dąbrowski M, Jagielak D, Witkowski A, Suwalski P, et al. Transcatheter aortic valve implantation. Expert Consensus of the Association of Cardiovascular Interventions of the Polish Cardiac Society and the Polish Society of Cardio-Thoracic Surgeons, approved by the Board of the Polish Cardiac Society Kardiol Pol. 2017; 75 (9): 937-964.

168. Phan K, Zhao DF, Wang N, Huo YR, Di Eusanio M, Yan TD. Transcatheter valve-in-valve implantation versus reoperative conventional aortic valve replacement: a systematic review. J Thorac Dis. 2016 Jan;8(1):E83-93.

169. Philip F, Athappan G, Tuzcu EM, Svensson LG, Kapadia SR. MitraClip for severe symptomatc mitral regurgitation in patients at high surgical risk: a comprehensive systematic review. Catheter Cardiovasc Interv. 2014 Oct 1;84(4):581-90.

170. Pibarot P, O'Gara PT. Prosthetic Heart Valves. In: Bonow: Braunwald's heart disease-a textbook of cardiovascular medicine, 11th ed. Saunders, an imprint of Elsevier, 2019. Ch 71.1455-62.

171. Pilgrim T, Lee JKT, O'Sullivan CJ, Stortecky S, Ariotti S, Franzone A, et al. Early versus newer generation devices for transcatheter aortic valve implantation in routine clinical practice: a propensity score matched analysis. Open Heart. 2018 Jan 20;5(1):e000695.

172. Plessis J, Hascoët S, Baruteau A, Godart F, Le Gloan L, Warin Fresse K, et al. Edwards SAPIEN Transcatheter Pulmonary Valve Implantation: Results From a French Registry. JACC Cardiovasc Interv. 2018 Oct 8;11(19):1909-1916.

173. Popma JJ, Adams DH, Reardon MJ, Yakubov SJ, Kleiman NS, Heimansohn D, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. Am Coll Cardiol. 2014 May 20;63(19):1972-81.

174. Popma JJ, Reardon MJ, Khabbaz K, Harrison JK, Hughes GC, Kodali S, et al. Early Clinical Outcomes After Transcatheter Aortic Valve Replacement Using a Novel Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis Who Are Suboptimal for Surgery: Results of the Evolut R U.S. Study. JACC Cardiovasc Interv. 2017 Feb 13;10(3):268-275.

175. Popma JJ, Deeb GM, Yakubov SJ, Mumtaz M, Gada H, O'Hair D, et al; Evolut Low Risk Trial Investigators. Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients. N Engl J Med. 2019 May 2;380(18):1706-1715.

176. Puri R, Abdul-Jawad Altisent O, del Trigo M, Campelo-Parada F, Regueiro A, Barbosa Ribeiro H, et al. Transcatheter mitral valve implantation for inoperable severely calcified native mitral valve disease: A systematic review. Catheter Cardiovasc Interv. 2016 Feb 15;87(3):540-8.

177. Ramlawi B, Gammie JS. Mitral Valve Surgery: Current Minimally Invasive and Transcatheter Options. Methodist Debakey Cardiovasc J. 2016 Jan-Mar;12(1):20-6.

178. Ran L, Wang W, Secchi F, Xiang Y, Shi W, Huang W. Percutaneous pulmonary valve implantation in patients with right ventricular outflow tract dysfunction: a systematic review and meta-analysis. Ther Adv Chronic Dis. 2019 Jun 14;10:2040622319857635.

179. Raval J, Nagaraja V, Eslick GD, Denniss AR. Transcatheter valve-in-valve implantation: a systematic review of literature. Heart Lung Circ. 2014 Nov;23(11):1020-8.

180. Regueiro A, Ye J, Fam N, Bapat VN, Dagenais F, Peterson MD, et al. 2-Year Outcomes After Transcatheter Mitral Valve Replacement. JACC Cardiovasc Interv. 2017a Aug 28;10(16):1671-1678.

181. Regueiro A, Granada JF, Dagenais F, Rodés-Cabau J. Transcatheter Mitral Valve Replacement: Insights From Early Clinical Experience and Future Challenges. J Am Coll Cardiol. 2017b May 2;69(17):2175-2192.

182. Reardon MJ, Van Mieghem NM, Popma JJ, Kleiman NS, Søndergaard L, Mumtaz M, et al; SURTAVI Investigators. Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients. N Engl J Med. 2017 Apr 6;376(14):1321-1331.

183. Reardon MJ, Van Mieghem NM, Popma JJ. Surgical or Transcatheter Aortic-Valve Replacement. N Engl J Med. 2017 Jul 13;377(2):197-198.

184. Reardon MJ, Feldman TE, Meduri CU, Makkar RR, O'Hair D, Linke Aet al; Reprise III Investigators. Two-Year Outcomes After Transcatheter Aortic Valve Replacement With Mechanical vs Self-expanding Valves: The REPRISE III Randomized Clinical Trial. JAMA Cardiol. 2019 Mar 1;4(3):223-229.

185. Reynolds MR, Magnuson EA, Lei Y, Leon MB, Smith CR, Svensson LG, et al; Placement of Aortic Transcatheter Valves (PARTNER) Investigators. Health-related quality of life after transcatheter aortic valve replacement in inoperable patients with severe aortic stenosis. Circulation: 2011 Nov 1;124(18):1964-72.

186. Rodés-Cabau J, Webb JG, Cheung A, Ye J, Dumont E, Osten M, Feindel CM, et al. Long-term outcomes after transcatheter aortic valve implantation: insights on prognostic factors and valve durability from the Canadian multicenter experience. J Am Coll Cardiol. 2012 Nov 6;60(19):1864-75.

187. Rogers T, Torguson R, Bastian R, Corso P, Waksman R. Feasibility of transcatheter aortic valve replacement in low-risk patients with symptomatic severe aortic stenosis: Rationale and design of the Low Risk TAVR (LRT) study. Am Heart J. 2017 Jul;189:103-109.

188. Rosengart TK, Feldman T, Borger MA, Vassiliades TA Jr, Gillinov AM, Hoercher KJ, et al; American Heart Association Council on Cardiovascular Surgery and Anesthesia; American Heart Association Council on Clinical Cardiology; Functional Genomics and Translational Biology Interdisciplinary Working Group; Quality of Care and Outcomes Research Interdisciplinary Working Group. Percutaneous and minimally invasive valve procedures: a scientific statement from the American Heart Association Council on Cardiovascular Surgery and Anesthesia, Council on Clinical Cardiology, Functional Genomics and Translational Biology Interdisciplinary Working Group, and Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation. 2008 Apr 1;117(13):1750-67.

189. Ruiz CE, Pasala TKR. Are We Ready for Transcatheter Pulmonary Valve Replacement in Native Right Ventricular Outflow Tract? JACC Cardiovasc Interv. 2018 Aug 27;11(16):1651-1653.

190. Sanchez C, Arshi A, Yakubov S. Valvular Heart Disease. In: Conn’s Current Therapy, Elsevier, 2020. 160-6.

191. Seeger J, Gonska B, Otto M, Rottbauer W, Wöhrle J. Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement Significantly Reduces Death and Stroke Compared With Unprotected Procedures. JACC Cardiovasc Interv. 2017 Nov 27;10(22):2297-2303.

192. Seferovic PM, Ponikowski P, Anker SD, Bauersachs J, Chioncel O, Cleland JGF, et al. Clinical practice update on heart failure 2019: pharmacotherapy, procedures, devices and patient management. An expert consensus meeting report of the Heart Failure Association of the European Society of Cardiology. Eur J Heart Fail. 2019 Oct;21(10):1169-1186.

193. Siemieniuk RA, Agoritsas T, Manja V, Devji T, Chang Y, Bala MM, et al. Transcatheter versus surgical aortic valve replacement in patients with severe aortic stenosis at low and intermediate risk: systematic review and meta-analysis. BMJ. 2016 Sep 28;354:i5130.

194. Silaschi M, Wendler O, Seiffert M, Castro L, Lubos E, Schirmer J, et al. Transcatheter valve-in-valve implantation versus redo surgical aortic valve replacement in patients with failed aortic bioprostheses. Interact Cardiovasc Thorac Surg. 2017 Jan;24(1):63-70.

195. Sinha S, Aboulhosn J, Asnes J, Bocks M, Zahn E, Goldstein BHet al. Initial results from the off-label use of the SAPIEN S3 valve for percutaneous transcatheter pulmonary valve replacement: A multi-institutional experience. Catheter Cardiovasc Interv. 2019 Feb 15;93(3):455-463.

196. Siontis GCM, Overtchouk P, Cahill TJ, Modine T, Prendergast B, Praz F, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of symptomatic severe aortic stenosis: an updated meta-analysis. Eur Heart J. 2019 Oct 7;40(38):3143-3153.

197. Siontis GC, Praz F, Pilgrim T, Mavridis D, Verma S, Salanti G, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. Eur Heart J. 2016 Dec 14;37(47):3503-3512.

198. Smith CR, Leon MB, Mack MJ, Miller DC, Moses JW, Svensson LG, et al; PARTNER Trial Investigators. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med. 2011 Jun 9;364(23):2187-98.

199. Søndergaard L, Ihlemann N, Capodanno D, Jørgensen TH, Nissen H, Kjeldsen BJ, et al. Durability of Transcatheter and Surgical Bioprosthetic Aortic Valves in Patients at Lower Surgical Risk. J Am Coll Cardiol. 2019 Feb 12;73(5):546-553.

200. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al; COAPT Investigators. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. N Engl J Med. 2018 Dec 13;379(24):2307-2318.

201. Strauch JT, Scherner M, Haldenwang PL, Madershahian N, Pfister R, Kuhn EW, et al. Transapical minimally invasive aortic valve implantation and conventional aortic valve replacement in octogenarians. Thorac Cardiovasc Surg. 2012 Jul;60(5):335-42.

202. Takagi H, Hari Y, Kawai N, Ando T; ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. A meta-analysis of valve-in-valve and valve-in-ring transcatheter mitral valve implantation. J Interv Cardiol. 2018 Dec;31(6):899-906.

203. Takagi H, Ando T, Umemoto T; ALICE (All-Literature Investigation of Cardiovascular Evidence) Group. A review of comparative studies of MitraClip versus surgical repair for mitral regurgitation. Int J Cardiol. 2017 Feb 1;228:289-294.

204. Takagi H, Mitta S, Ando T. Meta-analysis of Valve-in-Valve Transcatheter versus Redo Surgical Aortic Valve Replacement. Thorac Cardiovasc Surg. 2019 Jun;67(4):243-250.

205. Tam DY, Vo TX, Wijeysundera HC, Ko DT, Rocha RV, Friedrich J, Fremes SE. Transcatheter vs Surgical Aortic Valve Replacement for Aortic Stenosis in Low-Intermediate Risk Patients: A Meta-analysis. Can J Cardiol. 2017 Sep;33(9):1171-1179.

206. Tam DY, Dharma C, Rocha RV, Ouzounian M, Wijeysundera HC, Austin PC, Chikwe J, Gaudino M, Fremes SE. Transcatheter ViV Versus Redo Surgical AVR for the Management of Failed Biological Prosthesis: Early and Late Outcomes in a Propensity-Matched Cohort. JACC Cardiovasc Interv. 2020 Mar 23;13(6):765-774.

207. Testa L, Latib A, Casenghi M, Gorla R, Colombo A, Bedogni F. Cerebral Protection During Transcatheter Aortic Valve Implantation: An Updated Systematic Review and Meta-Analysis. J Am Heart Assoc. 2018;7(10):e008463. Published 2018 May 4.

208. The PARTNER II Trial: Placement of AoRTic TraNscathetER Valves. Last updated September 16, 2021. Accessed October 8, 2021. Available at URL address: https://clinicaltrials.gov/ct2/show/NCT01314313?term=sapien+AND+aortic&rank=7

209. The Society for Thoracic Surgeons. STS Adult Cardiac Surgery Database Version 4.20.2 Accessed October 8, 2021. Available at URL address: http://riskcalc.sts.org/stswebriskcalc/#/calculate

210. Thomas JD, Bonow RO. Mitral Valve Disease. In: Bonow: Braunwald's heart disease-a textbook of cardiovascular medicine, 11th ed. Saunders, an imprint of Elsevier, 2019. Ch 62.1424-40.

211. Thourani VH, Kodali S, Makkar RR, Herrmann HC, Williams M, Babaliaros V, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet. 2016 May 28;387(10034):2218-25.

212. Thyregod HG, Steinbrüchel DA, Ihlemann N, Nissen H, Kjeldsen BJ, Petursson P, et al. Transcatheter Versus Surgical Aortic Valve Replacement in Patients With Severe Aortic Valve Stenosis: 1-Year Results From the All-Comers NOTION Randomized Clinical Trial. J Am Coll Cardiol. 2015 May 26;65(20):2184-94.

213. Thyregod HGH, Ihlemann N, Jørgensen TH, Nissen H, Kjeldsen BJ, Petursson P, Et al. Five-Year Clinical and Echocardiographic Outcomes from the Nordic Aortic Valve Intervention (NOTION) Randomized Clinical Trial in Lower Surgical Risk Patients. Circulation. 2019 Feb 1.

214. Tommaso CL, Bolman RM 3rd, Feldman T, Bavaria J, Acker MA, Aldea G, et al; American Association for Thoracic Surgery; Society for Cardiovascular Angiography and Interventions; American College of Cardiology Foundation; Society of Thoracic Surgeons. Multisociety (AATS, ACCF, SCAI, and STS) expert consensus statement: operator and institutional requirements for transcatheter valve repair and replacement, part 1: transcatheter aortic valve replacement. J Thorac Cardiovasc Surg. 2012 Jun;143(6):1254-63.

215. Tuttle MK, Nasiri N, Popma J. Self-expanding transcatheter aortic valve replacement. In: Topol E. Textbook of Interventional Cardiology. Philadelphia, PA: Elsevier; 2020: Ch. 54.

216. U.S. Food and Drug Adminstration. Company announcement: Boston Scientific Announces LOTUS Edge™ Aortic Valve System Voluntary Recall and Product Discontinuation. 1/11/2021. Accessed October 26, 2021. Available at URL address: https://www.fda.gov/safety/recalls-market-withdrawals-safety-alerts/boston-scientific-announces-lotus-edgetm-aortic-valve-system-voluntary-recall-and-product

217. U.S. Food and Drug Adminstration. 510(k) premarket approval. K192460. Sentinel Cerebral Protection System. Accessed October 18, 2021. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm?id=K192460

218. US. Food and Drug Adminstration, FDA news, Abbott Valve Replacement System Gets Breakthrough Device Designation, June 23, 2021. Accessed November 9, 2021. Available at URL address: https://www.fdanews.com/articles/203287-abbott-valve-replacement-system-gets-breakthrough-device-designation

219. U.S. Food and Drug Administration. De novo summary: Sentinel cerebral protection system. DEN160043. Accessed October 8, 2021. Available at URL address: https://www.fda.gov/about-fda/cdrh-transparency/evaluation-automatic-class-iii-designation-de-novo-summaries

220. U.S. Food and Drug Administration. Premarket Approval (PMA). Edwards SAPIEN Transcatheter Heart Valve. P100041. Accessed October 8, 2021. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

221. U.S. Food and Drug Administration. Premarket Approval (PMA). Edwards SAPIEN Transcatheter Heart Valve. P110021, S026. Accessed October 8, 2021. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

222. U.S. Food and Drug Administration. Premarket Approval (PMA). Edwards SAPIEN XT™ Transcatheter Heart Valve. P130009. Accessed October 8, 2021. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

223. U.S. Food and Drug Administration. Premarket Approval (PMA). SAPIEN 3 Transcatheter Heart Valve. P140031. Accessed October 8, 2021. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

224. U.S. Food and Drug Administration. Premarket Approval (PMA). Medtronic CoreValve System. P130021. Accessed October 8, 2021. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

225. U.S. Food and Drug Administration Device Approvals and Clearances. Humanitarian Device Approval, Medtronic Melody® Transcatheter Pulmonary Valve - H080002. Accessed October 8, 2021. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H080002

226. U.S. Food and Drug Administration. Premarket Approval (PMA). Melody® Transcatheter Heart Valve. P140017. Accessed October 8, 2021. Available at URL address: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

227. U.S. Food and Drug Administration. Premarket Approval (PMA). LOTUS Edge™ Valve System. P180029. April 23, 2019. Accessed October 8, 2021. Available at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P180029

228. U.S. Food and Drug Administration. Premarket Approval (PMA). Medtronic Harmony Transcatheter Pulmonary Valve (TPV) System – P200046. Accessed October 8, 2021. Availaible at URL address: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm

229. Vahanian A, Beyersdorf F, Praz F, Milojevic M, Baldus S, Bauersachs J, et al.; ESC/EACTS Scientific Document Group. 2021 ESC/EACTS Guidelines for the management of valvular heart disease. Eur Heart J. 2021 Aug 28:ehab395. doi: 10.1093/eurheartj/ehab395. Epub ahead of print. PMID: 34453165.

230. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Guidelines on the Management of Valvular Heart Disease. Eur J Cardiothorac Surg. 2012 Oct;42(4):S1-44.

231. Vandvik PO, Otto CM, Siemieniuk RA, Bagur R, Guyatt GH, Lytvyn L, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. BMJ. 2016 Sep 28;354:i5085.

232. Van Mieghem NM, van Gils L, Ahmad H, van Kesteren F, van der Werf HW, Brueren et al. Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial. EuroIntervention. 2016 Jul 20;12(4):499-507.

233. Veluz JS, Leary MC. Cerebral Vascular Complications of Cardiac Surgery. In: Primer on Cerebrovascular Diseases. 2nd edition. Philadelphia, PA: Elsevier; 2017: Ch 126; 650-55.

234. Vezmar M, Chaturvedi R, Lee KJ, Almeida C, Manlhiot C, McCrindle BW, Horlick EM, Benson LN. Percutaneous pulmonary valve implantation in the young 2-year follow-up. JACC Cardiovasc Interv. 2010 Apr;3(4):439-48.

235. Vipparthy SC, Ravi V, Avula S, et al. Meta-Analysis of Transcatheter Aortic Valve Implantation Versus Surgical Aortic Valve Replacement in Patients With Low Surgical Risk. Am J Cardiol. 2020;125(3):459-468.

236. Virtanen MPO, Eskola M, Jalava MP, Husso A, Laakso T, Niemelä M, et al. Comparison of Outcomes After Transcatheter Aortic Valve Replacement vs Surgical Aortic Valve Replacement Among Patients With Aortic Stenosis at Low Operative Risk. JAMA Netw Open. 2019 Jun 5;2(6):e195742.

237. Wagner R, Daehnert I, Lurz P. Percutaneous pulmonary and tricuspid valve implantations: An update. World J Cardiol. 2015 Apr 26;7(4):167-77.

238. Wagner R, Daehnert I, Lurz PC. Pulmonary and triscuspid valve interventions. In: Topol E. Textbook of Interventional Cardiology, Seventh Edition. Philadelphia, PA: Elsevier; 2016: Ch. 54: 834-846.

239. Waksman R, Rogers T, Torguson R, Gordon P, Ehsan A, Wilson SR, et al. Transcatheter Aortic Valve Replacement in Low-Risk Patients With Symptomatic Severe Aortic Stenosis. J Am Coll Cardiol. 2018 Oct 30;72(18):2095-2105.

240. Waksman R, Corso PJ, Torguson R, Gordon P, Ehsan A, Wilson SR, et al. TAVR in Low-Risk Patients: 1-Year Results From the LRT Trial. JACC Cardiovasc Interv. 2019 May 27;12(10):901-907.

241. Walther T, Schuler G, Borger MA, Kempfert J, Seeburger J, Rückert Y, et al. Transapical aortic valve implantation in 100 consecutive patients: comparison to propensity-matched conventional aortic valve replacement. Eur Heart J. 2010 Jun;31(11):1398-403.

242. Warnes CA, Williams RG, Bashore TM, Child JS, Connolly HM, Dearani JA, et al. ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to develop guidelines on the management of adults with congenital heart disease). Circulation. 2008 Dec 2;118(23):e714-833.

243. Webb JG, Wood DA, Ye J, Gurvitch R, Masson JB, Rodés-Cabau J, et al. Transcatheter valve-in-valve implantation for failed bioprosthetic heart valves. Circulation. 2010 Apr 27;121(16):1848-57.

244. Webb JG, Mack MJ, White JM, Dvir D, Blanke P, et al. Transcatheter Aortic Valve Implantation Within Degenerated Aortic Surgical Bioprostheses: PARTNER 2 Valve-in-Valve Registry. J Am Coll Cardiol. 2017 May 9;69(18):2253-2262.

245. Webb JG, Murdoch DJ, Alu MC, et al. 3-Year Outcomes After Valve-in-Valve Transcatheter Aortic Valve Replacement for Degenerated Bioprostheses: The PARTNER 2 Registry. J Am Coll Cardiol. 2019;73(21):2647-2655.

246. Wenaweser P, Pilgrim T, Kadner A, Huber C, Stortecky S, Buellesfeld L, Khattab AA, et al. Clinical outcomes of patients with severe aortic stenosis at increased surgical risk according to treatment modality. J Am Coll Cardiol. 2011 Nov 15;58(21):2151-62.

247. Wendt D, Al-Rashid F, Kahlert P, Eißmann M, El-Chilali K, Janosi A, et al. Low Incidence of Paravalvular Leakage With the Balloon-Expandable Sapien 3 Transcatheter Heart Valve. Ann Thorac Surg. 2015 Jun 24.

248. Whisenant B, Kapadia SR, Eleid MF, Kodali SK, McCabe JM, Krishnaswamy A, et al. One-Year Outcomes of Mitral Valve-in-Valve Using the SAPIEN 3 Transcatheter Heart Valve. JAMA Cardiol. 2020 Nov 1;5(11):1245-1252.

249. Whitlow PL, Feldman T, Pedersen WR, Lim DS, Kipperman R, Smalling R, et al.; EVEREST II Investigators. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. J Am Coll Cardiol. 2012 Jan 10;59(2):130-9.

250. Witberg G, Lador A, Yahav D, Kornowski R. Transcatheter versus surgical aortic valve replacement in patients at low surgical risk: A meta-analysis of randomized trials and propensity score matched observational studies. Catheter Cardiovasc Interv. 2018 Aug 1;92(2):408-416.

251. Witte KK, Lipiecki J, Siminiak T, Meredith IT, Malkin CJ, Goldberg SL, et al. The REDUCE FMR Trial: A Randomized Sham-Controlled Study of Percutaneous Mitral Annuloplasty in Functional Mitral Regurgitation. JACC Heart Fail. 2019 Nov;7(11):945-955.

252. Woitek FJ, Stachel G, Kiefer P, Haussig S, Leontyev S, Schlotter F, et al. Treatment of failed aortic bioprostheses: An evaluation of conventional redo surgery and transfemoral transcatheter aortic valve-in-valve implantation. Int J Cardiol. 2020 Feb 1;300:80-86.

253. Yoon SH, Whisenant BK, Bleiziffer S, Delgado V, Schofer N, Eschenbach L,et al. Transcatheter Mitral Valve Replacement for Degenerated Bioprosthetic Valves and Failed Annuloplasty Rings. J Am Coll Cardiol. 2017 Aug 29;70(9):1121-1131.

254. Xiong TY, Liao YB, Zhao ZG, Xu YN, Wei X, Zuo ZL, et al. Causes of Death Following Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis. J Am Heart Assoc. 2015 Sep 21;4(9):e002096.

255. Zahn EM, Hellenbrand WE, Lock JE, McElhinney DB. Implantation of the melody transcatheter pulmonary valve in patients with a dysfunctional right ventricular outflow tract conduit early results from the U.S. Clinical trial. J Am Coll Cardiol. 2009 Oct 27;54(18):1722-9.

256. Zahn EM, Chang JC, Armer D, Garg R. First human implant of the Alterra Adaptive Prestent(TM): A new self-expanding device designed to remodel the right ventricular outflow tract. Catheter Cardiovasc Interv. 2018 May 1;91(6):1125-1129.

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)

Treatment	Indication	Complications
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	Mortality (3% to 5%) • Stroke (6% to 7%) • Access complications (17%) • Pacemaker insertion

Treatment	Indication	Complications
	TAVR and a 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%*)	• 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	• 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	• 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.