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Louis Jacques, M.D., Director
Coverage & Analysis Group, OCSQ
Centers for Medicare and Medicaid Services
7500 Security Boulevard, C1-14-15
Baltimore, Maryland 21244

FORMAL REQUEST FOR TRANSCATHETER MITRAL VALVE REPAIR (TMVR) MEDICARE NATIONAL COVERAGE DETERMINATION (NCD)

Dear Dr. Jacques:

The Society of Thoracic Surgeons (STS), the American College of Cardiology (ACC), the Society for Cardiovascular Angiography and Interventions (SCAI), and the American Association for Thoracic Surgery (AATS) are submitting a joint formal request for the development of a NCD for TMVR procedures. That request is attached. It incorporates indications from the recent FDA approval of the Mitraclip, highlights the value of data collection for this emerging technology, and takes steps to ensure TMVR patients will be cared for by a collaborative heart team at high quality facilities.

We look forward to working with you during this process. Please do not hesitate to contact us if you need additional information to proceed.

Sincerely,

Douglas E. Wood, MD
STS President

Theodore A. Bass, MD
SCAI President

John Gordon Harold, MD
ACC President

David Sugarbaker, MD
AATS President

Enclosure

FORMAL REQUEST FOR A MEDICARE NATIONAL COVERAGE DETERMINATION (NCD)

Transcatheter Mitral Valve Repair Procedures

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1. Requesting Organizations

The Society of Thoracic Surgeons (STS), the American College of Cardiology (ACC), the Society for Cardiovascular Angiography and Interventions (SCAI), and the American Association for Thoracic Surgery (AATS); “the Societies.”

2. Development Track

Formal request for an NCD

3. Benefit categories

Physician services

Inpatient hospital services

4. Description of the Transcatheter Mitral Valve Repair (TMVR)

TMVR represents emerging technologies to treat high-risk and elderly symptomatic patients with Grade 3 (moderate to severe) or Grade 4 (severe) mitral regurgitation (MR) based on American Society of Echocardiography guidelines. Candidates for this technology are either non-operative candidates or high-risk operative candidates as determined using The Society of Thoracic Surgeons (STS) Risk Score, and a consensus from the heart team which includes an experienced mitral valve surgeon and interventional cardiologist who agree on the appropriate use of this technology. The surgeon and interventional cardiologist credentialing criteria will be developed by consensus opinion from the involved professional societies and are expected to be harmonized with the criteria established in prior FDA trials. In the US trials, a mitral valve surgeon needed to perform at least 25 mitral valve repairs/replacements per year and the Interventional cardiologist needed to be experienced in transseptal puncture techniques to participate.

TMVR procedures could involve clipping of the mitral valve leaflets, mitral valve annular reduction or implantation of new mitral valve supporting structures (chordal implants). All are done through catheter based technology. The mitral clipping and the annular reduction are done through a transvenous approach while the chordal implants are done via a limited left anterior thoracotomy and a transapical approach. Any of these approaches may require cardiopulmonary bypass.

There are several types of transcatheter therapies that are at various stages of development. The different techniques include the following:

1) Repair of the leaflets through edge-to-edge plication. The technique that is the farthest along in development in leaflet treatment and transcatheter mitral valve repairs overall is the MitraClip. The procedure is based on the double-orifice technique used in open heart mitral valve repair. This is similar to the open surgical technique when a suture is placed under direct visualization from the anterior to the posterior leaflet of the mitral valve. As a result, when the suture is placed in the middle of the valve, the valve will have a functional double orifice during diastole, thus the alternate name for the procedure "Double Orifice Repair." This procedure involves the insertion of a clip that is attached directly to the mitral valve leaflets. It is deployed using catheter-based technology. The Mitraclip is generally deployed using a percutaneous transvenous approach through a large peripheral vein. The procedure does not typically require cardiopulmonary bypass.
2) Repair of the annulus is another method of reducing MR. The technique that is the farthest along in development is the Carillon Mitral Contour System. This procedure involves the deployment of an implantable device that consists of a proximal anchor and a distal anchor that is connected by a shaping ribbon. The device reduces the mitral annulus dilatation upon deployment. The device is positioned in the coronary sinus and great cardiac vein. The device is deployed using standard cardiac catheterization techniques in the venous vasculature. There are also several other types of devices that are in different stages of clinical trials in Europe and the US that work to reduce or adjust the size of the mitral annulus.
3) Chordal implants are another technique that is being developed to treat MR. This procedure uses a device to replace damaged mitral valve chordae by delivering artificial chordae tendonae in a beating heart using minimally invasive techniques. This is done through a limited anterior thoracotomy and then through the apex of the heart similar to transapical Transcatheter Aortic Valve Replacement (TAVR)

Detailed description of the procedure

Percutaneous transcatheter mitral valve repair using a leaflet plication

After general anesthesia is induced, the patient is intubated. Both groin sites are prepped. Transesophageal echocardiography probe is inserted and positioned by a separate physician who is not the surgeon or interventional cardiologist. Bilateral venous access is obtained for right heart catheterization and evaluation of pulmonary pressures and transseptal puncture. Baseline right heart catheterization is performed to assess intra-cardiac hemodynamics, including cardiac output, pulmonary arterial pressure and pulmonary capillary wedge pressure. A wire is advanced from the right femoral

vein to the superior vena cava for placement of the transseptal sheath & needle. The transseptal sheath and needle are now inserted over the wire, and using echocardiographic guidance entry into the right atrium is confirmed. Transseptal puncture is performed with echo verification of correct puncture location. The patient is heparinized and the Activated Clotting Time (ACT) is checked. The activated clotting time [ACT] level should be > 250 seconds. Continue to check ACT every 30 min and readminister heparin during the procedure and check ACT to verify the patient is therapeutically anticoagulated. At this point a stiff guide wire in placed through the transseptal sheath into the left atrium and then pulmonary vein. The mitral valve repair device is prepared on the back table.

The femoral vein access site is progressively dilated with a series of dilators. The guide catheter is advanced over the wire into the left atrium, the wire is removed, and the guide catheter is de-aired. The mitral valve repair device and delivery system are advanced through the guide to the left atrium. Extreme care is required to prevent disruption of the interatrial septum and to avoid air embolus to the left heart. The prosthesis is then positioned above the mitral valve using echocardiographic and fluoroscopic guidance. Multiple echocardiographic and fluoroscopic views are utilized in a complex series of maneuvers to position the prosthesis at the proper position above the mitral valve, with careful avoidance of other structures. The device is then deployed, grasping and coapting the anterior and mitral leaflets at that site, reducing mitral regurgitation. Multiple grasps are often required. Echocardiographic and fluoroscopic imaging is then used to ensure proper device positioning and leaflet insertion into the device, and adequate reduction in the mitral regurgitation. If the evaluation is favorable the device is released in a series of steps. After final release the patient is again evaluated by angiographic, hemodynamic and echocardiographic criteria for suitability of the mitral valve repair and to ensure no complications. If there is no need for an additional device, the delivery system is withdrawn and removed from the body.

The patient's arterial pressure, EKG waveforms, and oxygen saturation are constantly monitored throughout the procedure. Right heart catheterization is often repeated to assess intracardiac hemodynamics, including cardiac output, pulmonary arterial pressure and pulmonary capillary wedge pressure. Images are reviewed to ensure no additional views are required before leaving the procedure suite. The groin site is closed per physician and institutional practices. Anesthesia is reversed and the patient is extubated as appropriate. Hypertension, hypotension, bleeding and oxygen desaturation are potential complications and are treated accordingly with medications and/or oxygen as needed during the procedure.

Transcatheter mitral valve repair using annulus reduction via the coronary sinus

Conscious sedation is administered. Access sites are prepped. The echocardiographer obtains preprocedure transthoracic echocardiographic images of the mitral valve and individual leaflets, focus of the regurgitant jet is identified, and key measurements, such as quantitative assessment of mitral regurgitation (vena contracta, effective regurgitant orifice area and jet area/left atrial area) are performed. Right internal jugular (RIJ) vein access is obtained and arterial access is obtained from the femoral or radial artery. The patient is heparinized and the activated clotting time [ACT] is checked at the appropriate time interval to obtain ACT > 200 seconds. ACTs are checked every 30 minutes and heparin is readministered as necessary during the procedure to verify the patient is therapeutically anticoagulated.

Right coronary arteriography is done with a standard approach. Left coronary arteriography is done, to assess for coronary artery disease, which might require revascularization, and to provide a baseline appearance of the coronary anatomy. In addition, extended imaging is performed to visualize the coronary venous anatomy (venous follow-through), to assess the character of the coronary sinus/great cardiac vein, and to aid in engagement of the coronary sinus. This is done in a left anterior oblique view, typically with caudal or cranial angulation.

An angled catheter is loaded through a larger bore delivery catheter and this combination is advanced over a wire from the RIJ and directed toward the coronary sinus. Using the venous follow-through image of the coronary sinus as a road map, the angled catheter is used to catch the opening of the coronary sinus. The wire is advanced through the coronary sinus into the terminal branch of the great cardiac vein. The catheter is advanced over the wire to the distal aspect of the great cardiac vein. The delivery catheter is now telescoped over the angled catheter into position, and the wire and angled catheter are removed. The delivery catheter is carefully de-aired. A marker catheter is now advanced through the delivery catheter to its tip. The image intensifier is moved to a right anterior oblique with caudal angulation and left coronary arteriography is done, to establish the relationship of the circumflex coronary artery with the great cardiac vein (demarcated by the delivery and marker catheters). Venography of the cardiac vein and coronary sinus is then done to assist in sizing the device. The image intensifier is then moved to a left anterior oblique with caudal angulation and left coronary arteriography

is performed, followed by venography. At this point, the table and the image intensifier are not to be moved, as device positioning will be done based upon the fluoroscopic image on the fluoro screen.

The length of usable vein will be assessed. If there is insufficient vein length, the marker catheter is removed, and the wire and angled catheter are re-inserted to further advance the delivery catheter, up to the anterior interventricular vein. Provided there is optimal length, vein characteristics are assessed for optimal placement of the device. This assessment includes the size of the vein, curvature of the vein, tapering characteristics, presence of side branches and the relationship with the circumflex coronary artery. Vein measurements are made at the intervals within the intended placement of the device, using the marker catheter as a scaling device. An appropriate length of the device is selected.

The device is advanced through the delivery sheath to the coronary sinus and using the markings from the diagnostic venogram, the device is carefully positioned. Coronary artery injections may be done to assist in optimal placement and the distal aspect of the device is desheathed by withdrawing the delivery sheath somewhat. Left coronary angiography is done to ensure no compromise of the left circumflex. The proximal aspect of the device is then positioned, aided by injection in the side arm of the delivery catheter to identify the ostium of the coronary sinus, and/or echo assessment of mitral regurgitation improvement. Once the desired location is achieved, coronary arteriography is again done to look for coronary artery compromise. If compromise of the circumflex coronary artery is seen, the device is recaptured. Left coronary angiography is performed to ensure resolution of the circumflex compromise. Angiography of the vein is done to ensure there has not been any damage. Using the same techniques, a new delivery catheter is then placed slightly proximal to the first attempt and less tension is used in an attempt to modify the mitral annulus without compromising the left circumflex. If repeat left coronary angiography shows no compromise of the circumflex, the left coronary catheter is exchanged for a right coronary catheter and right coronary angiography is done. Transthoracic echo imaging of mitral regurgitation is done by the echocardiographer with quantitative assessment. If this demonstrates appropriate reduction in mitral regurgitation the device is released.

The patient's arterial pressure, EKG waveforms, and oxygen saturation are constantly monitored throughout the procedure. Right heart catheterization is typically repeated to assess intracardiac hemodynamics, including cardiac output, pulmonary arterial pressure and pulmonary capillary wedge pressure. Images are reviewed to ensure no additional views are required before leaving the procedure suite. The groin site is closed per physician and institutional practices. Anesthesia is reversed and the

patient is extubated as appropriate. Hypertension, hypotension, bleeding and oxygen desaturation are potential complications and are treated accordingly with medications and/or oxygen as needed during the procedure. The patient is transferred to the recovery suite for additional monitoring.

Transcatheter mitral valve repair using chordal implants

The heart is exposed through a small left anterior limited thoracotomy in the fifth or sixth intercostal space. Using echocardiographic guidance, the chordal implant is introduced through the lowest part of the heart (apex), into the left ventricle, and between the mitral valve leaflets. The prolapsed leaflet is then grasped using the expandable jaws of the device. When the monitor confirms that the leaflet has been adequately captured, the ePTFE suture is deployed and attached to the leaflet. The suture is then pulled through the apex of the heart as the device is removed. The correct length of the suture is determined by using real time echocardiographic guidance and observing the improvement in mitral valve regurgitation in the beating heart. The suture is then secured to the apex of the heart. At the completion of the chordal implant procedure, hemostasis is assured. Chest tube(s) are placed. The incision is closed in layers and dressings are placed.

5. The target Medicare population and medical conditions for which the TMVR can be used

The initial experience with TMVR for mitral regurgitation is with the MitraClip System and is based on recent clinical trials in the US, Canada, Europe, and other countries that have demonstrated the potential for a new treatment option for high risk and inoperable patients using a transcatheter mitral valve repair. Randomized trial data, as well as prospective and observational data, have been published dealing with this specific valve technology. Adoption of TMVR using the MitraClip system to populations beyond those described in the EVEREST II High Risk Registry and REALISM studies is not appropriate at the current time. However, in view of the promising results obtained in these limited population subsets, further randomized trials in other patient groups is strongly encouraged. Trials involving the other TMVR technologies are in development.

In accordance with current and potential future FDA-approved indications, patients must have moderate-to-severe (3+) or severe (4+) symptomatic degenerative mitral regurgitation and be deemed extremely high risk or inoperable for mitral valve surgery. The term “Prohibitive Risk” was used at the recent FDA Panel hearing and may also adequately describe this and other patient populations.

Patients will be selected by a multidisciplinary team involving specialists in heart failure, interventional cardiology, echocardiography and cardiac surgery. All patients should be adequately treated as per

applicable standards, such as for coronary artery disease, left ventricular dysfunction, mitral regurgitation, and/or heart failure if present. Patients must be considered at high risk or inoperable as was defined in the clinical trials. In the recent approval for MitraClip the patient population was defined as "Prohibitive Risk"

In accordance with the FDA-approved label, “Prohibitive risk is determined by the clinical judgment of a heart team, including a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, due to the presence of one or more of the following documented surgical risk factors:

- 30-day STS predicted operative mortality risk score of
    - ≥8% for patients deemed likely to undergo mitral valve replacement or
    - ≥6% for patients deemed likely to undergo mitral valve repair
- Porcelain aorta or extensively calcified ascending aorta
- Frailty (assessed by in-person cardiac surgeon consultation)
- Hostile chest
- Severe liver disease / cirrhosis (MELD Score >12)
- Severe pulmonary hypertension (systolic pulmonary artery pressure >2/3 systemic pressure)

Unusual extenuating circumstance, such as right ventricular dysfunction with severe tricuspid regurgitation, chemotherapy for malignancy, major bleeding diathesis, immobility, AIDS, severe dementia, high risk of aspiration, internal mammary artery (IMA) at high risk of injury, etc.”

Therefore, we recommend that CMS cover TMVR using a system that has received FDA premarket approval (PMA) for the treatment of MR when performed according to an FDA-approved indication.

The initial experience with TMVR for mitral regurgitation with the annuloplasty reduction system is based on prospective, non-randomized, non-blinded, multicentre trials in Europe, that have demonstrated the potential for a new treatment option of transcatheter mitral valve repair using this annuloplasty reduction technique. Clinical trial data, as well as prospective and observational data, have been published dealing with this specific valve technology. This technology is targeted for patients with dilated ischemic or non-ischemic cardiomyopathy; at least moderately severe (3+) functional mitral regurgitation (FMR); and reduced LV ejection fraction. There is no US experience with this technology. The initial experience with TMVR using a chordal implant is limited in the United States.

In summary, the target patient population for treatment of mitral regurgitation with TMVR within the Medicare population will be limited to Medicare beneficiaries who are considered high-risk operative candidates or inoperable or further defined by FDA labeling as prohibitive risk based on advanced age and/or other comorbidities as determined by the STS risk scores and the heart team that includes an interventional cardiologist having significant experience in transseptal puncture approaches to the mitral valve and a mitral valve surgeon with significant experience in mitral valve repair and replacement. These criteria will be developed by expert opinion consensus among the professional societies involved in the care of patients with mitral regurgitation. It is anticipated that the qualifications of the surgeon and interventional cardiologist will be derived from the criteria established in the Everest II Trial (mitral valve surgeon performing at a minimum 25 mitral valve repairs or replacements annually). Evaluation of the patient will be based on complete evaluation by a multidisciplinary Heart Team using American Heart Association/American College of Cardiology guidelines for intervention, the American Society of Echocardiography guidelines and the STS Predicted Risk of Mortality Score (STS PROM) which is available at http://www.sts.org/quality-research-patient-safety/quality/risk-calculator-and-models/risk-calculator.

Current evidence on transcatheter mitral valve repair for mitral regurgitation is limited to patients who are considered to have a poor prognosis without treatment and/or are at high risk if treated by conventional open heart mitral valve replacement. These patients carry a high mortality risk due to advanced age and/or the presence of concomitant illnesses. TMVR is not intended for use in Medicare beneficiaries who are considered acceptable operative candidates as defined by STS and ACC guidelines and the multidisciplinary team or in those patients with such advanced age and comorbidities that good clinical outcomes could not be achieved even with TMVR. Quality of life and functional status beyond one year following the procedure will be considered essential in deciding which patients will benefit from these procedures.

The multidisciplinary structural heart valve disease team, which includes the primary cardiologists, echocardiographers, cardiac surgeons experienced in mitral valve repair and interventional cardiologists experienced in transseptal approaches to the mitral valve, will be central in applying scoring systems to evaluate risk-benefit profiles in this diverse group of patients. The multidisciplinary team should have specific protocols for care related to pre-procedure assessment and screening. These protocols should be implemented and executed jointly by the multidisciplinary team. These protocols will involve screening for the presence, degree, and severity of comorbidities, issues related to the mitral pathology that may

affect outcome and identification of optimal strategies and other procedures that may be required to ensure good outcomes (e.g., the treatment of coronary obstructive lesions prior to the performance of a percutaneous TMVR). Such protocols and procedures should be contained in well-defined patient-care pathways. Adherence to these principles will not only prevent inappropriate use of these devices, but will ensure best patient outcomes and optimal device utilization.

6. Supporting medical and scientific information

a. Overview of the technology

Traditional mitral valve repair surgery through a median sternotomy or a more limited minimally invasive approach has been the mainstay of treatment for valvular heart disease. In general, when used in experienced centers with qualified surgeons, the results of traditional mitral valve repair and TMVR use have been excellent - improving morbidity and mortality as compared to medical therapy. TMVR technology is timely as invasiveness and recovery time for the patient have recently become an issue. Since the introduction of minimally invasive and catheter-based therapies, patients have wanted less invasive options for all types of medical procedures including general surgical, orthopedic, spinal, and urologic operations with the goal of decreasing morbidity and mortality and shortening recovery time. TMVR offers this technology and has been proven to be beneficial for select patients with mitral regurgitation.

TMVR utilizes a leaflet coaptation clip or an annuloplasty reduction device that is inserted using a catheter-based technology. The delivery can be accomplished using a percutaneous approach through a peripheral vein. Chordal implant devices may include a transthoracic approach through a limited thoracotomy. The transvenous approach is less invasive than traditional open heart surgery, which is currently the standard for mitral valve repair. Given the current minimally invasive approaches for traditional mitral valve repair a transthoracic approach for MV repair is yet to be proven to be more beneficial.

b. Estimated number of patients who qualify for the procedures

At this time, more than 9,588 invasive mitral valve repair procedures are performed per year in the United States from an open thoracic approach. It is estimated that less than 5,000 TMVR cases will be performed annually, with approximately 90% of cases representing Medicare. The procedure will be performed on patients who meet rigorous selection criteria that are based on advanced age and comorbidities and who are considered to be inoperable or high risk operative candidates as

determined by the heart team defined above. Selection criteria will be based on the experience gained from the Endovascular Valve Edge-to-Edge Repair (EVEREST II) Trial and on FDA labeling. As these emerging techniques continue to evolve and the number of clinical trials increases, utilization of these procedures over time is expected to increase albeit in a controlled fashion based on evolving evidence from further clinical trials or on evaluation of data from the TVT registry and consensus building among involved stakeholders.

c. General background

To date, one clinical trial has been conducted to evaluate the use, safety, and effectiveness of transcatheter mitral valve repair utilizing a percutaneous approach for the MitraClip insertion The Everest II trial has provided data that the treatment is safe and effective for a select group of patients. In addition, the trial data underscored the importance of a controlled environment for delivery of these procedures. In order to ensure safe and effective practices for TMVR insertions, it is important to implement guidelines that ensure the procedures are performed in specialized heart centers with specialized equipment, sufficient volume, and properly trained and credentialed multidisciplinary teams (Heart Teams) that have agreed upon joint decision making and co-management principles involving the selection and technical aspects of treatment of patients at risk. Continued review of data and outcomes with necessary refinements to guidelines and protocols utilizing a joint TVT registry is felt to be essential. Mandatory inclusive data entry in this registry will provide a level of patient safety considered essential in rational dispersion of these technologies.

d. Basic research

The Everest II randomized clinical trial provided initial data on the protocols and guidelines that need to be followed to provide safe, effective and appropriate treatment of mitral regurgitation in selected patients with mitral regurgitation using the MitraClip. The Everest II high risk registry and REALISM continued access study have shown that TMVR provides a safe and effective treatment for a high surgical risk patient population. The technology has been shown to be effective in treating mitral regurgitation in select high risk patient populations in a well-defined, controlled environment. In addition the clinical trials in the U.S have shown that positive outcomes can be assured by the necessary advanced equipment and trained multidisciplinary providers in specialized centers to ensure good clinical outcomes utilizing the TMVR technology.

e. The devices

The TMVR devices will fall into three categories: repairs to the leaflet, annulus reduction, or placement of artificial cords. The approaches used will be similar regardless of what type of device is used in that they allow for transcatheter deployment of the device utilizing either a percutaneous or transthoracic approach. There are approximately 9 different companies involved in the development of transcatheter mitral valve repair devices. Some of the companies that are involved the development of TMVR devices include the following: MitraClip (Abbott Laboratories), Carillon Mitral Contour System (Cardiac Dimensions), NeoChord DS 1000 (NeoChord, Inc.), Cardioband with Transfemoral delivery system (Valtech Cardio Ltd), The GDS Accucinch System (Guided Delivery Systems), enCorSQ (MiCardia), MitraFlex (TransCardiac Therapeutics), Mitra-Spacer / Percu-Pro (Cardiosolutions), Mitraalign Annuloplasty (Mitralign, Inc). The MitraClip is currently being evaluated by clinical trial in the United States for functional MR (COAPT trial).

f. Clinical experience

The pivotal Everest II trial has received a great deal of interest. Specific details about patient selection, protocols used, endpoints, and statistical evaluation are crucial. The Everest II trial consisted of two parallel trials that enrolled the highest-risk patients ever seen in any cardiovascular trial by virtue of their age and severity of their comorbidities: 1) patients within the EVEREST II High Risk Study who met eligibility criteria for being too high risk to undergo mitral valve surgery; and (2) patients within the EVEREST II Continued Access Study/Registry (High Risk Registry) who were too high risk for surgery using identical eligibility inclusion criteria.

Patients enrolled in the EVEREST II HRR Study were considered high surgical risk if the cardiothoracic surgeon at the investigational site assessed a predicted surgical mortality for mitral valve surgery of ≥ 12% based on either:

I) STS (Society of Thoracic Surgeons) mortality risk ≥ 12%, or
II) The presence of at least one of the following:
    1) Porcelain aorta or mobile ascending aortic atheroma
    2) Post-radiation mediastinum
    3) Previous mediastinitis
    4) Functional MR with EF < 40%
    5) Over 75 years old with EF < 40%
    6) Prior re-operation with patent grafts

7) Two or more prior chest surgeries
8) Hepatic cirrhosis
9) Three or more of the following STS high risk factors:
    i. Creatinine > 2.5 mg/dL
    ii. Prior chest surgery
    iii. Age over 75
    iv. EF<35%

The trial enrolled both degenerative and functional MR etiologies (41% DMR, 59% FMR).
The primary safety endpoint of the EVEREST II HRR Study was procedural mortality at 30 days or prior to discharge, whichever was longer. The observed procedural mortality was statistically significantly lower than the predicted surgical mortality, thus the trial met the primary endpoint of lower procedural mortality than predicted for surgery.

For this high surgical risk population with limited options, safe reduction of MR is clinically meaningful, as observed in the following endpoints:

- Reduction of MR to 2+ or less can be achieved in a majority of patients and is durable through 2 years
- Improvements in NYHA Functional Class and SF-36 Quality of Life
- Reduction in left ventricular size
- Significant decrease in the rate of hospitalization for heart failure after treatment with the device
- Reduced mortality for high surgical risk patients compared to predicted mortality from the STS database and publications
- Shorter ICU time, hospital length of stay and requirement for nursing or rehabilitation care post hospitalization compared to mitral valve surgery in non-high risk surgical patients
- Mortality at 12 months was within the range expected based on medical therapy and surgical literature

Results in High Surgical Risk Patients

In December 2012, data from the EVEREST II HR Study (N = 78 patients with 2 years of follow-up) and the EVEREST II REALISM Continued Access High Risk arm (133 patients with

1 year of follow-up) were pooled as described in the REALISM protocol and reported to FDA in support of a high surgical risk indication (hereafter referred to as EVEREST High Risk Cohort, N = 211). These patients had a large range of co-morbidities that elevated their risk of surgical mortality. Approximately 2/3 of patients in this cohort had functional MR etiology.

Procedural results in high surgical risk patients who underwent the MitraClip procedure are very favorable even when compared to results in non-high risk patients who underwent mitral valve surgery. Procedural mortality was significantly lower than the predicted surgical mortality. EVEREST High Risk Cohort patients undergoing the MitraClip procedure had shorter anesthesia durations, post-procedure ICU/CCU/PACU duration and post-procedure hospital stay, and were discharged home without home healthcare more often than the non- high risk Control patients who underwent mitral valve surgery in the EVEREST II RCT.

To provide perspective on the procedural mortality results on this cohort of patients, Abbott Vascular compared data collected from the high surgical risk patients to the following:

- Medical therapy and surgical literature for patients with MR
- Retrospectively gathered Concurrent Control[3] consisting of patients who were screened for the EVEREST II HR Study, but did not enroll
- A single center analysis of mortality for high risk patients with a diagnosis of any grade of MR (mild to severe) who underwent non-surgical management (Ohio State University (OSU) Cardiac Database)
- A single center analysis of mortality for a propensity matched cohort of high risk patients with a diagnosis of moderate-to-severe or severe MR (Duke University Medical Center) who underwent non-surgical management Procedural (30 day) mortality in EVEREST High Risk Cohort patients was:
    - lower than in-hospital mortality reported in the literature in elderly patients undergoing mitral valve surgery
    - statistically significantly lower than the predicted surgical mortality, and comparable with that observed in high surgical risk patients in the Concurrent Control (no MitraClip)
    - consistent with 30-day mortality observed in high surgical risk patients post-diagnosis of any MR who underwent non-surgical management from the Ohio

State University Cardiac database

- comparable to 30-day mortality observed in high surgical risk patients post-diagnosis of moderate-to-severe or severe MR who underwent non-surgical management from the Duke University Medical Center

A low rate of major adverse events (MAE) was also noted at 30 days. The MAE rate in the EVEREST High Risk Cohort was much lower than that in the non-high risk Control patients who underwent mitral valve surgery in the EVEREST II RCT. These results support the MitraClip as a safe procedure in these high surgical risk patients with extensive baseline co-morbidities.

High surgical risk patients with untreated clinically significant MR are highly symptomatic, have a high rate of heart failure hospitalizations, poor quality of life and impaired functional capacity. EVEREST High Risk Cohort patients treated with the MitraClip experienced immediate (post-procedure) clinically and statistically significant improvements in quality of life, heart failure symptoms, functional capacity and left ventricular volumes and dimensions, which were sustained through 12 months. These patients also experienced substantially lower rate of heart failure hospitalizations in the 12 months post-MitraClip procedure than in the preceding 12 months.

The consistent improvement across the multiple measures observed post-treatment with the MitraClip device are expected benefits of mechanical reduction of MR. Similar clinical benefits have been observed in non-high risk patients treated surgically for MR.

Any clinical benefit with the MitraClip device must be balanced with the long- term safety of the device, i.e., no elevated risk for long-term mortality. It is therefore important to assess 12-month mortality in symptomatic patients treated with the MitraClip that are extremely high risk for mitral valve surgery. Since no parallel control was included in the EVEREST II high risk studies, long-term mortality outcomes in the EVEREST High Risk Cohort were assessed against the same comparators as those described for 30-day mortality.

The 12-month mortality rate in the EVEREST High Risk patients (N = 211) was 24%. The 12-month mortality post-MitraClip implant in the EVEREST High Risk Cohort is not excessive in

comparison with that reported in the literature, the Concurrent Control, and the Ohio State University Cardiac database, and is accompanied by substantial clinical benefits. In a propensity matched cohort of 127 of 211 EVEREST High Risk patients, mortality was reduced by 30% in comparison with high surgical risk patients with moderate-to-severe or severe MR in the Duke University database who underwent non- surgical management.

g. FDA documentation

At this time, the Abbott MitraClip is the only TMVR device that has received FDA approval.

7. FDA Information

At this time, the Abbott MitraClip is the only TMVR device that has received FDA approval.

8. Explanation of design, purpose, and method of using the item or equipment, including whether the item or equipment is for use by health care practitioners or patients

a. Establishment of regional centers of excellence for heart valve diseases

Criteria for centers performing interventional therapy in valvular and structural heart disease will be established though consensus building by the Societies and other interested parties. The availability of devices and reimbursement for those procedures should be limited to centers meeting those criteria.

In the case of TMVR, the specialized expertise, experience, imaging equipment, and facilities equipped to optimize outcomes are not available in all programs. Because of the myriad of specialists, imaging equipment, procedural facilities, and support infrastructure necessary to build a valve center, it is recommended that access to TMVR should not be universal and immediate but should be implemented in a controlled and regulated fashion. In the United States, many cardiac surgical centers and catheterization laboratories have a very low volume of structural heart disease cases. Outcomes for patients undergoing surgery for valvular heart disease have clearly been demonstrated to be related to center procedural volume. The complexities of the management of valvular heart disease will require the infrastructure available only in regional referral centers with acceptable patient volume in valvular heart disease as established by the Societies.

In order to create specialized regional centers, detailed lists of facilities and personnel experience in addition to pre- and post-procedural care protocols as well as management strategies for complications must be developed and implemented.

b. Multidisciplinary heart teams

The concept of a multidisciplinary professional heart team has received increasing interest, beginning particularly with the SYNTAX (SYNTAX Study: TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries) trial of patients with advanced coronary artery disease. In the SYNTAX trial, following angiography, the interventional cardiologist and cardiovascular surgeon reviewed the angiographic films together in the context of the clinical setting. If the patient was deemed to be an acceptable candidate for either procedure, both physician and surgeon—ideally together—would interview both patient and family to formulate an optimal plan. This "heart team" concept has been endorsed and recommended in the recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines on Myocardial Revascularization and should become the standard of care.

The heart team concept has been extended to treatment of valvular heart disease. In the PARTNER Trial, the pivotal U.S. trial of a new device for TAVR, patients were routinely evaluated by "partners" of cardiologists and surgeons together to determine patient eligibility and optimal treatment strategy. This required pre-procedural evaluation in valvular heart disease clinics, multidisciplinary team conferences, immediate surgical backup for the procedure, as well as postoperative care. Since commercialization of TAVR the heart team has become an increasingly important part of appropriate care delivery for complex decision making for patients with severe symptomatic aortic stenosis. The basis for this approach to care delivery is well described in a recent article in the Journal of the American College of Cardiology (JACC). Such a heart team will be even more critical as the issues with structural heart disease become more complex moving beyond aortic valve disease, as the treatment expands to more centers, and as new technology is applied outside of the constraints of randomized clinical trials. The success of this team concept has also been demonstrated in heart transplant centers in which patient treatment decisions and care are managed by heart failure cardiologists, transplant and ventricular assist device surgeons, experts in immunosuppression, as well as specialists in

echocardiography and anesthesia, all of whom collaborate as a multidisciplinary team. Key members of the multidisciplinary team for structural heart valve disease management include primary cardiologists, interventional cardiologists, cardiac surgeons, noninvasive and heart failure cardiologists, echocardiographers and cardiac imaging specialists, cardiac anesthesiologists, nurse practitioners, physician assistants, research coordinators, administrators, dietary and rehabilitation specialists, and social workers. Each component will need to develop and implement specific protocols depending on the individual patient and specific technical procedure.

The multidisciplinary team will be central in applying a standardized scoring system to evaluate risk-benefit profiles in this diverse group of patients. The patient's values and goals need to be central in benefit-risk assessment and treatment decisions.

Primary cardiologists

The primary cardiologists typically have seen these patients longitudinally over the course of their diseases and have a unique perspective of patient and family dynamics. These physicians coordinate care, ensure complete evaluation, order and evaluate diagnostic studies, implement medical care, and ensure involvement of patients and families in the decision-making process. Primary cardiologists also resume care of the patient after the procedure and need to be cognizant of the follow-up needs and protocols; accordingly, these individuals are an essential component of the heart team to enhance patient-centered care. The patient's values and goals need to be central in benefit-risk assessment and treatment decisions.

Cardiac surgeons and interventional cardiologists

Depending on the mitral valve repair technique used, cardiac surgeons or interventional cardiologists who have had appropriate training and experience as defined by the joint consensus statement being developed by the Societies will provide treatment and management for transcatheter valve insertions patients. In some cases the cardiac surgeon and the interventional cardiologist will evaluate and perform the procedure together. Typically, only one physician will perform the procedure. In either situation, the physician who performs the procedure (alone or jointly) will have responsibility in the technical aspect of the procedure. In either case an experienced cardiac surgeon performing adequate numbers of mitral valve replacements and repairs/year will evaluate the patient prior to the procedure to ensure that they are an appropriate

candidate. In the Everest II Trial, 25 repairs/replacements were the minimum standard. The cardiac surgeon will also need to provide emergency surgical backup for the interventional cardiologist if complications occur and it is deemed appropriate. As part of the heart team, the cardiac surgeon and the interventional cardiologist will share the decision-making about which patients are appropriate for the use of this technology. The physician who performs the procedure will need to possess adequate catheter based skills as well as surgical skills to accomplish the technical aspects of the device deployment, knowledge of the criteria for patient selection to assist in the decision making process, and adequate knowledge and support to provide post operative patient management. Each will have a responsibility to the other to ensure that their decision making, technical ability, and expertise in using the device is done in an appropriate and safe manner for Medicare Beneficiaries. Minimum ongoing case volumes will be established by the Societies and monitored to ensure that interventional cardiologists and surgeons continue to have the required skills to participate in the use of this technology and that both have the required experience to make patient centric and safe decisions about which Medicare Beneficiaries are acceptable candidates for these technologies.

Echocardiographers and imaging specialists

Echocardiography will be critical, with collection of standardized definition sets. Mandatory imaging modalities necessary for a structural heart disease program include 2- and 3-dimensional transthoracic and transesophageal echocardiography. An important screening component for TMVR involves a transthoracic echocardiography that establishes the severity of mitral regurgitation using the guidelines based on echocardiography ACC/AHA guidelines and the American Society of Echocardiography Recommendations for Evaluation of The Severity of Native Valvular Regurgitation with Two-Dimensional and Doppler Echocardiography. Individuals with this level of knowledge and experience will be Level 3 echocardiographers. The echocardiography is used to determine that the patient has moderate to severe (3+) or severe (4+) mitral valve regurgitation as defined echocardiographically by a minimum of three of the following six criteria, one of which must be quantitative (i.e., 3, 4, 5 or 6):

1. Color flow jet may be central and large (> 6 cm^2 or > 30% of LA area) or smaller if eccentric, encircling the left atrium
2. Pulmonary vein flow may show systolic blunting or systolic flow reversal
3. Vena contracta width > 0.5 cm measured in the parasternal long axis view
4. Regurgitant volume of ≥45 ml/beat (degenerative); ≥30ml/beat (functional)

5. Regurgitant fraction ≥ 40%
6. Regurgitant orifice area ≥ 0.30 cm^2 (degenerative); ≥0.20 cm^2 (functional)

Heart failure specialists

An increasing number of patients with advanced valvular heart disease have a component of left ventricular dysfunction. For patients with mitral regurgitation, left ventricular dysfunction may render the assessment of the severity of the mitral regurgitation difficult, thus complicating decision making about the need for or performance of a procedure. In addition, heart failure specialists will need to help assess the potential for reversibility or worsening of left ventricular dysfunction following TMVR. Identification of appropriate patients with mitral regurgitation and heart failure who may benefit from a catheter-based approach is best accomplished by consultation with heart failure specialists.

Anesthesiologists

The anesthesiologist determines the most appropriate anesthesia and monitoring techniques for the patient and provides technical expertise in advanced imaging. Like interventional cardiologists and cardiac surgeons, anesthesiologists will need to form dedicated teams to safely apply this technology to a high risk Medicare beneficiary population.

c. Establishment of a national registry for valvular heart disease (See TVT Registry summary from application supplemental documents)

The success of the combined STS and ACC TVT registry is established. Mandatory reporting to the STS/ACC TVT registry under coverage with evidence development (CED) through a supplementary module will allow for post-market surveillance, long-term outcome measurement, and comparative effectiveness research. The registry module to supplement the existing TVT registry for TAVR will be developed by the STS and ACC in conjunction with input from the specialty societies and other relevant stakeholders.

d. Training and credentialing criteria

Operator training is a crucial component for treating structural valvular heart disease using a TMVR approach. Construction of a training curriculum is essential. Formation of criteria for fellowship training programs as well as postgraduate training with appropriate experience for

adequate patient care leading to guidelines for credentialing will be established by the Societies in an expert consensus statement currently under development.

There will be minimal case volume requirements for catheter based and surgical based approaches. Both the cardiologist and surgeon will need to have appropriate training in order to establish a TMVR program. Following the establishment of a program all members of the multidisciplinary team will need to maintain minimal volume requirements for continued participation and will be monitored on an ongoing basis to ensure acceptable outcomes as defined by the Societies' criteria. The institutional structural requirements and cardiology/cardiac surgeon volume and outcomes criteria for TMVR will be developed using the CMS criteria for heart transplant centers and TAVR as a template. The criteria will be based on retrospective analyses of outcomes.

9. Benefits and relevance of procedure to the Medicare population

a. An explanation of the relevance of the evidence selected

Prior to the TMVR technology, there were Medicare beneficiaries who were not considered to have any effective treatment for their mitral regurgitation other than medical management. Historically they have had poor outcomes. Often they were denied operative intervention based on advanced age and other comorbidities. Based on the results of the Everest II Trial, TMVR now offers an effective alternative to medical management with acceptable morbidity and mortality for this elderly population whose quality of life and longevity was severely compromised by their mitral regurgitation.

Patients in the Everest II trial needed to meet all of the following criteria to have access to the technology:

1. Symptomatic functional MR (≥3+)

In the judgment of the interventional cardiologist, the patient had been adequately treated per applicable standards, including for coronary artery disease, left ventricular dysfunction, mitral regurgitation and heart failure and are in New York Heart Association (NYHA) Functional Class III or IV.

The patient was extremely high risk or inoperable for open mitral valve surgery due to co-morbidities such that the calculated STS mortality risk was ≥ 8% or the Heart Team concluded that co-morbidities result in extremely high operative risk of stroke or death.

Transseptal catheterization and femoral vein access was determined to be anatomically feasible.
Patients could NOT meet any of the following exclusion criteria:
The subject has severe LV dysfunction based on a transthoracic echocardiogram (TTE) as defined as Left Ventricular End Systolic Dimension (LVESD) >60mm or Left Ventricular Ejection Fraction (LVEF) <20%).
Untreated clinically significant coronary artery disease

Existing co-morbidities would preclude the expected benefit from correction of MR.

b. Rationale for how the evidence selected demonstrates the medical benefits for the target Medicare population

Medicare patients with mitral regurgitation who were previously considered inoperable or high-risk operative candidates for mitral valve repair surgery now have access to safe and effective therapies for previously untreated mitral regurgitation. The safe and appropriate application of TMVR in the Medicare population should be limited to structural heart valve centers of excellence with appropriately credentialed surgeons and interventional cardiologists, cardiac anesthesiologists, and other members of the identified multidisciplinary team. The results of the Everest II Trial in such established centers have demonstrated that this technology can be used in a high risk Medicare population with acceptable results.

c. Information that examines the magnitude of the medical benefit

The TMVR technology will benefit a select portion of the Medicare population. It is currently estimated that in the initial year post-commercialization 5,000 transcatheter mitral valve repair procedures will be performed. Of those procedures, it is estimated that approximately 90% (4500) of those patients will be Medicare patients. It is anticipated that the impact on the volume of Medicare Beneficiaries receiving these technologies will grow as the technology matures to include other devices and to include mitral valve replacement

d. Reasoning for how coverage of the item or service will help improve the medical benefit to the target population

Directed coverage of the TMVR procedures will allow previously untreated or untreatable Medicare patients with a diagnosis of mitral regurgitation to receive safe and effective treatment of their disease that has not been available until now. This allows the target Medicare population with mitral regurgitation that was previously untreatable due to the patient being inoperable or high risk a treatment option to either prolong life and/or improve their quality of life.

10. A description of any clinical trials or studies currently underway that might be relevant to a decision regarding coverage of the item or service

COAPT IDE Trial:

Abbott Vascular is currently evaluating MitraClip in moderate to severe or severe (3+/4+) functional mitral regurgitation patients with symptomatic heart failure.

- Target enrollment of 430 subjects at up to 75 sites
- Randomize 1:1 MitraClip therapy or optimal medical management
- Primary safety endpoint – freedom from device related complications
- Primary effectiveness endpoint – freedom from heart failure hospitalizations

11. Use of drug or device subject to FDA regulations and the status of the current FDA regulatory review

There are currently multiple companies involved in the development of transcatheter mitral valve repair devices. Some of the companies that are involved the development of TMVR devices include the following: MitraClip (Abbott Laboratories), Carillon Mitral Contour System (Cardiac Dimensions), NeoChord DS 1000 (NeoChord, Inc.), Cardioband with Transfemoral delivery system (Valtech Cardio Ltd), The GDS Accucinch System (Guided Delivery Systems), enCorSQ (MiCardia), MitraFlex (TransCardiac Therapeutics), Mitra-Spacer / Percu-Pro (Cardiosolutions), Mitraalign Annuloplasty (Mitralign, Inc). The MitraClip is currently being evaluated by clinical trial in the United States.
Source of product information and descriptions provided below:

Publication: Surgical Technology International XV - Cardiovascular Surgery
Article title: Advanced Technologies for Cardiac Valvular Replacement, Transcatheter Innovations and Reconstructive Surgery

MitraClip (Abbott Laboratories),

The MitraClip system (Abbott Laboratories, http://www.abbottvascular.com/int/mitraclip.html) is a catheter-based therapy intended to reduce mitral regurgitation (MR). This less-invasive mitral valve repair therapy is adapted from the open surgical double-orifice technique. The device is attached directly to the mitral valve, without opening the patient's chest. To access the mitral valve, the Guide Catheter is inserted into the femoral vein to reach the heart. Using the catheter, the Clip Delivery System delivers and deploys the MitraClip device. The procedure is performed under general anesthesia without the use of a heart-lung machine, and post-procedure recovery is typically one to three days.

Carillon Mitral Contour System (Cardiac Dimensions)

The Carillon Mitral Contour System **(Cardiac Dimensions, Inc.,** http://www.cardiacdimensions.com/PhysicianResources/index.html**)** implantable device consists of a proximal anchor and a distal anchor connected by a shaping ribbon. The device is intended to reduce mitral annulus dilatation upon deployment. The device is designed to be positioned in the coronary sinus and great cardiac vein using standard cardiac catheterization techniques via the venous vasculature. The implant is a fixed length; double anchor device designed to plicate the tissue next to the mitral valve annulus during the deployment process.

NeoChord DS 1000 (NeoChord, Inc.)

The NeoChord DS 1000 Device (NeoChord, Inc., http://www.neochord.com/index.php) replaces damaged chordae by delivering artificial chordae tendinae or "neochords" in a beating heart using minimally invasive techniques

Cardioband with Transfemoral delivery system (Valtech Cardio Ltd)

The Cardioband with Transfemoral delivery system (Valtech Cardio Ltd, http://www.valtechcardio.com/products/cardioband/) combines an implantable annuloplasty band, similar to the surgical band, with a transfemoral venous delivery system. Connection of the band to the mitral annulus is sutureless, using specially designed anchors. Size tuning of the implant is done under beating heart conditions and echocardiographic guidance for optimal results.

The GDS Accucinch System (Guided Delivery Systems)

The GDS Accucinch System (Guided Delivery Systems, http://www.gdsmed.com) is a small adjustable ring of anchors interlinked with a cable is implanted percutaneously into the muscle below the mitral

valve. The "cinching" effect improves the ability of the mitral valve to close properly and reduces the mitral regurgitation.

enCorSQ (MiCardia)

The enCorSQ (MiCardia, http://www.micardia.com/micardia-technology/) allows for late adjustment without additional surgery. It is an annuloplasty device to treat Mitral Regurgitation (MR) with unique features that enable the physician to adjust the device at a later date without another surgery. This late adjustment capability corrects recurrent mitral valve regurgitation that results from the progressive nature of the underlying cardiovascular disease. The late adjustment can be achieved weeks to months post implantation without the need for a repeat high risk surgical procedure.

MitraFlex (TransCardiac Therapeutics)

The MitraFlex (TransCardiac Therapeutics, http://www.transcardiac.com/products/**)** is a mitral valve repair system designed for direct thorascopic approach through the apex of a beating heart. The MitraFlex™ system performs the following functions on a beating heart: Stabilization and centering of the mitral valve leaflets, automatic capturing and connection of the approximate midpoint of the leaflets, implantation of an artificial cordae tendonae that controls the movement of the valve leaflets and reduces the annulus thereby reducing or eliminating mitral valve regurgitation. It provides a minimally invasive correction of mitral regurgitation due to annular dilatation or chordal rupture. The artificial cordae tendonae gives the physician the ability to adjust the opening of the mitral valve, thereby potentially eliminating the need for a secondary procedure to reduce the annulus.
Mitra-Spacer / Percu-Pro (Cardiosolutions),

Mitralign Annuloplasty (Mitralign, Inc.)

The Mitralign Annuloplasty (Mitralign, Inc.) is a set of catheters that enable the physician to position and place sutures and anchors through the posterior (back) annulus of the mitral valve under the guidance of echocardiography and fluoroscopy. Once the anchored sutures are in place, the sutures are pulled together. When the valve leaflets are close together, the sutures are locked with at least one stainless steel lock. The Bident Translation Catheter allows implantation of two pairs of pledgets. Each pair of pledgets plicates the annulus and then the pledgets are locked together from the ventricular side with a lock.

12. References

Lim DS, Reynolds MR, Feldman T, Kar S, Herrmann HC, Wang A, Whitlow, PL, Gray WA, Grayburn P, Mack MJ, Glower D, Improved Functional Status and Quality of Life in Prohibitive Surgical Risk Patients With Degenerative Mitral Regurgitation Following Transcatheter Mitral Valve Repair with the MitraClip® System, *Journal of the American College of Cardiology* (2013), doi: 10.1016/j.jacc.2013.10.021.

Dang NC, Aboodi MS, Sakaguchi T, Wasserman HS, Argenziano M, Cosgrove DM, Rosengart TK, Feldman T, Block PC, Oz MC. Surgical revision after percutaneous mitral valve repair with a clip: initial multicenter experience. Ann Thorac Surg. 2005 Dec;80(6):2338-42.

Feldman T, Wasserman HS, Herrmann HC, Gray W, Block PC, Whitlow P, St Goar F, Rodriguez L, Silvestry F, Schwartz A, Sanborn TA, Condado JA, Foster E. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. J Am Coll Cardiol. 2005 Dec 6;46(11):2134-40. Epub 2005 Oct 19.

Herrmann HC, Rohatgi S, Wasserman HS, Block P, Gray W, Hamilton A, Zunamon A, Homma S, Di Tullio MR, Kraybill K, Merlino J, Martin R, Rodriguez L, Stewart WJ, Whitlow P, Wiegers SE, Silvestry FE, Foster E, Feldman T. Mitral valve hemodynamic effects of percutaneous edge-to-edge repair with the MitraClip device for mitral regurgitation. Catheter Cardiovasc Interv. 2006 Dec;68(6):821-8.

Luk A, Butany J, Ahn E, Fann JI, St Goar F, Thornton T, McDermott L, Madayag C, Komtebedde J. Mitral repair with the Evalve MitraClip device: histopathologic findings in the porcine model. Cardiovasc Pathol. 2008 Aug 12; [Epub ahead of print]

Silvestry FE, Rodriguez LL, Herrmann HC, Rohatgi S, Weiss SJ, Stewart WJ, Homma S, Goyal N, Pulerwitz T, Zunamon A, Hamilton A, Merlino J, Martin R, Krabill K, Block PC, Whitlow P, Tuzcu EM, Kapadia S, Gray WA, Reisman M, Wasserman H, Schwartz A, Foster E, Feldman T, Wiegers SE. Echocardiographic guidance and assessment of percutaneous repair for mitral regurgitation with the Evalve MitraClip: lessons learned from EVEREST I. J Am Soc Echocardiogr. 2007 Oct;20(10):1131-40. Epub 2007 Jun 13.

Mauri L, Garg P, Massaro JM, Foster E, Glower D, Mehoudar P, Powell F, Komtebedde J, McDermott E, Feldman T. The EVEREST II Trial: design and rationale for a randomized study of the evalve mitraclip system compared with mitral valve surgery for mitral regurgitation. Am Heart J. 2010 Jul;160(1):23-9.

Fann JI, St Goar FG, Komtebedde J, Oz MC, Block PC, Foster E, Butany J, Feldman T, Burdon TA. Beating heart catheter-based edge-to-edge mitral valve procedure in a porcine model: efficacy and healing response. Circulation. 2004 Aug 24;110(8):988-93. Epub 2004 Aug 9.

St Goar FG, Fann JI, Komtebedde J, Foster E, Oz MC, Fogarty TJ, Feldman T, Block PC. Endovascular edge-to-edge mitral valve repair: short-term results in a porcine model. Circulation. 2003 Oct 21;108(16):1990-3. Epub 2003 Oct 6.

Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS; 2006 Writing Committee Members; American College of Cardiology/American Heart Association Task Force. 2008 Focused

update incorporated into the ACC/AHA 2006 guidelines 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 (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2008 Oct 7;118(15):e523-661. Epub 2008 Sep 26. No abstract available.

Borgia F, Di Mario C, Franzen O. Adenosine-induced asystole to facilitate MitraClip placement in a patient with adverse mitral valve morphology. Heart. 2010 Oct 29; [Epub ahead of print] No abstract available.

Tamburino C, Immè S, Barbanti M, Mulè M, Pistritto AM, Aruta P, Cammalleri V, Scarabelli M, Mangiafico S, Scandura S, Ussia GP. Reduction of mitral valve regurgitation with Mitraclip percutaneous system. Minerva Cardioangiol. 2010 Oct;58(5):589-98.

Ciobanu A, Bennett S, Azam M, Clark A, Vinereanu D. Incremental value of three-dimensional transoesophageal echocardiography for guiding double percutaneous MitraClip(R) implantation in a 'no option' patient. Eur J Echocardiogr. 2010 Sep 27; [Epub ahead of print]

Lim DS, Kunjummen BJ, Smalling R. Mitral valve repair with the MitraClip device after prior surgical mitral annuloplasty. Catheter Cardiovasc Interv. 2010 Sep 1;76(3):455-9.

Kalarus Z, Kukulski T, Lekston A, Streb W, Sikora J, Nadziakiewicz P, Gasior M, **Poloski** L, Zembala M. [Methodology and safety of transvascular reduction of severe ischaemic mitral insufficiency with MitraClip in high-surgical-risk patients - first three cases in Poland]. Kardiol Pol. 2010 Jun;68(6):729-35. Polish.
Geidel S, Ostermeyer J, Lass M, Schmoeckel M. Complex surgical valve repair after failed percutaneous mitral intervention using the MitraClip device. Ann Thorac Surg. 2010 Jul;90(1):277-9.

Jönsson A, Settergren M. MitraClip catheter-based mitral valve repair system. Expert Rev Med Devices. 2010 Jul;7(4):439-47.

Ussia GP, Barbanti M, Tamburino C. Feasibility of percutaneous transcatheter mitral valve repair with the MitraClip system using conscious sedation. Catheter Cardiovasc Interv. 2010 Jun 1;75(7):1137-40.

Tamburino C, Ussia GP, Maisano F, Capodanno D, La Canna G, Scandura S, Colombo A, Giacomini A, Michev I, Mangiafico S, Cammalleri V, Barbanti M, Alfieri O. Percutaneous mitral valve repair with the MitraClip system: acute results from a real world setting. Eur Heart J. 2010 Jun;31(11):1382-9. Epub 2010 Mar 18.

Franzen O, Baldus S, Rudolph V, Meyer S, Knap M, Koschyk D, Treede H, Barmeyer A, Schofer J, Costard-Jäckle A, Schlüter M, Reichenspurner H, Meinertz T. Acute outcomes of MitraClip therapy for mitral regurgitation in high-surgical-risk patients: emphasis on adverse valve morphology and severe left ventricular dysfunction. Eur Heart J. 2010 Jun;31(11):1373-81. Epub 2010 Mar 10.

Argenziano M, Skipper E, Heimansohn D, Letsou GV, Woo YJ, Kron I, Alexander J, Cleveland J, Kong B, Davidson M, Vassiliades T, Krieger K, Sako E, Tibi P, Galloway A, Foster E, Feldman T, Glower D; EVEREST Investigators. Surgical revision after percutaneous mitral repair with the MitraClip device. Ann Thorac Surg. 2010 Jan;89(1):72-80; discussion p 80.

Rogers JH, Yeo KK, Carroll JD, Cleveland J, Reece TB, Gillinov AM, Rodriguez L, Whitlow P, Woo YJ, Herrmann HC, Young JN. Late surgical mitral valve repair after percutaneous repair with the MitraClip system. J Card Surg. 2009 Nov-Dec;24(6):677-81. Epub 2009 Jul 24.

Feldman T, Kar S, Rinaldi M, Fail P, Hermiller J, Smalling R, Whitlow PL, Gray W, Low R, Herrmann HC, Lim S, Foster E, Glower D; EVEREST Investigators. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) Cohort. J Am Coll Cardiol. 2009 Aug 18;54(8):686-94.

Herrmann HC, Kar S, Siegel R, Fail P, Loghin C, Lim S, Hahn R, Rogers JH, Bommer WJ, Wang A, Berke A, Lerakis S, Kramer P, Wong SC, Foster E, Glower D, Feldman T; EVEREST Investigators. Effect of percutaneous mitral repair with the MitraClip device on mitral valve area and gradient. EuroIntervention. 2009 Jan;4(4):437-42.

Luk A, Butany J, Ahn E, Fann JI, St Goar F, Thornton T, McDermott L, Madayag C, Komtebedde J. Mitral repair with the Evalve MitraClip device: histopathologic findings in the porcine model. Cardiovasc Pathol. 2008 Aug 12; [Epub ahead of print]

Whitlow PL, Feldman T, Pedersen WR, Lim DS, Kipperman R, Smalling R, Bajwa T, Herrmann HC, Lasala J, Maddux JT, Tuzcu M, Kapadia S, Trento A, Siegel RJ, Foster E, Glower D, Mauri L, Kar S; 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.

Siegel RJ, Biner S, Rafique AM, Rinaldi M, Lim S, Fail P, Hermiller J, Smalling R, Whitlow PL, Herrmann HC, Foster E, Feldman T, Glower D, Kar S; EVEREST Investigators. The acute hemodynamic effects of MitraClip therapy. J Am Coll Cardiol. 2011 Apr 19;57(16):1658-65.

Feldman T, Foster E, Glower DG, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L; EVEREST II Investigators. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med. 2011 Apr 14;364(15):1395-406. Epub 2011 Apr 4.

Ladich E, Michaels MB, Jones RM, McDermott E, Coleman L, Komtebedde J, Glower D, Argenziano M, Feldman T, Nakano M, Virmani R; Endovascular Valve Edge-to-Edge Repair Study (EVEREST) Investigators. Pathological healing response of explanted MitraClip devices. Circulation. 2011 Apr 5;123(13):1418-27. Epub 2011 Mar 21.

Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN Trial. Tomasz Siminiak, Justina C. Wu, Michael Haude, Uta C. Hoppe, Jerzy Sadowski, Janusz Lipiecki, Jean Fajadet, Amil M. Shah, Ted Feldman, David M. Kaye, Steven L. Goldberg, Wayne C. Levy, Scott D. Solomon, David G. Reuter European Journal of Heart Failure : May 21, 2012 Results of the TITAN trial evaluating the CARILLON® Mitral Contour System® in treating functional mitral regurgitation in symptomatic heart failure patients.

Percutaneous mitral annuloplasty device leaves free access to cardiac veins for resynchronization therapy. Hoppe UC, Brandt MC, Degen H, Dodos F, Schneider T, Stoepel C, Kroener A, Haude M.

[PMID: 19472350] Catheter Cardiovasc Interv 2009 Apr 27. Study documenting ability to insert CRT lead through previously deployed CARILLON device.

Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. Schofer J, Siminiak T, Haude M, Herrman JP, Vainer J, Wu JC, Levy WC, Mauri L, Feldman T, Kwong RY, Kaye DM, Duffy SJ, Tubler T, Degen H, Brandt M, Van Bibber R, Goldberg S, Reuter DG, Hoppe UC. [PMID: 19597051] Circulation. 2009; 120: 326-333. First clinical trial evaluating the CARILLON® Mitral Contour System® used to treat functional mitral regurgitation in symptomatic heart failure patients.

Effectiveness and safety of percutaneous coronary sinus-based mitral valve repair in patients with dilated cardiomyopathy (from the AMADEUS trial). Siminiak T, Hoppe UC, Schofer J, Haude M, Herrman JP, Vainer J, Firek L, Reuter DG, Goldberg SL, Van Bibber R. [PMID: 19660613] Am J Cardiol. 2009 Aug 15;104(4):565-70. Procedural results from the AMADEUS trial using the CARILLON® Mitral Contour System®.

Acute and chronic reduction of functional mitral regurgitation in experimental heart failure by percutaneous mitral annuloplasty. Maniu CV, Patel JB. Reuter DG. et al. [PMID: 15489099] J Am Coll Cardiol 2004; 44: 1652-61 Pre-clinical study demonstrating acute and chronic efficacy of CARILLON therapy in an animal heart failure model.

The Heart Team of Cardiovascular Care. Holmes DR, Rich JB, Zoghbi WA, Mack MJ. [PMID:23449424] Journal of the American College of Cardiology. March 2013; 61(9):903-907. How to implement multidisciplinary Heart Teams to facilitate the process of patient centric evidence-based care.