Transcatheter Mitral Valve Repair

Description

Transcatheter mitral valve repair (TMVR) is an alternative to surgical therapy for mitral regurgitation (MR). MR is a common valvular heart disease that can result from a primary structural abnormality of the mitral valve (MV) complex or a secondary dilatation of an anatomically normal MV due to a dilated left ventricle caused by ischemic or dilated cardiomyopathy. Surgical therapy may be underutilized, particularly in patients with multiple comorbidities, suggesting that there is an unmet need for less invasive procedures for MV repair. One device, MitraClip, has approval from the U.S. Food and Drug Administration for the treatment of severe symptomatic MR due to a primary abnormality of the MV (primary MR) in patients considered at prohibitive risk for surgery and for patients with heart failure and moderate-to-severe or severe symptomatic secondary MR despite the use of maximally tolerated guideline-directed medical therapy.

OBJECTIVE

The objective of this evidence review is to determine whether transcatheter mitral valve repair improves the net health outcome in patients with primary (degenerative) or secondary (functional) mitral regurgitation.

POLICY STATEMENT

Transcatheter mitral valve repair with a device approved by the U.S. Food and Drug Administration for use in mitral valve repair may be considered medically necessary for patients with symptomatic, primary mitral regurgitation who are considered at prohibitive risk for open surgery (see Policy Guidelines section).

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Transcatheter mitral valve repair with a device approved by the U.S. Food and Drug Administration may be considered medically necessary for patients with heart failure and moderate-to-severe or severe symptomatic secondary mitral regurgitation despite the use of maximally tolerated guideline-directed medical therapy (see Policy Guidelines section).

Transcatheter mitral valve repair is considered investigational in all other situations.

**POLICY GUIDELINES**

*Prohibitive risk* for open surgery may be determined based on:

- Presence of a Society for Thoracic Surgeons predicted mortality risk of 12% or greater and/or
- Presence of a logistic EuroSCORE of 20% or greater.

Moderate to severe or severe MR may be determined by:

- Grade 3+ (moderate) or 4+ (severe) MR confirmed by echocardiography
- New York Heart Association (NYHA) functional class II, III, or IVa (ambulatory) despite the use of stable maximal doses of guideline-directed medical therapy and cardiac resynchronization therapy (if appropriate) administered in accordance with guidelines of professional societies.

Optimal medical therapy may be determined by guidelines from specialty societies (e.g., American Heart Association/American College of Cardiology Guideline for the Management of Patients with Valvular Heart Disease, European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines for the Management of Valvular Heart Disease, American Heart Association/American College of Cardiology/Heart Failure Society of America Guideline for the Management of Heart Failure (refer to supplemental materials for guideline citations).

**BENEFIT APPLICATION**

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

**FDA REGULATORY STATUS**

**Direct Leaflet Approximation**

One device that undertakes direct leaflet repair, the MitraClip Clip Delivery System (Abbott Vascular), has been approved through the premarket approval process by the U.S. Food and Drug Administration (FDA) for use in certain patients with symptomatic primary MR (see Regulatory Status section). Of the transcatheter MV repair devices under investigation, MitraClip has the largest body of evidence evaluating its use; it has been in use in Europe since 2008. The MitraClip system is deployed percutaneously and approximates the open Alfieri edge-to-edge repair approach to treating MR. The delivery system consists of a catheter, a steerable sleeve, and the MitraClip device, which is a 4-mm wide clip fabricated from a cobalt-chromium alloy and polypropylene fabric. MitraClip is deployed via a transfemoral approach, with transseptal puncture used to access the left side of the heart and the MV. Placement of MitraClip leads to coapting of the mitral leaflets, thus creating a double-orifice valve.
Other Mitral Valve Repair Devices

Devices for transcatheter MV repair that use different approaches are in development. Techniques to repair the mitral annulus include those that target the annulus itself (direct annuloplasty) and those that tighten the mitral annulus via manipulation of the adjacent coronary sinus (indirect annuloplasty). Indirect annuloplasty devices include the Carillon Mitral Contour System (Cardiac Dimension) and the Monarc™ device (Edwards Lifesciences). The CE-marked Carillon Mitral Contour System is comprised of self-expanding proximal and distal anchors connected with a nitinol bridge, with the proximal end coronary sinus ostium and the distal anchor in the great cardiac vein. The size of the connection is controlled by manual pullback on the catheter (CE-marked). The Carillon system was evaluated in the Carillon Mitral Annuloplasty Device European Union Study and the follow-up Tighten the Annulus Now study, with further studies planned. The Monarc system also involves two self-expanding stents connected by a nitinol bridge, with one end implanted in the coronary sinus via internal jugular vein and the other in the great cardiac vein. Several weeks after implantation, the biologically degradable coating over the nitinol bridge degrades, allowing the bridge to shrink and the system to shorten. It has been evaluated in the Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for the Treatment of Mitral Regurgitation trial.

Direct annuloplasty devices include the Mitralign Percutaneous Annuloplasty System (Mitralign) and the AccuCinch System (Guided Delivery Systems), both of which involve transcatheter placement of anchors in the MV; they are cinched or connected to narrow the mitral annulus. Other transcatheter direct annuloplasty devices under investigation include the enCorTC™ device (MiCardia), which involves a percutaneously insertable annuloplasty ring that is adjustable using radiofrequency energy, a variation on its CE-marked enCor sq™ Mitral Valve Repair System, and the Cardioband™ Annuloplasty System (Valtech Cardio), an implantable annuloplasty band with a transfemoral venous delivery system.

Transcatheter Mitral Valve Replacement

PermaValve™ (Micro Interventional Devices), under investigation in the U.S., is a transcatheter MV replacement device that is delivered via the transapical approach. On June 5, 2017, the SAPIEN 3 Transcatheter Heart Valve (Edwards Lifesciences) was approved by the FDA as MV replacement device. These replacement valves are outside the scope of this evidence review.

Regulatory Status

In October 2013, the MitraClip Clip Delivery System (Abbott Vascular) was approved by the FDA through the premarket approval process for treatment 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 a prohibitive risk for mitral valve surgery by a heart team." FDA product code: NKM.

In March 2019, the FDA approved a new indication for MitraClip, for "treatment of patients with normal mitral valves who develop heart failure symptoms and moderate-to-severe or severe mitral regurgitation because of diminished left heart function (commonly known as secondary or functional mitral regurgitation) despite being treated with optimal medical therapy. Optimal medical therapy includes combinations of different heart failure medications along with, in certain patients, cardiac resynchronization therapy and implantation of cardioverter defibrillators."

RATIONALE

Summary of Evidence

For individuals who have symptomatic primary MR and at prohibitive risk for open surgery who receive transcatheter mitral valve repair (TMVR) using MitraClip, the evidence includes a single-arm prospective cohort with historical cohort and registry studies. Relevant outcomes are overall survival (OS), morbid events, functional outcomes, and treatment-related morbidity. The primary evidence includes
the pivotal EVEREST II HRR and EVEREST II REALISM studies and Transcatheter Valve Therapy Registry studies. These studies have demonstrated that MitraClip implantation is feasible with a procedural success rate greater than 90%, 30-day mortality ranging from 2.3% to 6.4% (less than predicted Society of Thoracic Surgeons mortality risk score for MR repair or replacement; range, 9.5%-13.2%), post-implantation MR severity grade of 2+ or less in 82% to 93% of patients, and a clinically meaningful gain in quality of life (5- to 6-point gains in 36-Item Short-Form Health Survey scores). At 1 year, freedom from death and MR more than 2+ was achieved in 61% of patients but the 1-year mortality or heart failure hospitalization rates remain considerably high (38%). Conclusions related to the treatment effect on mortality based on historical controls cannot be made because the control groups did not provide unbiased or precise estimates of the natural history of patients eligible to receive MitraClip. Given that primary MR is a mechanical problem and there is no effective medical therapy, a randomized controlled trial (RCT) comparing MitraClip with medical management is not feasible or ethical. The post-marketing data from the U.S. is supportive that MitraClip surgery is being performed with short-term effectiveness and safety in select patient population. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have heart failure and symptomatic secondary MR despite the use of maximally tolerated guideline-directed medical therapy who receive TMVR using MitraClip, the evidence includes a systematic review, two RCTS as well as multiple observational studies. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. The trials had discrepant results potentially related to differences in primary outcomes. The larger trial, with patients selected for nonresponse to maximally tolerated therapy, found a significant benefit for MitraClip after two years compared to medical therapy alone. The systematic review confirmed the benefit of MitraClip found in the larger RCT, but had important methodological limitations. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have symptomatic primary or secondary mitral regurgitation (SMR) and are surgical candidates who receive TMVR using MitraClip, the evidence includes a systematic review, 1 RCT and a retrospective comparative observational study in individuals aged ≥ 75 years. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. The RCT found that MitraClip did not reduce MR as often or as completely as the surgical control, although it could be safely implanted and was associated with fewer adverse events at one year. Long-term follow-up from the RCT showed that significantly more MitraClip patients required surgery for MV dysfunction than conventional surgery patients. For these reasons, this single trial is not definitive in demonstrating improved clinical outcomes with MitraClip compared with surgery. Additional RCTs are needed to corroborate these results. The observational study in individuals aged ≥ 75 years found that although MitraClip was associated with improved 1-year survival and a lower rate of all acute complications compared with surgical repair, it had lower 5-year survival and greater MR recurrence. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have symptomatic primary or secondary MR who receive TMVR using devices other than MitraClip, the evidence includes primarily noncomparative feasibility studies. Relevant outcomes are OS, morbidity events, functional outcomes, and treatment-related morbidity. The body of evidence consists only of very small case series and case reports. Controlled studies, preferably RCTs, are needed to draw conclusions about the net health benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

American College of Cardiology

The American College of Cardiology and American Heart Association (2017) released guidelines on the management of valvular heart disease. Table 1 provides the relevant recommendations.

Table 1. Recommendations on Primary and Secondary MR

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Transcatheter mitral valve repair may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe primary MR (stage D) who have favorable anatomy for the repair procedure and a reasonable life expectancy but who have a prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal guideline-directed medical therapy for heart failure. 

Mitral valve surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR.

Mitral valve repair or replacement may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for HF.


European Society of Cardiology and European Association for Cardio-Thoracic Surgery

The European Society of Cardiology and the European Association for Cardio-Thoracic Surgery (2017) released joint guidelines on the management of valvular heart disease (see Table 2). 

Table 2. Recommendations on Management of Valvular Heart Disease

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<thead>
<tr>
<th>Recommendation</th>
<th>SOR</th>
<th>LOE</th>
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<tr>
<td>Primary MR</td>
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<tr>
<td>Percutaneous edge-to-edge procedure may be considered in patients with symptomatic severe primary mitral regurgitation who fulfill the echocardiographic criteria of eligibility and are judged inoperable or at high surgical risk by the Heart Team, avoiding futility.</td>
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<td>Secondary MR</td>
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<td>&quot;Percutaneous edge-to-edge repair for secondary mitral regurgitation is a low risk option, but its efficacy to reduce mitral regurgitation remains inferior to surgery. It can improve symptoms, functional capacity and quality of life and may induce reverse LV remodelling. Similar to surgery, a survival benefit compared with &lt;91&gt;optimal medical therapy according to current guidelines has not yet been proven.&quot;</td>
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LOE: level of evidence; LV: left ventricular; SOR: strength of recommendation.

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services (2015) issued a national coverage decision for the use of transcatheter mitral valve repair (TMVR).
The Centers for Medicare & Medicaid Services determined that it would cover TMVR under Coverage with Evidence Development for the treatment of significant symptomatic MR when all of the following conditions are met:

"1. The procedure is performed with a complete TMVR system that has received FDA [Food and Drug Administration] premarket approval (PMA) for that system’s FDA approved indication.

2. Both a cardiothoracic surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease have independently examined the patient face-to-face and evaluated the patient’s suitability for mitral valve surgery and determination of prohibitive risk; and both surgeons have documented the rationale for their clinical judgment and the rationale is available to the heart team.

3. The patient (pre-operatively and post-operatively) is under the care of a heart team....

TMVR must be furnished in a hospital and with the appropriate infrastructure that includes but is not limited to:

a. On-site active valvular heart disease surgical program with >2 hospital-based cardiothoracic surgeons experienced in valvular surgery;

b. Cardiac catheterization lab or hybrid operating room catheterization lab equipped with a fixed radiographic imaging system with flat-panel fluoroscopy, offering catheterization laboratory-quality imaging,

c. Non-invasive imaging expertise including transthoracic/transesophageal/3D echocardiography, vascular studies, and cardiac CT studies; ...

d. e. Post-procedure intensive care facility with personnel experienced in managing patients who have undergone open-heart valve procedures;

f. Adequate outpatient clinical care facilities

g. Appropriate volume requirements per the applicable qualifications below.

There are institutional and operator requirements for performing TMVR. The hospital must have the following:

a. A surgical program that performs > 25 total mitral valve surgical procedures for severe MR per year of which at least 10 must be mitral valve repairs;

b. An interventional cardiology program that performs > 1000 catheterizations per year, including > 400 percutaneous coronary interventions (PCIs) per year, with acceptable outcomes for conventional procedures compared to National Cardiovascular Data Registry (NCDR) benchmarks;

c. The heart team must include:

1. An interventional cardiologist(s) who:

performs > 50 structural procedures per year including atrial septal defects (ASD), patent foramen ovale (PFO) and trans-septal punctures; and,

must receive prior suitable training on the devices to be used; and,

must be board-certified in interventional cardiology or board-certified/eligible in pediatric cardiology or similar boards from outside the United States;

2. Additional members of the heart team, including: cardiac echocardiographers, other cardiac imaging specialists, heart valve and heart failure specialists, electrophysiologists, cardiac anesthesiologists, intensivists, nurses, nurse practitioners, physician assistants, data/research coordinators, and a dedicated administrator;

d. All cases must be submitted to a single national database;

e. Ongoing continuing medical education (or the nursing/technologist equivalent) of 10 hours per year of relevant material;

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f. The cardiothoracic surgeon(s) must be board-certified in thoracic surgery or similar foreign equivalent.

4. The heart teams [sic] interventional cardiologist or a cardiothoracic surgeon must perform the TMVR. Interventional cardiologist(s) and cardiothoracic surgeon(s) may jointly participate in the intra-operative technical aspects of TMVR as appropriate.

5. The heart team and hospital are participating in a prospective, national, audited registry that: 1) consecutively enrolls TMVR patients; 2) accepts all manufactured devices; 3) follows the patient for at least one year; and, 4) complies with relevant regulations relating to protecting human research subjects.

The registry should collect all data necessary and have a written executable plan....

B. TMVR for MR uses that are not expressly listed as an FDA-approved indication when performed within a FDA-approved randomized clinical trial that fulfills all of the following:

1. TMVR must be performed by an interventional cardiologist or a cardiac surgeon. Interventional cardiologist(s) and cardiothoracic surgeon(s) may jointly participate in the intra-operative technical aspects of TMVR as appropriate.

2. As a fully-described, written part of its protocol, the clinical research study must critically evaluate the following questions at 12 months of longer follow-up:

What is the patient's post-TMVR quality of life (compared to pre-TMVR) at one year?

What is the patient's post-TMVR functional capacity (compared to pre-TMVR) at one year?

In addition, the clinical research study must address a series of questions at one year postprocedure as outlined in the proposed decision memo.

REFERENCES

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<th>Date</th>
<th>Action</th>
<th>Description</th>
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<tbody>
<tr>
<td>September 2016</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 30, 2016; references 25, 29, 31, 37, and 41 added. Policy statements unchanged.</td>
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<tr>
<td>September 2018</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 5, 2018; references 27-29, 34-36, and 53 added. &quot;Cleared&quot; changed to &quot;approved&quot; in the medically necessary policy statement. In the policy degenerative mitral regurgitation was replaced with primary mitral regurgitation and functional mitral regurgitation was replaced with secondary mitral regurgitation including the policy statement to be in consistent with language used in the guidelines. Data from FDA documents were added.</td>
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<tr>
<td>September 2019</td>
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<td>Policy updated with literature review through March 6, 2019, references 50-51 added. Regulatory status section updated with new indication. Policy statement added; transcatheter mitral valve repair with an FDA-approved device considered medically necessary for patients with heart failure and secondary mitral regurgitation despite the use of maximally tolerated guideline-directed medical therapy. Information regarding optimal medical therapy added to the Policy Guidelines section.</td>
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<tr>
<td>September 2020</td>
<td>Replace policy</td>
<td>Policy updated with literature review through March 23, 2020; references added. Policy statements unchanged.</td>
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