Transcatheter mitral valve repair with a device approved by the U.S. Food and Drug Administration (FDA) 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).

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 mitral regurgitation (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/Cardiac Resynchronization Therapy (CRT) Guideline for the Management of Heart Failure [see Supplemental Information section for guideline citations]).

Coding

The following are category I CPT codes for this procedure:

- 33418: Transcatheter mitral valve repair, percutaneous approach, including transseptal puncture when performed; initial prosthesis
- 33419: Transcatheter mitral valve repair, percutaneous approach, including transseptal puncture when performed; additional prosthesis(es) during same session (List separately in addition to code for primary procedure)

The following is a category III CPT code for the procedure when performed via the coronary sinus:

- 0345T: Transcatheter mitral valve repair percutaneous approach via the coronary sinus
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.

Related Policies

- Transcatheter Aortic Valve Implantation for Aortic Stenosis
- Transcatheter Pulmonary Valve Implantation

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

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

Background

Mitral Regurgitation

Epidemiology and Classification

MR is the second most common valvular heart disease, occurring in 7% of people older than age 75 years and accounting for 24% of all patients with valvular heart disease.\(^1,2\) MR with accompanying valvular incompetence leads to left ventricular (LV) volume overload with secondary ventricular remodeling, myocardial dysfunction, and left heart failure. Clinical signs and symptoms of dyspnea and orthopnea may also be present in patients with valvular dysfunction.\(^3\) MR severity is classified as mild, moderate, or severe disease on the basis of echocardiographic and/or angiographic findings (1+, 2+, and 3-4+ angiographic grade, respectively).

Patients with MR generally fall into two categories: primary (also called degenerative) and secondary (also called functional) MR. Primary MR results from a primary structural abnormality in the valve, which causes it to leak. This leak may result from a floppy leaflet (called prolapse) or a ruptured cord that caused the leaflet to detach partially (called flail).\(^4\) Because the primary cause is a structural abnormality, most cases of primary MR are surgically corrected. Secondary MR results from LV dilatation due to ischemic or dilated cardiomyopathy. This causes the mitral value (MV) leaflets not to coapt or meet in the center.\(^3\) Because the valves are structurally normal in secondary MR, correcting the dilated LV using medical therapy is the primary treatment strategy used in the United States.

Standard Management

Surgical Management

In symptomatic patients with primary MR, surgery is the main therapy. In most cases, MV repair is preferred over replacement, as long as the valve is suitable for repair and personnel with appropriate surgical expertise are available. The American College of Cardiology and the American Heart Association have issued joint guidelines on the surgical management of MV, which are outlined in Table 1.\(^4\)

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV surgery is recommended for the symptomatic patient with acute severe MR.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>MV surgery is beneficial for patients with chronic severe MR and NYHA functional class II, III, or IV symptoms in the absence of severe LV dysfunction (severe LV dysfunction is defined as ejection fraction less than 0.30) and/or end-systolic dimension greater than 55 mm.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>MV surgery is beneficial for asymptomatic patients with chronic severe MR and mild-to-moderate LV dysfunction, ejection fraction 0.30 to 0.60, and/or end systolic dimension greater than or equal to 40 mm.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>MV repair is recommended over MV replacement in the majority of patients with severe chronic MR who require surgery, and patients should be referred to surgical centers experienced in MV repair.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>MV repair is also reasonable for asymptomatic patients with chronic severe MR with preserved LV function ... in whom the high likelihood of successful MV repair without residual MR is greater than 90%</td>
<td>Ila</td>
<td>B</td>
</tr>
<tr>
<td>MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and new onset of atrial fibrillation</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and pulmonary hypertension ....</td>
<td>Ila</td>
<td>C</td>
</tr>
<tr>
<td>MV surgery is reasonable for patients with chronic severe MR due to a primary abnormality of the mitral apparatus and NYHA functional class III-IV symptoms and severe LV dysfunction ... in whom MV repair is highly likely</td>
<td>Ila</td>
<td>C</td>
</tr>
</tbody>
</table>

COR: class of recommendation; LOE: level of evidence; LV: left ventricular; MR: mitral regurgitation; MV: mitral valve; NYHA: New York Heart Association.
The use of standard open MV repair is limited by the requirement for thoracotomy and cardiopulmonary bypass, which may not be tolerated by elderly or debilitated patients due to their underlying cardiac disease or other conditions. In a single-center evaluation of 5737 patients with severe MR in the U.S., Goel et al (2014) found that 53% of patients did not have MV surgery performed, suggesting an unmet need for such patients.5, Isolated MV surgery (repair or replacement) for severe chronic secondary MR is not generally recommended because there is no proven mortality reduction and an uncertain durable effect on symptoms. Recommendations from major societies6,7, regarding MV surgery in conjunction with coronary artery bypass graft surgery or surgical aortic valve replacement are weak because the current evidence is inconsistent on whether MV surgery produces a clinical benefit.8-11.

**Transcatheter Mitral Valve Repair**

Transcatheter approaches have been investigated to address the unmet need for less invasive MV repair, particularly among inoperable patients who face prohibitively high surgical risks due to age or comorbidities. MV repair devices under development address various components of the MV complex and generally are performed on the beating heart without the need for cardiopulmonary bypass.1,12, Approaches to MV repair include direct leaflet repair,13, repair of the mitral annulus via direct annuloplasty, or indirect repair based on the annulus's proximity to the coronary sinus. There are also devices in development to counteract ventricular remodeling, and systems designed for complete MV replacement via catheter.

**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 2008.13, 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.14 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.15, 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 enCoraq™ 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™ (MicroInterventional 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.

Medical Management
The standard treatment for patients with chronic secondary MR is medical management. Patients with chronic secondary MR should receive standard therapy for heart failure with reduced ejection fraction; standard management includes angiotensin converting enzyme inhibitor (or angiotensin II receptor blocker or angiotensin receptor-neprilysin inhibitor), b-blocker and mineralocorticoid receptor antagonist, and diuretic therapy as needed to treat volume overload.4,3 Resynchronization therapy may provide symptomatic relief, improve LV function, and in some patients, lessen the severity of MR.

Literature Review
This review was informed, in part, by a Blue Cross Blue Shield Association Technology Evaluation Center (TEC) Assessment (2014) that evaluated the use of transcatheter mitral valve repair (TMVR) in patients with symptomatic primary mitral regurgitation (MR) at prohibitive risk for mortality during open surgery.17

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function- including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, two domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

MitraClip
Primary Mitral Valve Regurgitation at Prohibitive Surgical Risk

Clinical Context and Therapy Purpose
The purpose of TMVR using MitraClip in patients who have primary MR and are at prohibitive risk for open surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies.
The question addressed in this evidence review is: Does TMVR using MitraClip improve the net health outcome in patients with symptomatic primary MR and at prohibitive risk for open surgery?

The following PICOs were used to select literature to inform this review.

**Patients**
The relevant population of interest are patients with symptomatic primary MR and at prohibitive risk for open surgery.

MR severity is classified as mild, moderate, or severe disease on the basis of echocardiographic and/or angiographic findings (1+, 2+, and 3-4+ angiographic grade, respectively). MR with accompanying valvular incompetence leads to left ventricular (LV) volume overload with secondary ventricular remodeling, myocardial dysfunction, and left heart failure. Clinical signs and symptoms of dyspnea and orthopnea may also present in patients with valvular dysfunction.

**Intervention**
The therapy being considered is TMVR using MitraClip.

**Comparators**
The following therapies are currently being used to make decisions about TMVR using MitraClip. Comparators of interest are medical management. Given that primary MR is a mechanical problem and there is no effective medical therapy, an RCT comparing MitraClip with medical management is not feasible or ethical.

**Outcomes**
The general outcomes of interest are overall survival (OS), morbid events, functional outcomes, and treatment-related morbidity.

No RCTs have been published evaluating MitraClip in prohibitive surgical risk populations.

A TEC Assessment (2014) evaluated the evidence on the use of MitraClip for primary MR, a U.S. Food and Drug Administration (FDA)-approved indication. The Assessment included five case series reporting outcomes of patients with primary MR considered at high-risk of surgical mortality who underwent MitraClip placement. Three of the five case series were rated as poor because of low or unknown follow-up rates and are not discussed further. Tables 2 and 3 summarize patient characteristics and health outcomes of the case series by Reichenspurner et al (2013) and Lim et al (2013), which were considered higher quality. The Reichenspurner et al (2013) study reported data on 117 primary MR patients who were enrolled in a European postmarketing registry. The Lim et al (2013) study reported data on 127 patients enrolled in the Endovascular Valve Edge-to-Edge REpair Study (EVEREST II) High Risk Registry (HRR) and the Real World Expanded Multicenter Study of the MitraClip System (REALISM) registry and then retrospectively identified as meeting the definition of prohibitive risk and were followed for 1 year. The 30-day mortality rates were 6.0% and 6.3%, and 12- and 25-month mortality rates were 17.1% and 23.6%, respectively. In evaluable patients at 12 months, the percentages of patients who had an MR severity grade of 2 or less were 83.3% and 74.6% in the 2 studies; the percentages with New York Heart Association (NYHA) class I or II functional status were 81% and 87% and the percentages who improved at least 1 NYHA class level were 68% and 88%, respectively.

**Table 2. Key Case Series Characteristics**

<table>
<thead>
<tr>
<th>Study; Trial;</th>
<th>Country</th>
<th>Participants</th>
<th>Treatment Delivery</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichenspurner et al (2013)18; ACCESS-EU</td>
<td>Europe</td>
<td>• N=117</td>
<td>MitraClip</td>
<td>71 had 1-y follow-up data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• EF &lt;40% or mean EF: 9.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• NYHA class ≥3: 74%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Study; Trial | Country | Participants | Treatment | Follow-Up
--- | --- | --- | --- | ---
Lim et al (2014)\(^{20}\); subset of patients at prohibitive risk of open surgery from EVEREST II HRR and REALISM | U.S. | N: 127 | MitraClip | 1.47 y
- MR severity ≥3+: 96.6%
- Mean EuroSCORE: 15.5%
- N: 127
- EF <40% or Mean EF: 61%
- NYHA class ≥3: 87%
- MR severity ≥3+: 100%
- Mean STS score: 13.2%

Table 3. 12-Month Outcomes for Key Case Series of MitraClip for Primary Mitral Valve Disease

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Original N</th>
<th>MR Grade at 12 Months, % (n/N)</th>
<th>NYHA Class at 12 Months, % (n/N)</th>
<th>Other Pertinent Outcomes at 12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reichenspurner et al (2013)(^{18}); ACCESS-EU</td>
<td>117</td>
<td>MR severity ≤2+: 74.6% (53/71)</td>
<td>Class I/II: 81% (63/78)</td>
<td>Change in MLHFQ from baseline, 13.3 points (p=0.03), n=44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved ≥1 class: 68% (53/78)</td>
<td>SF-36 PCS score change, 6.0 (95% CI, 4.0 to 8.0), n=76</td>
<td></td>
</tr>
<tr>
<td>Lim et al (2014)(^{20}); subset of patients at prohibitive risk of open surgery from EVEREST II HRR and REALISM</td>
<td>127</td>
<td>MR severity ≤2+: 83.3% (70/84)</td>
<td>Class I/II: 86.9% (73/84)</td>
<td>SF-36 PCS score change, 5.6 (95% CI, 2.3 to 8.9), n=76</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Improved ≥1 class: 86.9% (73/84)</td>
<td>SF-36 MCS score change, 5.6 (95% CI, 2.3 to 8.9), n=76</td>
<td></td>
</tr>
</tbody>
</table>

The FDA compared the cohort reported by Lim et al (2014; discussed above) with a historical cohort (n=65) generated from the patient-level data Duke Registry of primary MR patients with MR of 3+ or more. The Duke cohort of 65 patients with primary MR was derived from a dataset of 953 patients with an MR severity grade of 3+ or 4+ who were retrospectively identified as being at a prohibitively high-risk for surgery based on the same high-risk criteria as those in the EVEREST II HRR and REALISM studies (i.e., Society of Thoracic Surgeons (STS) mortality risk calculation of 12% or higher or protocol-specified surgical risk factors). For the cohort described by Lim et al (2014), compliance to follow-up visits in continuing patients was 98%, 98%, and 95% at 30 days, 12 months, and 2 years, respectively. Cohort characteristics and results are summarized in Tables 4 and 5. There were no iniprocedural deaths and the MitraClip was implanted successfully in 95% of patients. Eight patients died within 30 days of the procedure or discharge postprocedure, resulting in a procedural mortality rate of 6.4% that increased to 24.8% at 12 months. Comparative mortality rates in the Duke cohort at 30 days and 12 months were 10.9% and 30.6%, respectively.

The TEC Assessment identified multiple limitations with use of historical controls. Specifically, patients in the Duke group did not appear to have been evaluated specifically for the MitraClip procedure (i.e., their anatomic eligibility to receive the device). Data were not available on patient status at beginning of follow-up, which could have had a critical impact on short-term mortality. These control groups are therefore likely to have higher mortality rates than MitraClip groups. In comparing the clinical characteristics of Duke group with patients receiving MitraClip, although mean predicted surgical mortality risks were similar, subjects differed greatly in NYHA functional class and ejection fraction, among other characteristics. Neither of these control groups provides unbiased or precise estimates of the natural history of patients eligible to receive MitraClip. Due to the lack of an appropriate control group and clear evidence about the natural history of patients with primary MR considered at high-risk for surgery, the TEC Assessment concluded that a determination whether MitraClip improved, had no effect, or worsened mortality than nonsurgical management could not be made.
The FDA, on the contrary, concluded that totality of the evidence demonstrated reasonable assurance of safety and effectiveness of MitraClip to reduce MR and provide patient benefit in this discreet and specific patient population based on the following:

- It is broadly accepted that primary MR is a mechanical problem in which there is a primary abnormality of the mitral apparatus and the “leaflets are broken”. There is no medical therapy for reducing primary MR, which must be treated with mechanical correction of the MV.
- The observed procedural mortality rate with MitraClip was 6.4% (95% CI, 2.8% to 12.0%) at 30 days. This rate was lower than the predicted mortality rate of 13.2% (95% CI, 11.9% to 14.5%) using STS Replacement Risk Score or 9.5% (95% CI, 11.3% to 13.7%) using STS Repair Score for the Lim et al (2014) cohort.
- While acknowledging the pitfalls of using historical controls from the Duke Registry, the FDA found no elevated risk of mortality in MitraClip cohort patients over nonsurgical management and both immediate and long-term improvement in MR severity. MR severity grade of 2+ or less and of 1+ or less was observed in 82% and 54% of surviving patients at discharge, respectively. This improvement was sustained at 12 months, with the majority (83.3%) of surviving patients reporting MR severity grade of 2+ or less and 36.9% reporting MR severity grade of 1+ or less. At 12 months, freedom from death and MR severity grade greater than 2+ was 61.4% and freedom from death and MR severity grade greater than 1+ was 27.2%.
- Quality of life was assessed using the SF-36. The mean difference in the Physical Component Summary and Mental Component Summary scores from baseline to 12 months improved by 6 and 5.6 points, respectively, which is above the 2- to 3-point minimally important difference threshold reported in the literature. Sensitivity analyses showed that these effectiveness results were robust to missing data.
- The commercial postregistry data of over 8300 patients (one-third primary MR and two-thirds secondary MR) outside the U.S. suggests that mortality rates reported in patients at prohibitive risk of surgery undergoing the MitraClip procedure do not appear to be elevated and are not unexpected given the age and burden of comorbidities of the patients treated. Reported mortality ranges were: in-hospital mortality, 0% to 4%; 30-day mortality, 0% to 9.1% and 6- to 12-month mortality, 8% to 24%. Reported clinical benefits were: improvement in MR severity grade of 2+ or less after MitraClip in more than 75% of patients; improvement in 6-minute walk distance of 60 to >100 meters (the generally accepted threshold is >40 m), and percentages of patients who improved to a NYHA class of I or II ranged from 48% to 97%.
- The probable adverse event risks of the MitraClip included procedure-related complications such as death (6.3%), stroke (3.4%), prolonged ventilation (3.1%), and transfusion greater than 2 units (12.6%), major vascular complications (5.4%), noncerebral thromboembolism (1.6%), new onset of atrial fibrillation (3.9%), and atrial septal defect (1.6%).

Table 4. Key Observational Comparative Study Characteristics

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Country</th>
<th>Dates</th>
<th>Participants</th>
<th>Treatment</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single cohort with historical comparator</td>
<td>U.S.</td>
<td>Unclear</td>
<td>MitraClip cohort</td>
<td>MitraClip</td>
<td>1 y</td>
</tr>
<tr>
<td>N=127</td>
<td>Age: 82.4 y</td>
<td>&gt;75 y: 84%</td>
<td>NYHA class III: 87%</td>
<td>STS predicted mortality: 13.2%</td>
<td>LVEF: 61%</td>
</tr>
<tr>
<td>Duke cohort</td>
<td>N=65</td>
<td>Age: 76.8 y</td>
<td>&gt;75 y: 68%</td>
<td>NYHA class III: 44%</td>
<td>STS predicted mortality: 13.3%</td>
</tr>
</tbody>
</table>

FDA: Food and Drug Administration; FU: follow-up; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons.
Table 5. Key Observational Comparative Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Percent Event Free (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At 30 Days</td>
</tr>
<tr>
<td>MitraClip</td>
<td>93.6 (87.6 to 96.8)</td>
</tr>
<tr>
<td>Duke cohort</td>
<td>89.1 (78.5 to 94.7)</td>
</tr>
</tbody>
</table>


Subsequent to the FDA approval of MitraClip in 2013, patients who received MitraClip under Medicare coverage were required to enroll in the joint STS and American College of Cardiology Transcatheter Valve Therapy Registry as part of coverage under evidence development (see the Medicare National Coverage section). Initial results from this U.S.-based registry were reported in 2016 (short-term outcomes) and in 2017 (long-term outcomes) and summarized in Table 6.22,23. In the initial results of 564 patients enrolled between 2013 to 2014 from 561 U.S. centers, the median STS predicted risk of mortality scores for MV repair and replacement were 7.9% (range, 4.7%-12.2%) and 10.0% (range, 6.3%-14.5%), respectively.22 The in-hospital mortality rate was 2.3% and the 30-day mortality rate was 5.8%. These results are consistent with those reported in the cohort by Lim et al (2014) used by the FDA for approval20, and supports that a favorable benefit-risk ratio is attainable outside a clinical trial setting in appropriately selected patients. At 1 year, the proportion of patients who died was 25.8%, had a repeat hospitalization for heart failure was 20.2%, and cumulative incidence of mortality or rehospitalization for heart failure was 37.9%.23 Higher age, lower baseline LV ejection fraction, worse postprocedural MR, moderate or severe lung disease, dialysis, and severe tricuspid regurgitation were associated with higher mortality or rehospitalization for heart failure. The persistency of mortality (25.8%) and heart failure rehospitalization (20.2%) at 1 year despite of the effectiveness of MitraClip remains a concern. However, the results observed in the Transcatheter Valve Therapy Registry at 1 year were comparable with the 1-year rates observed in the analysis of high-risk patients in the EVEREST II (23.8%) and REALISM (18.0%) studies.24

Table 6. Summary of U.S.-Based TVT Registry Data

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Primary MR, %</th>
<th>Secondary MR, %</th>
<th>Postimplantation MR Grade ≤2, %</th>
<th>In-Hospital Death, %</th>
<th>30-Day Death, %</th>
<th>1-Year Death, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorajja et al (2016)22</td>
<td>564</td>
<td>86</td>
<td>14</td>
<td>93</td>
<td>2.3</td>
<td>5.8</td>
<td>-</td>
</tr>
<tr>
<td>Sorajja et al (2017)23</td>
<td>2392</td>
<td>86</td>
<td>9</td>
<td>92</td>
<td>2.7</td>
<td>5.2</td>
<td>25.8</td>
</tr>
</tbody>
</table>

MR: mitral regurgitation; TVT: Transcatheter Valve Therapy.

Other multiple subgroup analyses and systematic reviews have been reported using the EVEREST II HRR, REALISM, and other European/Non-European studies/registries but are not discussed further because they did not report results stratified by MR etiology (primary MR or secondary MR) or were of poor quality or did not add substantial clarity to the evidence already discussed herein.24-38.

Section Summary: Primary Mitral Valve Regurgitation at Prohibitive Surgical Risk

The evidence for the use of MitraClip among patients with primary MR at prohibitive surgical risk consists primarily of single-arm prospective cohort and registry studies. Included are the pivotal EVEREST II HRR and EVEREST II REALISM studies and the Transcatheter Valve Therapy Registry studies. These studies have demonstrated that MitraClip implantation is feasible, with procedural success rate greater than 90%, 30-day mortality rates ranging from 2.3% to 6.4% (less than predicted STS mortality score for MR repair or replacement [range, 9.5%-13.2%]), MR severity of 2+ or less in 82% to 93% patients, and clinically meaningful gains in quality of life (5- to 6-point gain in SF-36 scores). However, the 1-year mortality or heart failure hospitalization rates remained
considerably high (38%) compared with U.S.-based registry data thereby raising uncertainty about the long-term benefits.

**Heart Failure and Secondary Mitral Valve Regurgitation**

**Clinical Context and Therapy Purpose**
The purpose of TMVR using MitraClip in patients who have heart failure and moderate-to-severe or severe symptomatic secondary mitral regurgitation (SMR) is to provide a treatment option that is an alternative to an improvement on existing therapies.

The question addressed in this evidence review is: Does TMVR using MitraClip improve the net health outcome in patients who have heart failure and moderate-to-severe or severe symptomatic SMR trial regurgitation despite the use of maximally tolerated guideline-directed medical therapy?

The following PICOs were used to select literature to inform this review.

**Patients**
The relevant population of interest are patients with heart failure and moderate-to-severe or severe symptomatic SMR despite the use of maximally tolerated guideline-directed medical therapy.

Symptomatic SMR occurs when coronary disease with myocardial infarction or primary dilated cardiomyopathy cause a combination of LV wall motion abnormalities, mitral annular dilatation, papillary muscle displacement and reduced closing force that prevent the MV from coapting (to bring together) normally. This results in regurgitation, or backflow, of the MV. Symptoms include shortness of breath, fatigue, and swelling. MR severity is classified as mild, moderate, or severe disease on the basis of echocardiographic and/or angiographic findings (1+, 2+, and 3-4+ angiographic grade, respectively).

**Intervention**
The therapy being considered is TMVR using MitraClip. TMVR with MitraClip uses an implanted clip to perform the edge-to-edge repair technique on the MV to reduce MR.

**Comparators**
The following therapies are currently being used to make decisions about TMVR in patients with heart failure and SMR.

Comparators of interest are medical management. First line treatment is guideline-directed medical therapy. Resynchronization therapy may provide symptomatic relief, improve LV function, and in some patients, lessen the severity of MR.

**Outcomes**
The general outcomes of interest are OS, morbid events, functional outcomes, and treatment-related morbidity. Function in patients with heart failure is measured by the NYHA Class. The NYHA Class is based on a four-step grading scale from Class I, which is no limitation of physical activity to Class IV, which is unable to carry on any physical activity without discomfort.

**Randomized Controlled Trials**
The evidence for the use of MitraClip in patients with SMR consists of two RCTs, the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) and the Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (Mitra-FR) (Tables 7 and 8). Both trials compared MitraClip plus medical therapy to medical therapy alone in patients with SMR and heart failure, but they differed in their eligibility criteria, primary outcome measures, and duration of follow-up. COAPT enrolled 614 patients at 78 centers in the U.S. and Canada. Mitra-FR enrolled 304 patients at 37 centers in France.
COAPT found a significant benefit for Mitraclip on the primary efficacy outcome (all HF hospitalizations within 24 months) and the primary safety outcome (freedom from device-related complications at 12 months). In contrast, the MITRA-FR investigators found no significant differences between Mitra-Clip plus medical therapy and medical therapy alone on the composite primary outcome (death from any cause or unplanned HF hospitalization at 12 months) or any secondary outcome, including all-cause mortality at 12 months and cardiovascular death at 12 months (See Table 8).

Although the reasons for these discrepant results are not entirely clear, differences in the studies’ design and conduct have been proposed as possible explanations. The severity of MR and heart failure among the patients in the trials differed. COAPT participants had more severe MR at baseline (effective regurgitant orifice area 41 vs 31 mm²) and remained symptomatic despite the use of maximal doses of guideline-directed medical therapy. In both trials, eligible patients had to be symptomatic despite the use of optimal medical therapy. In COAPT, however, a central eligibility committee confirmed that the patient was using maximal doses of guideline-directed medical therapy prior to enrollment, and patients who improved with medical therapy were excluded. MITRA-FR had less stringent eligibility criteria and patients had more changes in medical therapy during the trial, indicating their treatment might not have been optimized. Additionally, patients in MITRA-FR had further progressed heart failure as indicated by LV dilation, and may have been less likely to benefit from MR treatment.

There is some evidence that technical success and procedural safety differed between the trials. Procedural complications were higher in MITRA-FR than in COAPT, and more patients in MITRA-FR experienced residual MR class >3+ post-procedure (both acutely and at 12 months). A shorter follow-up duration (12 months vs 24 months in COAPT) could have been a factor in the negative results seen in MITRA-FR. For example, at 12 months, the hazard ratio for all-cause mortality was not statistically significant in either trial, but by year 2, the HR in COAPT was significant at 0.62 (0.46 to 0.82; p<0.001).

Table 7. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone et al (2018); 39, COAPT</td>
<td>US and Canada</td>
<td>78</td>
<td>2012-2017</td>
<td>Ischemic or nonischemic cardiomyopathy with LVEF 20% to 50% moderate-to-severe (grade 3+) or severe (grade 4+) secondary MR; symptomatic (NYHA functional class II, III, or IVa) despite use of stable maximal doses of guideline-directed medical therapy and cardiac resynchronization therapy</td>
<td>N=302 MitraClip plus medical therapy</td>
</tr>
<tr>
<td>Obadia et al (2018); 40, MITRA-FR</td>
<td>France</td>
<td>37</td>
<td>2013-2017</td>
<td>Severe SMR with a regurgitant volume of greater than 30 ml per beat or an EROA ≥20 mm²; NYHA functional class II, III, or IV despite optimal standard of care therapy for heart failure according to investigator LVEF between 15% and 40% not appropriate for MV surgery by local heart team assessment</td>
<td>N=152 MitraClip plus medical therapy</td>
</tr>
</tbody>
</table>

RCT: randomized controlled trial; LVEF: left ventricular ejection fraction; SMR: secondary mitral regurgitation; EROA: effective regurgitant orifice area; NYHA: New York Heart Association; MR: mitral regurgitation; MV: mitral valve.
Table 8. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Primary Outcome: HF hospitalizations within 24 months</th>
<th>Primary Outcome: Death from any cause or unplanned HF hospitalization at 12 months</th>
<th>All-cause mortality at 12 months</th>
<th>Cardiovascular death at 12 months</th>
<th>All-cause mortality at 24 months</th>
<th>Cardiovascular death at 24 months</th>
<th>MR grade 2+ or lower at 12 months</th>
<th>NYHA functional class I or II at 12 months</th>
<th>Primary Safety Outcome: Freedom from device-related complications at 12 months Kaplan-Meier estimate of event-free rate (lower 95% confidence limit)</th>
<th>Serious Adverse events at 1 year&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Periprocedural complications during device implantation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone (2018)&lt;sup&gt;39&lt;/sup&gt;; COAPT</td>
<td>612</td>
<td>612</td>
<td>612</td>
<td>612</td>
<td>385</td>
<td>469</td>
<td>302</td>
<td></td>
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</tr>
<tr>
<td>Sample size</td>
<td>283/416.8 (67.9%)</td>
<td>57 (19.1%)</td>
<td>121/312 (46.1%)</td>
<td>97 (38.2%)</td>
<td>82/175 (46.9%)</td>
<td>115/232 (49.6%)</td>
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</tr>
<tr>
<td>Medical therapy alone</td>
<td>160/446.5 (35.8%)</td>
<td>70 (23.2%)</td>
<td>80/302 (29.1%)</td>
<td>61 (23.5%)</td>
<td>171/237 (72.2%)</td>
<td>96.6% (94.8%)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>MitraClip + medical therapy</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>HR (95% CI); p-value</td>
<td>0.53 (0.40 to 0.70); p&lt;0.001</td>
<td>0.81 (95% CI 0.57 to 1.15); &lt;0.001</td>
<td>0.62 (0.46 to 0.81); p=0.001</td>
<td>0.59 (90.43 to 0.81); p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
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<td></td>
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</tr>
<tr>
<td>NNT</td>
<td>3.1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obadia (2018)&lt;sup&gt;40&lt;/sup&gt;; MITRA-FR</td>
<td>304</td>
<td>304</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample size</td>
<td>78/152 (51.3%)</td>
<td>34/152 (22.4%)</td>
<td>31/152 (20.4%)</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medical therapy alone</td>
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<tr>
<td>MitraClip + medical therapy</td>
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<td></td>
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</tr>
<tr>
<td>HR (95% CI); p-value</td>
<td>1.16 (0.73 to 1.84); p=0.53</td>
<td>1.11 (0.69 to 1.77)</td>
<td>1.09 (0.67 to 1.78)</td>
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<td></td>
</tr>
</tbody>
</table>

HF: heart failure; NYHA: New York Heart Association; MR: mitral regurgitation; CI: confidence interval; HR: hazard ratio; NNT: number needed to treat; RCT: randomized controlled trial.

1 Composite of single leaflet device attachment, device embolization, endocarditis requiring surgery, mitral stenosis requiring surgery, left ventricular assist device implant, heart transplant, or any device related complication requiring non-elective cardiovascular surgery.

2 Includes prespecified adverse events heart transplantation or mechanical cardiac assistance, ischemic or hemorrhagic stroke, myocardial infarction, need for renal-replacement therapy, severe hemorrhage, and infections.
Tables 9 and 10 display notable gaps identified in COAPT and MITRA-FR. Patients enrolled in MITRA-FR had less severe MR and more severe heart failure than those who are likely to benefit from MV treatment, and the trial duration may not have been sufficient to show a benefit for the intervention. Design and conduct gaps in both trials include their open-label design and lack of information on allocation concealment. Lack of blinding is less of a concern with objective outcome measures but could impact the validity of measures of symptoms and quality of life. At baseline, more patients in the intervention group in MITRA-FR had a previous myocardial infarction. Otherwise, there were no significant differences between groups at baseline.

Table 9. Relevance Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone (2018);39, COAPT</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

- Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
- Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
- Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

Table 10. Study Design and Conduct Gaps

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocation</th>
<th>Blinding</th>
<th>Selective Reporting</th>
<th>Data Completeness</th>
<th>Power</th>
<th>Statistical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stone (2018);39, COAPT</td>
<td>3</td>
<td>1,2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obadia (2018);40, MITRA-FR</td>
<td>3</td>
<td>1,2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The evidence gaps stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.

- Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).
- Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.
- Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Section Summary: Heart Failure and Secondary Mitral Regurgitation

The evidence for the use of MitraClip in patients with SMR consists of two RCTs. The trials had disparate results, but the larger trial, with a longer duration and patients selected for nonresponse to maximally tolerated therapy, found a significant benefit for MitraClip after two years compared to medical therapy alone.
Primary or Secondary Mitral Regurgitation in Surgical Candidates
Clinical Context and Therapy Purpose
The purpose of TMVR using MitraClip in patients who have symptomatic primary or SMR and are surgical candidates is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does TMVR using MitraClip improve the net health outcome in patients who have symptomatic primary or SMR and are surgical candidates?

The following PICOs were used to select literature to inform this review.

Patients
The relevant population of interest are patients who have symptomatic primary or SMR and are surgical candidates.

Interventions
The therapy being considered is TMVR using MitraClip.

Comparators
The following therapies practices are currently being used to make decisions about TMVR. Relevant comparators are open MV repair and open MV replacement.

In symptomatic patients with primary MR, surgery is the main therapy. In most cases, MV repair is preferred over replacement, as long as the valve is suitable for repair and personnel with appropriate surgical expertise are available.

Isolated MV surgery (repair or replacement) for severe chronic SMR is not generally recommended because there is no proven mortality reduction and an uncertain durable effect on symptoms. Recommendations from major societies regarding MV surgery in conjunction with coronary artery bypass graft surgery or surgical aortic valve replacement are weak because the current evidence is inconsistent on whether MV surgery produces a clinical benefit.

Outcomes
The general outcomes of interest are OS, morbid events, functional outcomes, and treatment-related morbidity.

Systematic Review
A systematic review by Takagi et al (2017) identified 1 RCT and 6 nonrandomized comparative studies evaluating MitraClip and surgery.44 The RCT (EVEREST II) is described below. The systematic review conducted several pooled analyses. The meta-analysis did not detect a statistically significant difference in early (30-day or in-hospital) mortality between the MitraClip and surgery groups (pooled odds ratio, 0.54; 95% CI, 0.27 to 1.08; p=0.08). Similarly, a pooled analysis of late survival (≥6 months) did not find a statistically significant difference between the MitraClip and surgery groups (pooled odds ratio /hazard ratio, 1.17; 95% CI, 0.77 to 1.78; p=0.46). However, there was a significantly higher incidence of recurrent MR in the MitraClip than in the surgery group (pooled odds ratio /hazard ratio, 4.80; 95% CI, 2.58 to 8.93; p<0.001).

Randomized Controlled Trial
Feldman et al (2011) reported on the results of EVEREST II, an RCT that evaluated symptomatic or asymptomatic patients with grade 3+ or 4+ chronic MR who had SMR or primary MR etiology to TMVR; patients were randomized to MitraClip or open MV repair/replacement (see Table 1).45,46 Most patients (73%) had primary MR. Patients were excluded if they had an MV orifice area less than 4.0 cm or leaflet anatomy that precluded MitraClip device implantation, proper MitraClip positioning, or sufficient reduction in MR. MitraClip was considered to have acute procedural success if the clip deployed and MR grade was reduced to less than 3+.
Trial results are summarized in Table 12. In the intention-to-treat (ITT) analysis, for patients who did not have acute procedural success with MitraClip and subsequently underwent open MV repair, the efficacy endpoint was considered met for MitraClip group subjects if they were free from death, reoperation for MR, and MR grade greater than 2+ at 12 months. The trial had a predetermined efficacy endpoint of noninferiority of the MitraClip strategy, with a margin of 25% for the ITT analysis and 31% for prespecified per-protocol analyses. This implies that the MitraClip strategy would be noninferior to surgery at 12 months if the upper bound of difference in the proportion of patients achieving the primary efficacy endpoint between the 2 groups did not exceed 25 percentage points for the ITT analysis and 31% percentage points for the per-protocol analysis. Results showed that TMVR was less effective at reducing MR than conventional surgery before hospital discharge. MitraClip group subjects were more likely to require surgery for MV dysfunction, either immediately post-MitraClip implantation or in the 12 months following. Twenty percent (37/181) of the MitraClip group and 2% (2/89) of the surgery group required reoperation for MV dysfunction (p<0.001). Although in the ITT analysis rates of MR severity grades of 3+ or 4+ at 12 months were similar between groups, in the published per-protocol analysis, patients in the MitraClip group were more likely to have severity grades of 3+ or 4+ (17.2% [23/134] vs 4.1% [3/74], p=0.01), which would suggest that a larger proportion of patients with grade 1+ or 2+ MR in the MitraClip group had had surgical repair. As expected, rates of major adverse events at 30 days were lower in the MitraClip group (15% [27/181]) than in the surgery group (48% [45/89]; p<0.001). Rates of transfusion of more than 2 units of blood were the largest component of major adverse events in both groups, occurring in 13% (24/181) of the MitraClip group and 45% (42/89; p<0.001) of the surgery group. Long-term follow-up at four years and five years, showed that significantly more MitraClip patients required surgery for MV dysfunction during the follow-up period.

In the FDA per protocol analysis, MitraClip did not reduce MR as often or as completely as the surgical control, although it could be safely implanted and reduced MR severity in most patients. The FDA concluded that the data did not demonstrate an appropriate benefit-risk profile when compared with standard MV surgery and were inadequate to support device approval for the surgical candidate population.

### Table 11. Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldman et al</td>
<td>U.S., Canada</td>
<td>37</td>
<td>2005-2008</td>
<td>N=279</td>
<td>Active: TMVR (n=184)</td>
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<tr>
<td>(2011); EVEREST II</td>
<td></td>
<td></td>
<td></td>
<td>Comparator:</td>
<td>Open MV repair or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>repair/replacement (n=95)</td>
<td></td>
</tr>
</tbody>
</table>

- AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MR: mitral regurgitation; MV: mitral valve; RCT: randomized controlled trial; TMVR: transcatheter mitral valve repair.

### Table 12. Key RCT Results

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Freedom From Death, Socket for MR Dysfunction, and Grade 3+ or 4+ MR</th>
<th>Major AE at 30 Daysa</th>
<th>Surgery for MV Dysfunctionb</th>
<th>Death</th>
<th>Grade 3+ or 4+ MR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldman et al</td>
<td>270</td>
<td>274</td>
<td>270</td>
<td>270</td>
<td>270</td>
</tr>
<tr>
<td>(2011); EVEREST II</td>
<td>(1 year)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TMVR</td>
<td>100/181 (55%)</td>
<td>27/180 (15%)</td>
<td>37/181 (20%)</td>
<td>11/181 (6%)</td>
<td>38/181 (21%)</td>
</tr>
<tr>
<td>Open repair</td>
<td>65/89 (73%)</td>
<td>45/94 (48%)</td>
<td>2/94 (2%)</td>
<td>5/94 (6%)</td>
<td>18/94 (20%)</td>
</tr>
<tr>
<td>p</td>
<td>0.007</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>Study; Trial</td>
<td>Freedom From Death, Surgery for MR Dysfunction, and Grade 3+ or 4+ MR</td>
<td>Major AE at 30 Days&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Surgery for MV Dysfunction&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Death</td>
<td>Grade 3+ or 4+ MR</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----------------------------------------------------------------------</td>
<td>---------------------------------</td>
<td>---------------------------------------</td>
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<td>------------------</td>
</tr>
<tr>
<td>FDA (2013)&lt;sup&gt;16;&lt;/sup&gt; EVEREST II (1 year)</td>
<td>Range, 156-208</td>
<td>274</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>TMVR</td>
<td>97/134 (72%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>27/180</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>37/82 (45%)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>(15%)</td>
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<tr>
<td>Open repair</td>
<td>65/74 (88%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>45/94 (48%)</td>
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<td>Not reported</td>
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<td>51/74 (69%)&lt;sup&gt;e&lt;/sup&gt;</td>
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<tr>
<td>p</td>
<td>0.001&lt;sup&gt;d,f&lt;/sup&gt;</td>
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<td></td>
<td>0.169&lt;sup&gt;e,f&lt;/sup&gt;</td>
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<tr>
<td>TMVR</td>
<td>NR</td>
<td>NR</td>
<td>40/161 (25%)</td>
<td>28/161 (17%)</td>
<td>35/161 (22%)</td>
</tr>
<tr>
<td>Open repair</td>
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<td>p</td>
<td>NR</td>
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<td>Feldman et al (2015)&lt;sup&gt;48;&lt;/sup&gt; EVEREST II (5 years)</td>
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<td>197</td>
<td>197</td>
<td>197</td>
</tr>
<tr>
<td>TMVR</td>
<td>NR</td>
<td>NR</td>
<td>43/154 (28%)</td>
<td>32/154 (21%)</td>
<td>19/154 (19%)</td>
</tr>
<tr>
<td>Open repair</td>
<td>NR</td>
<td>NR</td>
<td>5/56 (9%)</td>
<td>15/56 (27%)</td>
<td>1/56 (2%)</td>
</tr>
<tr>
<td>p</td>
<td>NR</td>
<td>NR</td>
<td>0.003</td>
<td>0.36</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values are n/N (%) unless otherwise noted.

AE: adverse event; FDA: Food and Drug Administration; MR: mitral regurgitation; MV: mitral valve; NR: not reported; RCT: randomized controlled trial; TMVR: transcatheter mitral valve repair.

<sup>a</sup> The composite primary safety endpoint was major AEs at 30 days, defined as freedom from death, myocardial infarction, nonelective cardiac surgery for AEs, renal failure, transfusion of ≥2 units of blood, reoperation for failed surgery, stroke, gastrointestinal complications requiring surgery, ventilation for ≥48 hours, deep wound infection, septicemia, and new onset of permanent atrial fibrillation.

<sup>b</sup> The rate of the first MV surgery in the percutaneous repair group and the rate of reoperation for MV dysfunction in the surgery group.

<sup>c</sup> Crossover to surgery in the immediate postprocedure period if MitraClip failed to adequately reduce MR was considered a successful treatment strategy.

<sup>d</sup> Freedom from death, MV surgery, or reoperation and MR severity grade of >2+.

<sup>e</sup> Freedom from death, MV surgery, or reoperation and MR severity grade of >1+.

<sup>f</sup> As per FDA, noninferiority statistical methods were used to calculate this p value, however, noninferiority was not implied due to the large margin. Therefore, this test shows whether the results show decreased effectiveness by the margin specified of -31%.

Section Summary: MitraClip in Surgical Candidates

The evidence for the use of MitraClip in patients considered candidates for open MV repair surgery includes an RCT (EVEREST II) and a systematic review. 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 of the RCT showed that significantly more MitraClip patients required surgery for MV dysfunction than conventional surgery. EVEREST II had some methodologic limitations. The noninferiority margin of 25% (ITT) or 31% (per-protocol) was large, indicating that MitraClip could be somewhat inferior to surgery and, yet, the test for noninferiority margin would be met. Crossover to surgery was allowed for patients who had an MR severity grade of 3+ or higher prior to discharge, and 23% of patients assigned to MitraClip met this criterion. This large crossover rate would bias results toward the null on ITT analysis, thus increasing the likelihood of meeting the noninferiority margin. In an analysis by treatment received, this crossover would result in a less severely ill population in the MitraClip group and bias the results in favor of MitraClip. A high proportion of patients required open MV replacement or repair during the first year postprocedure, thus limiting the number of patients who had long-term success without surgical intervention. For these reasons, this single trial is not definitive in demonstrating improved clinical outcomes using MitraClip compared with surgery. Further RCTs are needed to corroborate these results.
Other Transcatheter Mitral Valve Repair Devices

Clinical Context and Therapy Purpose

The purpose of TMVR using devices other than MitraClip in patients with symptomatic primary or SMR is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does TMVR using devices other than MitraClip improve the net health outcome in patients with symptomatic primary or SMR?

The following PICO's were used to select literature to inform this review.

Patients
The relevant population of interest are patients with symptomatic primary or SMR.

Interventions
The therapy being considered is TMVR with devices other than MitraClip.

Comparators
The following therapies/tools/rules/practices are currently being used to make decisions about TMVR.

Relevant comparators are open MV repair, open MV replacement, and medical management.

Outcomes
The general outcomes of interest are OS, morbid events, functional outcomes, and treatment-related morbidity.

Several devices other than MitraClip are being investigated for TMVR, although none is FDA approved for use in the U.S.

Several indirect annuloplasty devices, the Carillon® Mitral Contour System (Cardiac Dimension) and the Monarc™ device (Edwards Lifesciences), have been evaluated. A case series evaluating use of the Carillon device in 53 patients with a SMR severity grade of 2+ at 7 European centers was reported by Siminiak et al (2012). Of the 53 patients who underwent attempted device implantation, 36 underwent permanent implantation and 17 had the device removed due to transient coronary compromise in 8 patients and less than 1 severity grade reduction in SMR in 9 patients. Echocardiographic measures of secondary MR improved in the implanted groups through 12-month follow-up, along with improvements in 6-minute walk distance. An earlier feasibility study of the Carillon device reported by Schoder et al (2009) who evaluated 48 patients with moderate-to-severe secondary MR; it demonstrated successful device placement in 30 patients, with 18 patients unable to be implanted due to access issues, insufficient acute secondary MR reduction, or coronary artery compromise. The Monarc™ device has been evaluated in a phase 1 safety trial at 8 European centers, as reported by Hamek et al (2011). Among 72 patients enrolled, the device was successfully implanted in 59 (82%) patients. The primary safety endpoint (freedom from death, tamponade, or myocardial infarction at 30 days) was met by 91% of patients at 30 days and by 82% at 1 year.

Section Summary: Other Transcatheter Mitral Valve Repair Devices

The evidence for the use of TMVR devices other than the MitraClip for patients with MR includes only small case series and case reports. Collectively, these data are insufficient to determine the effects of these technologies on health outcomes.

Summary of Evidence

For individuals who have symptomatic primary MR and at prohibitive risk for open surgery who receive TMVR using MitraClip, the evidence includes a single-arm prospective cohort with historical cohort and registry studies. The relevant outcomes are 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 STS mortality risk score for MR repair or replacement; range, 9.5%-13.2%), postimplantation 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 SF-36 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 RCT comparing MitraClip with medical management is not feasible or ethical. The postmarketing 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 SMR despite the use of maximally tolerated guideline-directed medical therapy who receive TMVR using MitraClip, the evidence includes two RCTs. The relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. The trials had conflicting results, but the larger trial, with a longer duration and patients selected for nonresponse to maximally tolerated therapy, found a significant benefit for MitraClip after two years compared to medical therapy alone. 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 SMR and are surgical candidates who receive TMVR using MitraClip, the evidence includes one RCT. The 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 evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have symptomatic primary or SMR who receive TMVR using devices other than MitraClip, the evidence includes primarily noncomparative feasibility studies. The relevant outcomes are OS, morbid 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

Clinical Input From Physician Specialty Societies and Academic Medical Centers
While the various physician specialty societies and academic medical centers may collaborate with and make recommendations during this process, through the provision of appropriate reviewers, input received does not represent an endorsement or position statement by the physician specialty societies or academic medical centers, unless otherwise noted.

In response to requests from Blue Cross Blue Shield Association, input was received from 4 academic medical centers, one of which provided 4 responses, for a total of 7 responses in 2015. Input supported the use of transcatheter mitral valve repair in patients with primary (degenerative) mitral regurgitation at prohibitive risk of open surgery. The greatest consensus for selection criteria to determine “prohibitive risk” was for the use of the Society of Thoracic Surgeons predictive operative risk of 12% or higher, or a logistic EuroSCORE of 20% or higher.
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 13 provides the relevant recommendations.

Table 13. Recommendations on Primary and Secondary Mitral Regurgitation

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>SOR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary MR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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 prohibitive surgical risk because of severe comorbidities and remain severely symptomatic despite optimal guideline-directed medical therapy for heart failure.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td><strong>Secondary MR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>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.</td>
<td>IIb</td>
<td>B-R</td>
</tr>
</tbody>
</table>


The American College of Cardiology, American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons (2014) issued a position statement on transcatheter therapies for mitral regurgitation (MR). This statement outlined critical components for successful transcatheter MR therapies and recommended ongoing research and inclusion of all patients treated with transcatheter MR therapies in a disease registry.

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 14). Table 14. Recommendations on Management of Valvular Heart Disease

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>SOR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary MR</strong></td>
<td></td>
<td></td>
</tr>
<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>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td><strong>Secondary MR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“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 remodeling. Similar to surgery, a survival benefit compared with ‘optimal’ medical therapy according to current guidelines has not yet been proven.”</td>
<td>a</td>
<td>a</td>
</tr>
</tbody>
</table>

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;
   e. Adequate outpatient clinical care facilities
   f. 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:
   • An interventional cardiologist(s) who:
     o performs >50 structural procedures per year including atrial septal defects (ASD), patent foramen ovale (PFO) and trans-septal punctures and,
     o must receive prior suitable training on the devices to be used; and,
     o must be board-certified in interventional cardiology or board-certified/eligible in pediatric cardiology or similar boards from outside the United States;
   • 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;

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.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 15.

Table 15. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT01920698</td>
<td>Multicentre Randomized Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR)</td>
<td>288</td>
<td>Apr 2019</td>
</tr>
<tr>
<td>NCT01626079</td>
<td>Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (The COAPT Trial)</td>
<td>610 (5-year follow-up per protocol)</td>
<td>July 2024</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.

Denotes industry-sponsored or cosponsored trial.

References


17. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Percutaneous mitral valve repair. TEC Assessments 2014;Volume 29:Tab 4. PMID.


### Documentation for Clinical Review

**Please provide the following documentation (if/when requested):**

- History and physical and/or consultation notes including:
  - Documented symptomatic, degenerative mitral regurgitation
  - Documented Society for Thoracic Surgeons predicted mortality risk and/or logistic EuroSCORE
- Name of FDA approved device

### Post Service

- Procedure report

### Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

**MN/IE**

The following services may be considered medically necessary in certain instances and investigational in others. Services may be considered medically necessary when policy criteria are met. Services may be considered investigational when the policy criteria are not met or when the code describes application of a product in the position statement that is investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPT</td>
<td>0345T</td>
<td>Transcatheter mitral valve repair percutaneous approach via the coronary sinus</td>
</tr>
</tbody>
</table>
|        | 0544T| Transcatheter mitral valve annulus reconstruction, with implantation of a adjustable annulus reconstruction device, percutaneous approach including transseptal puncture (**Code effective 7/1/2019**)
|        | 33418| Transcatheter mitral valve repair, percutaneous approach, including transseptal puncture when performed; initial prosthesis |
## Transcatheter Mitral Valve Repair

### Type | Code | Description
--- | --- | ---
 | 33419 | Transcatheter mitral valve repair, percutaneous approach, including transseptal puncture when performed; additional prosthesis(es) during same session (List separately in addition to code for primary procedure)

### HCPCS
None

### ICD-10 Procedure
- **02QG4ZZ** Repair Mitral Valve, Percutaneous Endoscopic Approach
- **02RG4JZ** Replacement of Mitral Valve with Synthetic Substitute, Percutaneous Endoscopic Approach
- **02UG4JZ** Supplement Mitral Valve with Synthetic Substitute, Percutaneous Endoscopic Approach

## Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

<table>
<thead>
<tr>
<th>Effective Date</th>
<th>Action</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>09/30/2014</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>01/01/2015</td>
<td>Coding update</td>
<td>Administrative Review</td>
</tr>
<tr>
<td>12/04/2015</td>
<td>Policy revision with position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/01/2016</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/01/2017</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>07/01/2018</td>
<td>Policy revision without position change</td>
<td>Medical Policy Committee</td>
</tr>
<tr>
<td>08/01/2019</td>
<td>Policy revision without position change Coding update</td>
<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

## Definitions of Decision Determinations

### Medically Necessary: A treatment, procedure, or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

### Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state government is required prior to use, but has not yet been granted.

### Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.
Questions regarding the applicability of this policy should be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.