



## Transcatheter Mitral Valve Repair

**Policy Number:** 2.02.30  
**Origination:** 9/2014

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**Next Review:** 10/2019

### Policy

Blue Cross and Blue Shield of Kansas City (Blue KC) will provide coverage for Transcatheter Mitral Valve Repair when it is determined to be medically necessary because the criteria shown below are met.

### When Policy Topic is covered

Transcatheter mitral valve repair with a device approved by the 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 Considerations section).

### When Policy Topic is not covered

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

### Considerations

"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.

### Description of Procedure or Service

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> <li>• With symptomatic primary mitral regurgitation and at prohibitive risk for open surgery</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Transcatheter mitral valve repair using MitraClip</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Medical management</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Morbid events</li> <li>• Functional outcomes</li> <li>• Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>• With symptomatic secondary mitral regurgitation and at prohibitive risk for open surgery</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>• Transcatheter mitral valve repair using MitraClip</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>• Medical management</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>• Overall survival</li> <li>• Morbid events</li> <li>• Functional outcomes</li> <li>• Treatment-related morbidity</li> </ul>
Individuals:	Interventions of	Comparators of	Relevant outcomes include:

<ul style="list-style-type: none"> <li>With symptomatic primary or secondary mitral regurgitation and are surgical candidates</li> </ul>	interest are: <ul style="list-style-type: none"> <li>Transcatheter mitral valve repair using MitraClip</li> </ul>	interest are: <ul style="list-style-type: none"> <li>Open mitral valve repair</li> <li>Open mitral valve replacement</li> </ul>	<ul style="list-style-type: none"> <li>Overall survival</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Treatment-related morbidity</li> </ul>
Individuals: <ul style="list-style-type: none"> <li>With symptomatic primary or secondary mitral regurgitation</li> </ul>	Interventions of interest are: <ul style="list-style-type: none"> <li>Transcatheter mitral valve repair using devices other than MitraClip</li> </ul>	Comparators of interest are: <ul style="list-style-type: none"> <li>Open mitral valve repair</li> <li>Open mitral valve replacement</li> </ul>	Relevant outcomes include: <ul style="list-style-type: none"> <li>Overall survival</li> <li>Morbid events</li> <li>Functional outcomes</li> <li>Treatment-related morbidity</li> </ul>

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.

## MitraClip

### ***Primary MR at Prohibitive Risk for Surgery***

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. Relevant outcomes are overall survival, 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%), 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 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 postmarketing data from the United States 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.

Clinical input obtained in 2015 supported the use of TMVR in patients with primary MR considered at a prohibitive risk for open surgery, which is the U.S. Food and Drug Administration–approved indication for the MitraClip device. Given the lack of other treatment options for this population, the suggestive clinical evidence, and supportive clinical input, TMVR with the MitraClip may be considered medically necessary for this patient population.

### ***Secondary MR at Prohibitive Risk for Surgery***

For individuals who have symptomatic secondary MR and at prohibitive risk for open surgery who receive TMVR using MitraClip, the evidence includes multiple observational studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related morbidity. Multiple observational studies from Europe have suggested that MitraClip reduces the severity of MR and improves functional class in patients with secondary MR. However, recommendations from major societies regarding mitral valve surgery (conventional or percutaneous) are weak because the current evidence is inconsistent on whether mitral valve surgery produces a clinical benefit in patients with secondary MR. A RCT comparing the safety and effectiveness of MitraClip (COAPT trial) in patients with secondary MR is currently underway and is expected to be completed in 2024. The evidence is insufficient to determine the effects of the technology on health outcomes.

### ***Primary or Secondary MR Not at Risk for Surgery***

For individuals who have symptomatic primary or secondary MR and are surgical candidates who receive TMVR using MitraClip, the evidence includes a systematic review and an RCT. Relevant outcomes are overall survival, 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 1 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.

### ***Devices Other Than MitraClip***

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 overall survival, 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.

## **Background**

### **Mitral Regurgitation**

#### **Epidemiology and Classification**

Mitral regurgitation (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.<sup>1,2</sup>

Patients with MR generally fall into 2 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).<sup>3</sup> Because the primary cause is a structural abnormality, most cases of primary MR are surgically corrected. In contrast, secondary MR results from left ventricular dilatation due to ischemic or dilated cardiomyopathy. This causes the mitral valve (MV) leaflets not to coapt or meet in the center.<sup>4</sup> Because the valves are structurally normal in secondary MR, correcting the dilated left ventricular using medical therapy is the primary treatment strategy used in the United States.

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 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.<sup>4</sup>

#### **Standard Management**

##### ***Medical Management***

Medical management has a primary role in secondary MR. 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),  $\beta$ -blocker and mineralocorticoid receptor antagonist, and diuretic therapy as needed to treat volume overload.<sup>3,4</sup>

##### ***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.<sup>3</sup>

**Table 1. Guidelines on Mitral Value Surgery**

<b>Recommendation</b>	<b>COR</b>	<b>LOE</b>
MV surgery is recommended for the symptomatic patient with acute severe MR.	I	B
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.	I	B
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.	I	B
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.	I	C
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%.	IIa	B
MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and new onset of atrial fibrillation	IIa	C
MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and pulmonary hypertension...	IIa	C
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	IIa	C

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 United States, Goel et al (2014) found that 53% of patients did not have MV surgery performed, suggesting an unmet need for such patients.<sup>5</sup>

### **Transcatheter MV 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.<sup>1,6</sup> Approaches to MV repair include direct leaflet repair, 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.<sup>7</sup> 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 MV 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 (AMADEUS) and the follow-up Tighten the Annulus Now study, with further studies planned.<sup>8</sup> The Monarc system also involves 2 self-expanding stents connected by a nitinol bridge, with 1 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 (EVOLUTION I) trial.<sup>9</sup>

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<sub>sq</sub>™ Mitral Valve Repair System, and the Cardioband™ Annuloplasty System (Valtech Cardio), an implantable annuloplasty band with a transfemoral venous delivery system.

### ***Transcatheter MV Replacement***

Permavalve™ (MicroInterventional Devices), under investigation in the United States, 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 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 FDA through the premarket approval process for treatment of “significant symptomatic mitral regurgitation (MR  $\geq$ 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.”<sup>10</sup>

## Rationale

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This evidence review was created in July 2014 and has been updated regularly with searches of the MEDLINE database. The most recent literature review covers the period through March 5, 2018.

This review was informed, in part, by a 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.<sup>11</sup>

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 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.

Two major categories of patients with MR are candidates for TMVR: those considered at prohibitively high risk for cardiac surgery and those considered surgical candidates. Studies addressing these 2 subsets of patients are reviewed separately. Although outcomes and etiology differ for secondary MR and primary MR, studies of MitraClip have most often evaluated the device in mixed populations. All such studies therefore were not included in the review unless authors stratified results.

## MitraClip

### Primary MV Regurgitation at Prohibitive Surgical Risk

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, the U.S. Food and Drug Administration (FDA)–approved indication.<sup>11</sup> The Assessment included 5 case series reporting outcomes of patients with primary MR considered at high risk of surgical mortality who underwent MitraClip placement. Three of the 5 case series were rated as poor because of low or unknown follow-up rates and are not discussed further. Tables 2 and 3 summarizes patient characteristics and health outcomes of the case series by Reichenspurner et al (2013)<sup>12</sup> and Lim et al (2013),<sup>13</sup> which were considered higher quality. The Reichenspurner study reported data on 117 primary MR patients who were enrolled in a European postmarketing registry. The Lin study reported data on 127 patients enrolled in the EVEREST II HRR and 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.<sup>12,14</sup> 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**

Study; Trial	Country	Participants	Treatment Delivery	Follow-Up
<b>Reichenspurner et al (2013)<sup>12</sup>; ACCESS-EU</b>	Europe	<ul style="list-style-type: none"> <li>• N=117</li> <li>• EF &lt;40% or mean EF: 9.4%</li> <li>• NYHA class ≥3: 74%</li> <li>• MR severity ≥3+: 96.6%</li> <li>• Mean EuroSCORE: 15.5%</li> </ul>	MitraClip	71 had 1-y follow-up data
<b>Lim et al (2014)<sup>14</sup>; subset of patients at prohibitive risk of open surgery from EVEREST II HRR and REALISM</b>	U.S.	<ul style="list-style-type: none"> <li>• N: 127</li> <li>• EF &lt;40% or Mean EF: 61%</li> <li>• NYHA class ≥3: 87%</li> <li>• MR severity ≥3+: 100%</li> <li>• Mean STS score: 13.2%</li> </ul>	MitraClip	1.47 y

Adapted from the TEC Assessment (2014).<sup>11</sup>

EF: ejection fraction; NR: not reported; MR: mitral regurgitation; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons surgical risk score.

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

Study; Trial	Original N	MR Grade at 12 Months, % (n/N)	NYHA Class at 12 Months, % (n/N)	Other Pertinent Outcomes at 12 Months
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Study; Trial	Original N	MR Grade at 12 Months, % (n/N)	NYHA Class at 12 Months, % (n/N)	Other Pertinent Outcomes at 12 Months
<b>Reichenspurner et al (2013)<sup>12</sup>; ACCESS-EU</b>	117	MR severity $\leq 2+$ : 74.6% (53/71)	<ul style="list-style-type: none"> <li>Class I/II: 81% (63/78)</li> <li>Improved <math>\geq 1</math> class: 68% (53/78)</li> </ul>	<ul style="list-style-type: none"> <li>Change in MLHFQ from baseline, 13.3 points (p=0.03), n=44</li> <li>Change in 6MWT from baseline, 77.4 m (p&lt;0.001), n=52</li> </ul>
<b>Lim et al (2014)<sup>14</sup>; subset of patients at prohibitive risk of open surgery from EVEREST II HRR and REALISM</b>	127	MR severity $\leq 2+$ : 83.3% (70/84)	<ul style="list-style-type: none"> <li>Class I/II: 86.9% (73/84)</li> <li>Improved <math>\geq 1</math> class: 86.9% (73/84)</li> </ul>	<ul style="list-style-type: none"> <li>SF-36 PCS score change, 6.0 (95% CI, 4.0 to 8.0), n=76</li> <li>SF-36 MCS score change, 5.6 (95% CI, 2.3 to 8.9), n=76</li> </ul>

Adapted from the TEC Assessment (2014).<sup>11</sup>

CI: confidence interval; MCS: Mental Component Summary; MLHFQ: Minnesota Living with Heart Failure 10 Questionnaire; MR: mitral regurgitation; NYHA: New York Heart Association; PCS: Physical Component Summary; 6MWT: 6-minute walk test; SF-36: 36-Item Short-Form Health Survey.

FDA compared the cohort reported by Lin 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 (ie, Society of Thoracic Surgeons (STS) mortality risk calculation of 12% or higher or protocol-specified surgical risk factors). For the cohort described by Lin 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 intraprocedural 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 (ie, 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.

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<sup>10</sup>:

- 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 mitral valve.
- 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 Lin cohort.
- While acknowledging the pitfalls of using historical controls from the Duke Registry, 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.<sup>15</sup> 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 United States 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**

Study	Design	Country	Dates	Participants	Treatment	Treatment	FU
<b>FDA (2013)<sup>10</sup></b>	Single cohort with historical comparator	U.S.	Unclear	<b>MitraClip cohort</b> <ul style="list-style-type: none"> <li>• N=127</li> <li>• Age: 82.4 y</li> <li>• &gt;75 y: 84%</li> <li>• NYHA class ≥III: 87%</li> <li>• STS predicted mortality: 13.2%</li> <li>• LVEF: 61%</li> </ul> <b>Duke cohort</b> <ul style="list-style-type: none"> <li>• N=65</li> <li>• Age: 76.8 y</li> <li>• &gt;75 y: 68%</li> <li>• NYHA class ≥III: 44%</li> <li>• STS predicted mortality: 13.3%</li> <li>• LVEF: 44%</li> </ul>	MitraClip	Nonsurgical management	1 y

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**

Study	Percent Event Free (95% CI), %				Freedom From Death and MR >2+	Freedom From Death and NYHA Class III/IV
	At 30 Days	At 6 Months	At 12 Months			
<b>FDA (2013)<sup>10</sup></b>	N=192	N=192	N=192		N range, 114-124	N range, 114-124
<b>MitraClip</b>	93.6 (87.6 to 96.8)	84.8 (77.2 to 90.0)	75.2 (66.1 to 82.1)		Baseline: 10% 30 d: 82% 12 mo: 61%	Baseline: 13% 30 d: 76% 12 mo: 64%
<b>Duke cohort</b>	89.1 (78.5 to 94.7)	79.6 (67.4 to 87.6)	69.4 (56.3 to 79.3)		-	-

FDA: Food and Drug Administration; MR: mitral regurgitation; NYHA: New York Heart Association.

Subsequent to 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.<sup>16,17</sup> 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.<sup>16</sup> 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 FDA for approval<sup>14</sup> 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%.<sup>17</sup> Higher age, lower baseline left ventricular 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.<sup>18</sup>

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

Study	No. of Patients	Primary MR, %	Secondary MR, %	Postimplantation MR Grade ≤2, %	In-Hospital Death, %	30-Day Death, %	1-Year Death, %
Sorajja et al (2016) <sup>16</sup>	564	86	14	93	2.3	5.8	-
Sorajja et al (2017) <sup>17</sup>	2952	86	9	92	2.7	5.2	25.8

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.<sup>18-32</sup>

### **Section Summary: Primary MV Regurgitation at Prohibitive Surgical Risk**

The evidence for the use of MitraClip among patients in 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.

## **Secondary MV Regurgitation at Prohibitive Surgical Risk**

The standard treatment for patients with chronic secondary MR is medical management (see Background section). Isolated mitral valve 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 societies<sup>33,34</sup> regarding mitral valve surgery in conjunction with coronary artery bypass graft surgery or surgical aortic valve replacement are weak because the current evidence is inconsistent on whether mitral valve surgery produces a clinical benefit.<sup>35-38</sup> Multiple observational studies, primarily from Europe, have suggested that TMVR using MitraClip can also reduce the severity of MR and improve functional class in patients with secondary MR.

However, data from RCTs are needed to evaluate the benefits and risks of TMVR vs medical management in patients with secondary MR. The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (The COAPT Trial) is currently underway (NCT01626079). Briefly, in the COAPT Trial, more than 600 patients with secondary MR will be optimized on medical therapy, and then randomized to continuing medical therapy or MitraClip implantation. This trial is ongoing and has an estimated completion date of July 2024. Trial has 2 coprimary end points related to safety (1 year) and effectiveness (survival status and heart failure hospitalizations up to 2 years).

### **Section Summary: Secondary MV Regurgitation at Prohibitive Surgical Risk**

The evidence for the use of MitraClip among patients in patients with secondary MR at prohibitive surgical risk consists primarily of observational studies from Europe; these studies have suggested that MitraClip reduces the severity of MR and improves functional class in patients with secondary MR. An RCT comparing the safety and effectiveness of MitraClip in patients with secondary MR is underway and expected to be completed in 2024.

## **Primary or Secondary MR in Surgical Candidates**

### **Systematic Reviews**

A systematic review by Takagi et al (2017) identified 1 RCT and 6 nonrandomized comparative studies evaluating MitraClip and surgery.<sup>39</sup> 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 [OR], 0.54; 95% CI, 0.27 to 1.08;  $p=0.08$ ). Similarly, a pooled analysis of late survival ( $\geq 6$  months) did not find a statistically significant difference between the MitraClip and surgery groups (pooled OR/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 OR/hazard ratio, 4.80; 95% CI, 2.58 to 8.93;  $p<0.001$ ).

## Randomized Controlled Trials

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 secondary MR or primary MR etiology to TMVR; patients were randomized to MitraClip or open MV repair/replacement (see Table 7).<sup>40,41</sup> 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 8. 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 end point 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 end point 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 end point 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 4 years<sup>42</sup> and 5 years<sup>43</sup> 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. FDA concluded that the data did not demonstrate an appropriate benefit-risk profile when compared with standard mitral valve surgery and were inadequate to support device approval for the surgical candidate population.

**Table 7. Key RCT Characteristics**

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
<b>Feldman et al (2011)<sup>40</sup>; EVEREST II</b>	U.S., Canada	37	2005- 2008	<ul style="list-style-type: none"> <li>N=279</li> <li>Grade 3+ or 4+ chronic MR</li> <li>Symptomatic (LVEF ≥25% and LVESD ≤55 mm) or asymptomatic (LVEF 25%-60% or LVESD 40-55 mm or new AF or pulmonary hypertension)</li> </ul>	TMVR (n=184)	Open MV repair or replacement (n=95)

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

**Table 8. Key RCT Results**

Study; Trial	Freedom From Death, Surgery for MR Dysfunction, and Grade 3+ or 4+ MR	Major AE at 30 Days <sup>a</sup>	Surgery for MV Dysfunction <sup>b</sup>	Death	Grade 3+ or 4+ MR
<b>Feldman et al (2011)<sup>40</sup>; EVEREST II<sup>c</sup> (1 year)</b>	270	274	270	270	270
<b>TMVR</b>	100/181 (55%)	27/180 (15%)	37/181 (20%)	11/181 (6%)	38/181 (21%)
<b>Open repair</b>	65/89 (73%)	45/94 (48%)	2/94 (2%)	5/94 (6%)	18/94 (20%)
<b>p</b>	0.007	<0.001	<0.001	1.00	1.00
<b>FDA (2013)<sup>10</sup>; EVEREST II (1 year)</b>	Range, 156-208	274	-	-	-
<b>TMVR</b>	97/134 (72%) <sup>d</sup> 37/82 (45%) <sup>e</sup>	27/180 (15%)	Not reported	Not reported	Not reported
<b>Open repair</b>	65/74 (88%) <sup>d</sup> 51/74 (69%) <sup>e</sup>	45/94 (48%)	Not reported	Not reported	Not reported
<b>p</b>	0.001 <sup>d,f</sup> 0.169 <sup>e,f</sup>	<0.001	Not reported	Not reported	Not reported
<b>Mauri et al (2013)<sup>42</sup>; EVEREST II (4 years)</b>	NR	NR	234	234	234
<b>TMVR</b>	NR	NR	40/161 (25%)	28/161 (17%)	35/161 (22%)
<b>Open repair</b>	NR	NR	4/73 (6%)	13/73 (18%)	18/73 (25%)
<b>p</b>	NR	NR	<0.001	0.914	0.745
<b>Feldman et al</b>			197	197	197

<b>(2015)<sup>43</sup>; EVEREST II (5 years)</b>					
<b>TMVR</b>	NR	NR	43/154 (28%)	32/154 (21%)	19/154 (19%)
<b>Open repair</b>	NR	NR	5/56 (9%)	15/56 (27%)	1/56 (2%)
<b>p</b>	NR	NR	0.003	0.36	0.02

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 end point was major AEs at 30 days, defined as freedom from death, myocardial infarction, nonelective cardiac surgery for AEs, renal failure, transfusion of  $\geq 2$  units of blood, reoperation for failed surgery, stroke, gastrointestinal complications requiring surgery, ventilation for  $\geq 48$  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 1 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 MV Repair Devices**

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

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 secondary MR severity grade of 2+ at 7 European centers was reported by Siminiak et al (2012).<sup>8</sup> 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 secondary MR 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.<sup>44</sup> The Monarc device has been evaluated in a phase 1 safety trial at 8 European centers, as reported by Harnek et al (2011).<sup>9</sup> Among 72 patients enrolled, the device was successfully implanted in 59 (82%) patients. The primary safety end point (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 MV 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**

### **MitraClip**

#### ***Primary MR at Prohibitive Risk for Surgery***

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. Relevant outcomes are overall survival, 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 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 postmarketing data from the United States 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.

### ***Secondary MR at Prohibitive Risk for Surgery***

For individuals who have symptomatic secondary MR and at prohibitive risk for open surgery who receive TMVR using MitraClip, the evidence includes multiple observational studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related morbidity. Multiple observational studies from Europe have suggested that MitraClip reduces the severity of MR and improves functional class in patients with secondary MR. However, recommendations from major societies regarding mitral valve surgery (conventional or percutaneous) are weak because the current evidence is inconsistent on whether mitral valve surgery produces a clinical benefit in patients with secondary MR. A RCT comparing the safety and effectiveness of MitraClip (COAPT trial) in patients with secondary MR is currently underway and is expected to be completed in 2024. The evidence is insufficient to determine the effects of the technology on health outcomes.

### ***Primary or Secondary MR Not at Risk for Surgery***

For individuals who have symptomatic primary or secondary MR and are surgical candidates who receive TMVR using MitraClip, the evidence includes a systematic review and an RCT. Relevant outcomes are overall survival, 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 1 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.

### **Devices Other Than MitraClip**

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 overall survival, 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, input was received from 4 academic medical centers, one of which provided 4 responses, for a total of 7 responses, while this policy was under review 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 released guidelines on the management of valvular heart disease in 2017.<sup>33</sup> Table 9 provides the relevant recommendations.

**Table 9. Recommendations on Primary and Secondary MR**

Recommendation	SOR	LOE
<b>Primary MR</b>		
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	I Ib	B
<b>Secondary MR</b>		
Mitral valve surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR.	I Ib	B
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.	I Ib	B-R

AVR: aortic valve replacement; B-R: moderate-quality evidence; CABG: coronary artery bypass grafting; GDMT: guideline-directed medical therapy; HF: heart failure; MR: mitral regurgitation; NYHA: New York Heart Association; LOE: level of evidence; SOR: strength of recommendation.

The American College of Cardiology, American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons issued a position statement on transcatheter therapies for mitral regurgitation (MR) in 2014.<sup>45</sup> 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

In 2017, the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery released joint guidelines on the management of valvular heart disease (see Table 10).<sup>46</sup>

**Table 10. Recommendations on Management of Valvular Heart Disease**

Recommendation	SOR	LOE
<b>Primary MR</b>		
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 fertility.	I Ib	C
<b>Secondary MR</b>		
"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 'optimal' medical therapy according to current guidelines has not yet been proven."	a	a

LOE: level of evidence; LV: left ventricular; SOR: strength of recommendation.

<sup>a</sup> No specific recommendations.

## U.S. Preventive Services Task Force Recommendations

Not applicable.

## Medicare National Coverage

In April 2015, the Centers for Medicare & Medicaid Services issued a national coverage decision for the use of transcatheter mitral valve repair (TMVR).<sup>47</sup>

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. 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:
    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;
  - f. The cardiothoracic surgeon(s) must be board-certified in thoracic surgery or similar foreign equivalent.
4. The heart team[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 1 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 11.

**Table 11. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<b>Ongoing</b>			
<b>NCT01920698</b>	Multicentre Randomized Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR)	288	Oct 2017
<b>NCT02444338</b>	A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation	380	Sep 2019
<b>NCT01626079</b>	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (The COAPT Trial)	610	July 2024

NCT: national clinical trial.

<sup>a</sup> Denotes industry-sponsored or cosponsored trial.

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## **Billing Coding/Physician Documentation Information**

- 0483T** Transcatheter mitral valve implantation/replacement (TMVI) with prosthetic valve; percutaneous approach, including transseptal puncture, when performed
- 0484T** Transcatheter mitral valve implantation/replacement (TMVI) with prosthetic valve; transthoracic exposure (eg, thoracotomy, transapical)
- 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)
- 93590** Percutaneous transcatheter closure of paravalvular leak; initial occlusion device, mitral valve (new code 1/1/2017)
- 93592** Percutaneous transcatheter closure of paravalvular leak; each additional occlusion device (List separately in addition to code for primary procedure) (new code 1/1/2017)
- 0345T** Transcatheter mitral valve repair percutaneous approach via the coronary sinus

### **ICD-10 Codes**

- I01.1;** Rheumatic mitral valve insufficiency code list
- I02.0;**
- I05.1;**
- I05.2;**
- I08.0;**
- I08.1;**

**I08.3**

**I34.0-** Nonrheumatic mitral valve disorders code range (I34.0 is mitral valve  
**I34.9** regurgitation)

Category III codes 0343T and 0344T were deleted effective 12/31/14 and replaced with Category I codes.

**Additional Policy Key Words**

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MitraClip

**Policy Implementation/Update Information**

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- 9/1/14 New Policy; considered investigational.
- 10/1/15 Notated that CPT 0343T, 0344T were deleted as of 12/31/14. No policy statement changes.
- 12/1/15 Transcatheter mitral valve repair considered medically necessary for degenerative mitral regurgitation in patients at prohibitive surgical risk.
- 10/1/16 No policy statement changes.
- 10/1/17 "Cleared" changed to "approved" in the medically necessary policy statement.
- 8/1/18 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. The rationale subsection that jointly addressed symptomatic degenerative or functional mitral regurgitation patients at prohibitive risk for open surgery was rewritten to separate primary from secondary mitral regurgitation patients at prohibitive risk for open surgery. Reports on multiple subgroup analyses and systematic reviews using the EVEREST II HRR and REALISM and other European/Non-European studies/registries were deleted from the Rationale. Data from FDA documents were added.
- 10/1/18 No policy statement changes.

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