Transcatheter Mitral Valve Repair

Policy Number: 2.02.30  Last Review: 10/2016
Origination: 9/2014  Next Review: 10/2017

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 cleared by the Food and Drug Administration for use in mitral valve repair may be considered medically necessary for patients with symptomatic, degenerative 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.

Description of Procedure or Service

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
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<td>Individuals:</td>
<td>Interventions of interest are:</td>
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<td>Relevant outcomes include:</td>
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<td>• With symptomatic DMR or FMR who are</td>
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DMR: degenerative mitral regurgitation; FMR: functional mitral regurgitation; MV: mitral valve.
Transcatheter mitral valve repair is a potential alternative to surgical therapy for mitral regurgitation. Mitral regurgitation is a common valvular heart disease that can result from either a primary structural abnormality of the mitral valve complex or a dilated left ventricle due to ischemic or dilated cardiomyopathy, which leads to secondary dilatation of an anatomically normal mitral valve. Surgical therapy may be underutilized, particularly in patients with multiple comorbidities, suggesting that there is an unmet need for less invasive procedures for mitral valve repair. One device, MitraClip, has approval from the U.S. Food and Drug Administration (FDA) for the treatment of severe symptomatic MR due to a primary abnormality of the mitral valve (MV) (degenerative mitral regurgitation [DMR]) in patients who are considered at prohibitive risk for surgery.

For individuals who have symptomatic DMR or functional mitral regurgitation (FMR) who are at prohibitive risk for open surgery who receive TMVR with MitraClip, the evidence includes primarily single-arm cohort studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related morbidity. The evidence for the use of MitraClip among patients who are not considered surgical candidates consists primarily of single-arm cohort studies. The available single-arm studies include the pivotal EVEREST II High Risk Registry (HRR) study and the EVEREST II Real World Expanded Multi-center Study of the MitraClip System (REALISM). These studies have demonstrated that MitraClip implantation is feasible, with high rates (on the order of at least 70% to 90%) of short-term reductions in MR grade to 2+ or less, and has a reasonable safety profile. A nonrandomized analysis matching patients in the EVEREST registries to similar nonsurgically treated patients found significantly lower 1-year morality rates in MitraClip-treated patients. However, the lack of concurrent control groups, especially in randomized trials, makes it difficult to draw conclusions about whether there is a net health benefit compared with alternative therapies in this population. There are no strong barriers to conducting controlled trials, including RCTs comparing MitraClip to continued medical management. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input supported the use of TMVR in patients with DMR considered at a prohibitive risk for open surgery, which is the FDA-approved indication for the MitraClip device. Given the lack of other treatment options for this population, the suggestive clinical evidence, and the support from clinical input, TMVR with the MitraClip may be considered medically necessary for this patient population.

For individuals who have symptomatic DMR or FMR who are surgical candidates who receive TMVR with MitraClip, the evidence includes 1 RCT (EVEREST II) and multiple comparative and noncomparative cohort studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related morbidity. The evidence for the use of MitraClip in patients who are considered candidates for open MV repair surgery includes 1 RCT (EVEREST II) and multiple comparative and noncomparative cohort studies. The most rigorous evidence related to MitraClip’s efficacy is from EVEREST II, which found that, for 1-year outcomes, MitraClip was noninferior to open surgery in terms of safety and effectiveness. At the 5-year follow-up, efficacy as assessed by a composite
outcome, was significantly higher in the surgery group than the MitraClip group. In EVEREST II, most patients who had persistent MV dysfunction after MitraClip developed it within the first year postprocedure and, among patients event-free at 1 year, 5-year efficacy was not significantly different in the MitraClip and surgery groups. The EVEREST II trial had some methodologic limitations. The noninferiority margin of 25% was large, indicating that MitraClip could be somewhat inferior to surgery and the noninferiority margin still met. Crossover to surgery was allowed for patients who had grade 3+ or more MR prior to discharge, and 23% of patients assigned to MitraClip met this criterion. This large rate of crossover would bias results toward the null on intention-to-treat 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. As a result of these factors, this single trial is not definitive in demonstrating improved clinical outcomes with MitraClip compared with surgery. Additional RCTs are needed to corroborate these results. A subsequent nonrandomized controlled trial, though not the optimal study design and with missing data, did not find the same low rates of long-term MR control in MitraClip patients who had an initial positive response to treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have DMR or FMR who receive TMVR with 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. 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 individuals over age 75 years and accounting for 24% of all patients with valvular heart disease.(1) MR can result from a heterogeneous set of disease processes that may affect one or more parts of the mitral valve (MV) complex. The functional anatomy of the MV complex includes the left ventricular (LV) myocardium, the subvalvular apparatus including the papillary muscles and chordae tendineae, the mitral annulus, the MV leaflets, and the left atrium.(2) The underlying cause of MR and the portion of the MV complex involved determine the underlying treatment strategy.

MR is classified into degenerative and functional MV disease. In degenerative MR (DMR), disease results from a primary structural abnormality of the MV complex. Common causes of degenerative MR include mitral valve prolapse syndrome with subsequent myxomatous degeneration, rheumatic heart disease, coronary artery disease, infective endocarditis, and collagen vascular disease.(3) In contrast, in
functional MR (FMR), the primary abnormality is a dilated left ventricle due to ischemic or dilated cardiomyopathy, which leads to secondary dilatation of an anatomically normal mitral valve. MR severity is classified into mild, moderate, and 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 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. MR can be acute or chronic. Acute MR can result from conditions such as ruptured chordae tendineae or infectious endocarditis, and when severe, can present with simultaneous shock and pulmonary congestion. Chronic MR may remain asymptomatic over a long period of time due to compensatory LV hypertrophy secondary to the LV overload. This leads to increased LV end-diastolic volume and, in turn, increased stroke volume (to restore forward cardiac output) and increased LV and left atrial size (to accommodate the regurgitant volume at lower filling pressure). Eventually, prolonged volume overload leads to contractile dysfunction, with increased end-systolic volume, further LV dilatation and increased LV filling pressure. These changes ultimately leading to reduced forward cardiac output and signs and symptoms of pulmonary congestion.

Mitral Regurgitation – Standard Management

**Medical management.** Medical management has role in a subset of MR cases. Among patients with chronic DMR, there is no generally accepted medical management. In FMR, medical management plays a much greater role given that the underlying pathophysiology is related to LV dysfunction and dilatation. Primary treatment of the LV systolic dysfunction with ACE inhibitors, beta blockers, and biventricular pacing can reduce LV pressures, decrease LV dilatation, improve cardiac output, and thus ameliorate clinical symptoms. Medical management has role in a subset of MR cases. Among patients with chronic DMR, there is no generally accepted medical management. In FMR, medical management plays a much greater role given that the underlying pathophysiology is related to LV dysfunction and dilatation. Primary treatment of the LV systolic dysfunction with ACE inhibitors, beta blockers, and biventricular pacing can reduce LV pressures, decrease LV dilatation, improve cardiac output, and thus ameliorate clinical symptoms.

**Surgical management.** In patients with symptoms of MR with preserved LV function (degenerative MR), surgery is the mainstay of therapy. In most cases, repair of the MV 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 (ACC) and the American Heart Association (AHA) have issued joint guidelines for the surgical management of MV, which are outlined as follows:

- MV surgery is recommended for the symptomatic patient with acute severe MR.
- MV surgery is beneficial for patients with chronic severe MR and New York Heart Association (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.
- 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.
• 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.

• MV repair is also reasonable for asymptomatic patients with chronic severe MR with preserved LV function who have a high likelihood of successful MV repair, who have new onset atrial fibrillation, or who have pulmonary hypertension, and in patients with chronic severe MR with NYHA functional class III-IV symptoms and severe LV dysfunction who have chronic severe MR due to a primary abnormality of the mitral apparatus and have a high likelihood of successful MV repair.

MV repair has classically been undertaken with a quadrangular leaf resection (if mitral valve prolapse is present), transposition of normal valve chords to other areas of prolapsing leaflet, and a remodeling annuloplasty with a ring prosthesis. Multiple types of annuloplasty rings and bands that are specific to the underlying cause of the MR are commercially available. In the 1990s, the edge-to-edge approximation technique (Alfieri repair) was introduced. Typically combined with an annuloplasty, the Alfieri repair involves suturing the anterior and posterior MV leaflets together at their midpoint, creating a double-orifice mitral valve.

However, there are limitations to the standard approaches for MV surgery. While surgical MV repair is typically durable, its use is limited by the requirement for thoracotomy and cardiopulmonary bypass, which is particularly a concern among patients who are elderly or debilitated due to their underlying cardiac disease or other conditions. In a 2007 study of 396 patients in Europe with severe, symptomatic MR, Mirabel et al found that about half of patients did not undergo surgical repair. Fifty-six percent and 32% of patients with DMR and FMR, respectively, did not undergo surgery. Older age, impaired LV ejection fraction, and presence of comorbidities were all associated with the decision not to operate. In a single-center evaluation of 5737 patients with severe MR in the US, Goel et al found that 53% of patients did not have MV surgery performed. Compared with those who received surgery, patients who did not receive surgery had lower ejection fractions (27 vs 42, p<0.0001) and were of higher surgical risk, as judged by a higher Society for Thoracic Surgeons score (median 5.8 vs 4.0, p<0.001). These findings suggest that there is an unmet need for less invasive procedures for MV repair.

Transcatheter Mitral Valve Repair

Transcatheter approaches have been investigated to address the unmet need for less invasive MV repair, particularly among patients who face prohibitively high surgical risks due to their ages or comorbidities. MV repair devices under development address various components of the mitral valve complex and generally are performed on the beating heart without the need for cardiopulmonary bypass. Approaches to MV repair include direct leaflet repair; repair of the mitral annulus via direct annuloplasty or through indirect approaches 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 mitral valve replacement via catheter.

Direct Leaflet Approximation
One device that undertakes direct leaflet repair, the MitraClip® Clip Delivery
System (Abbott Vascular, Menlo Park, CA), has approval through the Food and
Drug Administration (FDA) premarket approval process for use in certain patients
with symptomatic MR (see "Regulatory Status" section below). Of the
transcatheter MV repair devices under investigation, the MitraClip has the largest
body of evidence evaluating its use and has been in use in Europe since 2008.(9)
The MitraClip system is a percutaneously-deployed device that approximates the
open Alfieri edge-to-edge repair approach to treating MR. The delivery system
consists of a delivery catheter, a steerable sleeve and the MitraClip device, which
is a 4-mm wide clip fabricated from a cobalt-chromium alloy and polypropylene
fabric. The MitraClip is deployed via a transfemoral approach, with transseptal
puncture used to access the left side of the heart and the mitral valve. Placement
of the MitraClip leads to coapting of the mitral leaflets, thus creating a double-
orifice valve.

Other MV Repair Devices
Additional devices for transcatheter mitral valve repair that use various
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 Inc., Kirkland, WA) and the Monarc™ device
(Edwards Lifesciences, Irvine, CA). 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 has been evaluated in the
AMADEUS (Carillon Mitral Annuloplasty Device European Union Study and the
follow up TITAN (Tighten the Annuus Now) study, with further studies
planned.(10) 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 end in the great cardiac vein. Several weeks
following implantation, a biologically degradable coating over the nitinol bridge
degrades, allowing the bridge to shrink and the system to shorten. It has been
evaluated in the EVOLUTION I (Clinical Evaluation of the Edwards Lifesciences
Percutaneous Mitral Annuloplasty System for the Treatment of Mitral
Regurgitation) trial.(11)

Direct annuloplasty devices include the Mitralign Percutaneous Annuloplasty
System (Mitralign, Tewksbury, MA) and the Accucinch® System (Guided Delivery
Systems, Santa Clara, CA), both of which involve transcathether placement of
anchors in the mitral valve which are cinched or connected to narrow the mitral
annulus. Other transcutaneous direct annuloplasty devices under investigation
include the enCorTC™ device (Micardia Corporation, Irvine, CA), which involves a
percutaneously insertable annuloplasty ring that is adjustable using radiofrequency energy, a variation on its CE-marked enCorsq™ Mitral Valve Repair System, and the Cardioband™ Annuloplasty System (Valtech Cardio Ltd., Or- Yehuda, Israel), an implantable annuloplasty band with a transfemoral venous delivery system.

Transcatheter MV Replacement
Several devices are under development for transcathether mitral valve replacement, including the Endovalve™ (MicroInterventional Devices, Inc., Langhorne, PA), the CardiAQ™ (CardiAQ Valve Technologies, Inc., Irvine, CA) valve, and the Cardiovalve (Valtech Cardio Ltd., Or- Yehuda, Israel), Israel), and the Fortis Transcathether Mitral Valve (Edwards Lifesciences, Irvine, CA).

Regulatory Status
In October 2013, the MitraClip® Clip Delivery System received FDA approval through the premarket approval process. The device received approval 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.”(12)

The FDA’s approval was based on data from one randomized, controlled trial (RCT) and two patient registry databases.(9, 12) In the Endovascular Valve Edge-to-Edge Repair (EVEREST) II RCT, patients with severe, symptomatic MR were randomized to endovascular repair with the MitraClip or to open surgical repair. Concurrent with the EVEREST II RCT, study sponsors prospectively collected data from patients who were determined to be at prohibitively high surgical risk to be eligible for randomization but who underwent MitraClip placement, the EVEREST II High Risk Registry (HRR). After the EVEREST II RCT, study sponsors evaluated a second cohort of patients with symptomatic MR who underwent MitraClip placement through the Real World Expanded Multicenter Study of the MitraClip System (REALISM) registry.

Rationale
This evidence review was created in July 2014 based, in part, on a 2014 TEC Assessment that evaluated the use of transcathether mitral valve repair (TMVR) in patients with symptomatic degenerative mitral regurgitation (DMR) who are at prohibitive risk for mortality during open surgery and determined that the procedure did not meet TEC criteria.13 The evidence review has been updated periodically with literature reviews through searches of the MEDLINE database. The most recent update covered the period through March 30, 2016.

The literature search for this evidence review focused primarily on studies evaluating MitraClip, but evidence related to other devices is discussed. Assessment of efficacy for therapeutic interventions such as MitraClip involves a determination of whether the intervention improves health outcomes. The optimal study design for this purpose is a randomized controlled trial (RCT) that includes clinically relevant measures of health outcomes. Intermediate outcome measures,
also known as surrogate outcome measures, may be adequate if there is an
established link between the intermediate outcome and true health outcomes.
Nonrandomized comparative studies and uncontrolled studies can sometimes
provide useful information on health outcomes, but are prone to biases. For
MitraClip, the appropriate comparison group could be either open surgical repair
(for surgical candidates) or best medical therapy (among persons at prohibitive
surgical risk).

There are 2 major categories of patients with mitral regurgitation (MR) who are
potential candidates for TMVR: those who are considered to be at prohibitively
high risk for cardiac surgery and those considered surgical candidates. Studies
addressing these 2 subsets of patients are outlined separately. Although outcomes
and etiology differ for functional mitral regurgitation (FMR) and DMR, studies on
MitraClip most often evaluate the device in mixed populations. The MitraClip
device delivery system was approved by the Food and Drug Administration (FDA)
for use in DMR who are not candidates for open surgery.

**MitraClip in Prohibitive Surgical Risk Candidates**

**Systematic Reviews and Meta-Analyses**

A 2014 TEC Assessment evaluated the evidence on the use of MitraClip for DMR,
the FDA-approved indication. The Assessment included 5 case series reporting
outcomes of patients with DMR considered at high risk of surgical mortality who
underwent MitraClip placement. In the 2 studies the Assessment considered higher
quality, 30-day mortality rates were 6.0% and 6.3%, and 12- to 25-month
mortality rates were 17.1% and 23.6%, respectively. In evaluable patients at 12
months, the percentage of patients who had an MR grade of 2 or less was 83.3%
and 74.6% in the 2 studies; the percentage of patients with New York Heart
Association (NYHA) class I or II functional status was 81% and 87%; and
improvement of at least 1 NYHA class was present in 68% and 88% of patients,
respectively. Table 1 (adapted from the TEC Assessment) summarizes health
outcomes for the 5 studies that the Assessment reviewed.

**Table 1: Health Outcomes at 12 Months of Case Series of Studies of
MitraClip for Patients With Degenerative Mitral Valve Disease**

<table>
<thead>
<tr>
<th>Study</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 Assessed at 12 Months</th>
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</thead>
<tbody>
<tr>
<td>Lim et al (2014)</td>
<td>127</td>
<td>MR ≤2+, 83.3% (70/84)</td>
<td>NYHA I/II, 86.9% (73/84)</td>
<td>SF-36 PCS score change, 6.0 (95% CI, 4.0 to 8.0), n=76</td>
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<td></td>
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<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>
</tr>
<tr>
<td>Reichenspurner et al</td>
<td>117</td>
<td>MR ≤2+, 74.6% (53/71)</td>
<td>NYHA I/II, 81% (63/78)</td>
<td>Change in MLHFQ from baseline, 13.3 points (p=0.03), n=44</td>
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<tr>
<td>(2013)</td>
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<td>Improved ≥1 class, 68% (53/78)</td>
<td>Change in 6MWT from baseline, 77.4 m</td>
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</tbody>
</table>
Study | Original N | MR Grade at 12 Months, % (n/N) | NYHA Class at 12 Months, % (n/N) | Other Pertinent Outcomes Assessed at 12 Months
---|---|---|---|---
Estévez-Loureiro et al (2013) | 79 | NR | NR | (p<0.001), n=52
Grasso et al (2013) | 28 | NR | NR | Kaplan-Meier estimate of freedom from death, surgery, or ≥3+ MR, 70% (visual estimate from graph)
Chan et al (2012) | 15 | MR severity, 1.9<sup>a</sup> | NYHA class, 2.1<sup>a</sup>

Adapted from the TEC Assessment.

CI: confidence interval; MCS: Mental Component Summary; MLHFQ: Minnesota Living with Heart Failure 10 Questionnaire; MR: mitral regurgitation; NR: not reported; NYHA: New York Heart Association; PCS: Physical Component Summary; 6MWT: Six-Minute Walk Test; SF-36: 36-Item Short-Form Health Survey.

<sup>a</sup>Values are mean. Sample sizes unknown.

The Assessment reviewed the evidence on the natural history of patients with MR who were considered at high risk for surgery in an attempt to determine an appropriate comparison group for the uncontrolled case series of MitraClip in high surgical risk patients. The evidence included 1 published study by Whitlow et al and data presented to FDA as part of the device’s premarket approval application. The TEC Assessment concluded that these control groups may not provide unbiased or precise estimates of the natural history of patients who are eligible to receive MitraClip because most patients were either not evaluated for anatomic eligibility for MitraClip or were ineligible. As such, the control groups are likely to have higher mortality rates than patients eligible to receive MitraClip.

Due to the lack of an appropriate control group or clear evidence about the natural history of patients with DMR considered at high risk for surgery, the Assessment concluded that it cannot be determined whether the mortality rate associated with MitraClip use is improved, equivalent, or worse than medical treatment.

Also in 2014, Philip et al reported results of a systematic review of studies evaluating MitraClip or surgical mitral valve (MV) repair or replacement for severe symptomatic MR in patients at high surgical risk (logistic EuroSCORE >18 or Society for Thoracic Surgeons [STS] score >10). The review included 21 studies that used MitraClip (n=3198 patients) and surgical MV repair (n=490) or MV replacement (n=2775). MitraClip patients had a mean STS score of 14 and a mean EuroSCORE of 23. Acute procedural success did not differ significantly between groups. However, the 30-day pooled technical failure rate was 3.2% (95% confidence interval [CI], 1.5% to 7%) for MitraClip patients, compared with 0.6% (95% CI, 0.2% to 1.8%) for surgical repair/replacement patients (p=0.002). In pooled analysis, the 30-day mortality rate was 3% (95% CI, 2.6% to 4.2%) among MitraClip patients and 16% (95% CI, 13% to 20%) in surgical repair/replacement patients. Of the total sample, 1-year data were available for 1064 MitraClip patients (1-year data for surgical repair patients, limited to 47.
patients, was not reported). Overall, among MitraClip patients, the 1-year mortality rate was 13.0% (95% CI, 9% to 18.3%), the 1-year stroke rate was 1.6% (95% CI, 0.8% to 3.2%), and the need for repeat MV surgery was 1.3% (95% CI, 0.7% to 2.6%).

A systematic review by Munkholm-Larsen et al published in 2014 summarized safety and efficacy results from 12 publications evaluating the efficacy of MitraClip in surgically high-risk patients. The authors included studies that evaluated high-risk surgical patients with significant MR who underwent TMVR with the MitraClip device, and excluded studies with surgical candidates. All studies were prospective, observational studies from specialized tertiary centers, with 3 multicenter studies and 9 single-institution studies. The 3 largest studies included 202, 117, and 100 patients, respectively, while the rest included fewer than 100 patients. Follow-up duration ranged from 1 month to 14 months. Across the studies, 30-day mortality rates ranged from 0% to 7.8%. Most of the high surgical risk patients had successful reduction of MR of grade 2+ or less (73%-100% across studies). In studies that reported follow-up at 6 to 12 months, 61% to 99% of patients demonstrated continued MR reduction of grade 2+ or less, and 50% to 89% of patients demonstrated improvements in NYHA functional class to I to II. This systematic review suggests that MitraClip is associated with short-term improvements in echocardiographic parameters among high surgical risk patients, but does not provide evidence on clinical outcomes. Longer term follow-up studies are limited. In addition, most studies included both FMR and DMR, which limits the ability to assess outcomes stratified by etiology.

Several systematic reviews have focused on safety of MitraClip. In 2015, Bail et al reported results of a systematic review and meta-analysis of the safety and efficacy of MitraClip placement, which included 26 studies (3821 patients). Within the first 30 days postprocedure, 3.5% (95% CI, 2.9% to 4.2%) required open MV repair, 18.3% (95% CI 17.0% to 19.6%) experienced an adverse event, and 2.8% (95% CI, 2.3% to 4.4%) died. At 6 months, 4.5% (95% CI, 15.1% to 24.1%) required open MV repair, 18.9% (95% CI, 15.1% to 24.1%) experienced an adverse event, and the all-cause mortality rate was 11.9% (95% CI, 10.3 to 14.2%). By 12 months, 11.4% (95% CI, 9.6% to 13.5%) required open repair, and the all-cause mortality rate was 17.4% (95% CI, 15.1% to 18.9%).

In 2014, Vakil et al reported results of a systematic review of the safety and efficacy of the MitraClip system for moderate-to-severe or severe FMR or DMR; it included 16 studies (total N=2980 patients). Based on calculated STS score, EuroSCORE, or the surgeon’s discretion, 2689 patients in 14 studies were considered high risk for surgery and 291 patients in 2 studies were considered low risk for surgery. The pooled 30-day mortality rate (primary safety outcome) was 4.2%. During a mean follow-up of 310 days (range, 80 days to 4 years), 387 (15.8%) of 2457 deaths occurred. In the 8 studies reporting the cause of death, the pooled incidence of cardiac mortality was 3.7%.
Randomized Controlled Trials
No RCTs have been published evaluating MitraClip in prohibitive surgical risk populations.

Nonrandomized Comparative Studies
In 2014, Swaans et al reported results of a study comparing survival for MR patients considered at high surgical risk who underwent MitraClip placement with high-risk patients who had conservative management and with patients who had surgical repair. MitraClip-treated patients (n=139) included those treated at a single institution with MitraClip for symptomatic MR whose high surgical risk was based on a logistic EuroSCORE of at least 20, or who were denied surgery based on additional factors associated with increased mortality, as judged by the heart team. These patients were compared with a retrospectively defined cohort of patients with MR and indications for MV repair treated at the same institution in the 2 years prior to MitraClip availability who were treated with either conservative management (n=59) or open surgery (n=38). At baseline, patients treated with MitraClip had a higher logistic EuroSCORE than the other 2 groups (23.9 with MitraClip vs 14.2 with surgical repair vs 18.7 with conservative treatment; p<0.001). Rates of coronary artery disease and previous coronary artery bypass grafting were higher in the MitraClip group as well. At 1-year follow-up, survival rates were 85.8%, 82.2%, and 67.75% in the MitraClip, open surgery, and conservatively treated groups, respectively. Survival rates for the TMVR group were 75.5% and 62.3% after 2 and 3 years, respectively.

Single-Arm Studies
Evidence on the use of MitraClip in high surgical risk patients in practice is available through a number of single-arm cohort studies, including the pivotal EVEREST II High Risk Registry (HRR) study and the EVEREST II Real World Expanded Multi-center Study of the MitraClip System (REALISM) study, which included non-high-risk and high-risk arms in the United States. In addition, several single-arm cohort studies have reported experience with MitraClip in European centers, because the device has been CE marked for use in Europe since 2008. The EVEREST registry studies are described next.

EVEREST High-Risk Registries
Concurrent with the EVEREST II RCT, described in a subsequent section of the review, investigators enrolled patients into the EVEREST II HRR study who were deemed ineligible for surgery due to prohibitively high surgical risks. In addition, a continued access study (EVEREST II REALISM), which included a high-risk and a non-high-risk arm, was conducted. For inclusion in the EVEREST II HRR, patients were considered high surgical risk if either their STS predicted operative mortality risk was 12% or higher or the surgeon investigator determined the patient to be high risk (≥12% predicted operative mortality risk) due to the presence of 1 of several prespecified risk factors. Patients were excluded from the registry if they had left ventricular ejection fraction (LVEF) less than 20%, left ventricular end-systolic diameter (LVESD) greater than 60 mm, MV orifice area less than 4 cm², or leaflet anatomy that might preclude MitraClip device implantation and/or proper
MitraClip device positioning and/or sufficient reduction in MR. The REALISM registry high-risk arm had the same inclusion criteria as the EVEREST II HRR.

In 2014, Lim et al published outcomes from TMVR with MitraClip among high surgical risk patients with DMR who were included in the EVEREST II HRR and REALISM registries. For this analysis, prohibitive risk for surgical repair of DMR was defined as the presence of 1 or more of the following documented surgical risk factors: STS Risk Calculator predicted risk of 30-day mortality for MV replacement of 8% or greater, porcelain aorta or extensively calcified ascending aorta, frailty (assessed by ≥2 indices), hostile chest, severe liver disease or cirrhosis, severe pulmonary hypertension, severe pulmonary hypertension, or an “unusual extenuating circumstance” (eg, RV dysfunction with severe tricuspid regurgitation, chemotherapy for malignancy, major bleeding diathesis, AIDS, severe dementia).

One hundred forty-one patients with severe (≥3+) DMR who met the definition of prohibitive surgical risk were identified, 127 of whom had follow-up data available at 1 year. Of these, 25 patients were from the EVEREST II HRR, 98 were from the high-risk arm of the EVEREST REALISM study, and 4 were treated under compassionate use and met the definition of prohibitive risk and all MV anatomic criteria for entry. At baseline, patients had poor functional status, with 87% in NYHA functional status class III or IV.

MitraClip was successfully placed in 95.3% of patients. Thirty-day and 12-month mortality rates were 6.3% and 23.6%, respectively. MitraClip reduced MR to grade 2+ or less in 86.1% of patients with baseline MR of 3+ and in 68.4% of patients with baseline MR of 4+. Fifty-eight percent of patients with grade 3+ MR at baseline and 36.8% of patients with grade 4+ MR at baseline had MR reduced to 1+. Of 91 patients who had procedural reduction of MR to grade 2+ or less, 64 (70.3%) patients had sustained MR grade 2+ or less at 1 year, 10 (11.0%) experienced worsening MR to grade 3+ or 4+, and 17 (18.7%) died. Of 59 patients who had a procedural reduction of MR to grade 1 or less, 21 (35.6%) patients had sustained MR of grade 1+ or less at 1 year, 20 (33.9%) had an increase in MR grade to 2+, 8 (13.6%) had an increase in MR grade to 3+ or 4+, and 10 (16.9%) died. There were no significant differences in 12-month survival between those who were discharged with an MR grade of 1+ or less compared with those with an MR grade of 2+. At 1 year, 30.6% of the 98 patients with baseline NYHA functional class III or IV had an improvement of at least 2 classes. In this high surgical risk population, MitraClip use was associated with a relatively low rate of procedural complications and a high rate of short-term improvements in MR grade to 2+ or less, along with improvements in functional status. However, a major limitation of this trial is the lack of a control group. In addition, the cohort of high-risk patients with DMR was retrospectively identified, so all analyses were post hoc. There are questions about the validity of combining registry data from 2 separate registries that were collected over different time periods, along with the consistency of the inclusion criteria measures, because the STS Risk Calculator changed over time.

In 2014, Glower et al reported 12-month results for MitraClip use in the first 351 patients enrolled in either the Everest HRR (n=78) or high-risk patients in the
REALISM study (n=273), which had previously been presented to FDA. Seventy percent of patients had FMR. Following MitraClip implantation, 325 (86%) patients had MR reduced 2+ or less. At 12 months, 225 (84%) patients had MR of grade 2+ or less. By Kaplan-Meier analysis, survival at 12 months was 77.2%. Patients had improvements in quality of life scores and NYHA functional class.

In 2015, Velasquez et al published an industry-sponsored analysis comparing outcomes in patients from the Everest HRR and Everest REALISM registries who were matched with patients who were treated nonsurgically. The investigators used propensity score matching to create groups with characteristics as similar as possible. In the optimal matched cohorts (239 high-risk MitraClip patients, 239 high-risk nonsurgical patients), baseline characteristics were similar for all but 3 variables: MR etiology, LV internal dimensions, and STS score. Among patients in the optimally matched cohorts, Kaplan-Meier 1-year mortality estimates were significantly lower in the MitraClip group (22.4%) than in the nonsurgical control group (32.0%; adjusted hazard ratio [HR], 0.66; 95% CI, 0.45 to 0.99). Thirty-day mortality in the optimally matched cohorts was 4.2% in the MitraClip group and 7.2% in the nonsurgical group (HR and p value not reported).

Section Summary: MitraClip in Prohibitive Surgical Risk Candidates
The evidence for the use of MitraClip among patients who are not considered surgical candidates consists primarily of single-arm cohort studies. The available single-arm studies include the pivotal EVEREST II HRR and EVEREST II REALISM trials. These studies demonstrate that MitraClip implantation is feasible, with high rates (on the order of at least 70% to 90%) of short-term reductions in MR grade to 2+ or less, and has a reasonable safety profile. An analysis matching patients in the EVEREST registries to similar nonsurgically treated patients found significantly lower 1-year mortality rates in MitraClip-treated patients. However, the lack of concurrent control groups, especially those randomized to intervention, makes it difficult to draw conclusions whether there is a net health benefit compared with alternative therapies in this population. There are no strong barriers to conducting controlled trials, including RCTs comparing MitraClip to continued medical management.

MitraClip in Surgical Candidates
Systematic Reviews and Meta-Analyses
Four studies (1 RCT, described below, and 3 prospective observational studies) comparing MitraClip with surgery were summarized in a 2013 systematic review and meta-analysis by Wan et al. Across all studies, age was significantly higher in groups receiving MitraClip than those receiving surgery (weighted mean difference [WMD], 7.22; 95% CI, 1.75 to 12.70; p=0.01). In the 3 studies that reported logistic EuroSCORE, scores were significantly higher in the MitraClip group (WMD=14.25; 95% CI, 7.72 to 20.79; p<0.001). The proportion of patients with residual MR greater than grade 2 was significantly higher in the MitraClip group (17.2% vs 0.45%; odds ratio [OR], 20.72; 95% CI, 4.91 to 87.44; p<0.001). Thirty-day mortality, rates of NYHA functional class III or IV at 12 months, and 12-month mortality did not differ significantly between the MitraClip
and the surgical groups. Overall, the Wan analysis suggested that, despite baseline higher age and surgical risk, patients receiving MitraClip for MR have mortality and functional outcomes comparable to those receiving open surgery, but have higher rates of persistent MR. However, as the authors noted, the conclusions were limited by lack of subgroup analyses comparing outcomes for those with DMR and FMR and lack of consistent definitions of success across studies.

Randomized Controlled Trials
One RCT evaluating MitraClip in patients who are surgical candidates has been published. This trial, EVEREST II, was a pivotal multicenter designed to evaluate the efficacy of TMVR with MitraClip compared with open MV repair. Eligible patients had grade 3+ or 4+ MR and were all candidates for MV repair surgery. Symptomatic patients were required to have LVEF of more than 25% and a LVESD of 55 mm or less; asymptomatic patients were required to have at least 1 of the following: LVEF of 25% to 60%; LVESD of 40 to 55 mm; new atrial fibrillation; or pulmonary hypertension. 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. Two hundred seventy-nine patients were randomized 2:1 to transcatheter repair (184 patients) or standard MV surgery (95 patients).

The composite primary safety end point was major adverse events at 30 days, defined as freedom from death, myocardial infarction, nonelective cardiac surgery for adverse events, renal failure, transfusion of 2 or more units of blood, reoperation for failed surgery, stroke, gastrointestinal complications requiring surgery, ventilation for 48 or more hours, deep wound infection, septicemia, and new onset of permanent atrial fibrillation. The composite primary efficacy end point was freedom from MR at 2+ or higher, freedom from cardiac surgery for valve dysfunction, and survival beyond 12 months.

MitraClip was considered to have acute procedural success if the clip deployed and MR grade was reduced to less than 3+. The protocol’s safety and efficacy analyses were reported on both an intention-to-treat (ITT) and a per-protocol basis. In the ITT analyses presented in the main article, crossover to surgery in the immediate postprocedure period if MitraClip failed to adequately reduce MR was considered a successful treatment strategy. Thus, in the ITT analysis, for patients who did not have acute procedural success (and may have undergone 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.

For patients who did have acute procedural success, the efficacy end point was considered met for MitraClip group subjects if they were free from death, any MV surgery for MR, and MR greater than 2+ at 12 months. The study 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 is noninferior to surgery at 12 months if the rate of the primary efficacy end point for the MitraClip group is not
more than 25 percentage points less than that in the surgery group (for the ITT analysis).

The treatment groups were generally similar, except that a higher proportion of those in the MitraClip group had congestive heart failure (91% [167/184] vs 78% [74/95], p=0.005). Of 178 patients who were randomized to the MitraClip group and who did not withdraw from the study, 41 (23%) had grade 3+ or 4+ MR before hospital discharge and were referred for immediate surgery, which was performed in 28.

On an ITT basis, the study’s primary combined efficacy end point (rates of freedom from death, MV surgery, and grade 3+/4+ MR at 12 months), was 55% in the MitraClip group and 73% in the surgery group (noninferiority, p=0.007). Rates of death and grade 3+ or 4+ MR at 12 months postprocedure were similar between groups; however, 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 grade 3+ or 4+ MR at 12 months were similar between groups, in the study’s per-protocol analysis patients in the MitraClip group were more likely to have grade 3+ or 4+ MR (17.2% [23/134] vs 4.1% [3/74], p=0.01), which suggests that a larger proportion of patients with grade 1+ or 2+ MR in the MitraClip group had had surgical repair.

Rates of major adverse events at 30 days were lower in the MitraClip group than in the surgery group (15% [27/181] vs 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. In subgroup analysis, there was significant subgroup interaction between those with FMR and those with DMR (p=0.02), in which patients with DMR had more favorable rates of the primary efficacy end point with surgery.

In 2012, Glower et al, in a follow-up analysis of the EVEREST II study population, evaluated differences in subsequent surgical MV replacement between the MitraClip and the open surgery groups. In the year after enrollment, 37 (21%) of 178 of MitraClip patients underwent MV surgery, of whom 54% underwent MV repair (vs replacement). The number of MitraClip devices implanted (17 with no clip, 7 with 1 clip, 13 with 2 clips) was not associated with the likelihood of MV replacement (p=0.12). In the group randomized to surgery, 67 (84%) of 80 patients underwent MV repair surgery during the year following enrollment. The authors assessed characteristics predictive of MR repair versus replacement, and found that baseline characteristics, including age, etiology of the MR, prior cardiac surgery, and anterior/bilateral leaflet pathology, were not significantly associated with MR correction method (p=0.47). Of the 37 cases of MV surgery after MitraClip placement, 11 (30%) cases reported valve injury by the surgeon, although the surgical repair rate in patients who were noted to have MV injury did not significantly differ from the remaining patients who had MV surgery after MitraClip.
placement (54% in the valve injury group vs 58% in the remainder, p=0.95). This study suggests that MitraClip therapy is not associated with subsequent surgical MV replacement (vs repair).

In 2013, Mauri et al reported 4-year follow-up results for patients enrolled in the EVEREST II trial.\(^\text{36}\) Of patients randomized to the percutaneous repair group, 161 (88%) were included in the 4-year efficacy analysis; of those in the surgery group, 73 (77%) were included in the 4-year efficacy analysis. The study’s primary endpoint was a composite comprised of freedom from death, surgery for MV dysfunction, and grade 3+ and 4+ MR. The authors also evaluated interactions between treatment groups and 2 additional variables: age 70 years or older and FMR (vs DMR). At 4 years, 39.8% of those in the MitraClip group (64/161) achieved the primary efficacy end point of freedom from death, freedom from surgery for MV dysfunction, and freedom from grade 3+ or 4+ MR, compared with 53.4% (39/73) of the surgical group (p=0.070). However, significantly more MitraClip patients required surgery for MV dysfunction during the follow-up period (24.85% [40/161] in the MitraClip group vs 5.5% [4/73], p<0.001); in the MitraClip group, most of the MV surgery occurred before 12 months.

Tests of interaction between age and MR etiology were significant. Among those younger than 70, the difference between rates of the primary efficacy end point between the MitraClip and surgery groups was -28.5% (favoring surgery; 95% CI, -46% to -10.5%). Among those 70 or older, this difference was 3.3% (favoring MitraClip; 95% CI, -16.4 to 23.0). Among those with DMR, the difference in rates of the primary efficacy end point between the MitraClip and surgery groups was -24.85 (favoring surgery; 95% CI, -40.5 to -9.1). Among those with FMR, this difference was 11.4% (favoring MitraClip; 95% CI, -11.1% to 33.8%).

Five-year results of EVEREST II were reported by Feldman et al in 2015.\(^\text{37}\) This analysis included patients who completed the 5-year follow-up visit and had data on their MR grade, or who had died or had MV surgery before withdrawing from the trial. As with the 4-year analysis (described above), significantly more patients in the MitraClip group had MV surgery or reoperation during the follow-up period (27.9%) compared to the surgical group (8.9%; p=0.003). In addition, significantly more patients in the MitraClip group had grade 3+ or 4+ MR (12.3%) compared with the surgical group (1.8%; p=0.02). The primary outcome was a composite of freedom from death, freedom from surgery for MV dysfunction, and freedom from grade 3+ or 4+ MR. The rate of this composite outcome was 44.2% (68/154) in the MitraClip group and 64.3% (36/56) in the surgical group (p=0.01). The mortality rate did not differ significantly between groups (20.8% in the MitraClip group vs 26.8% in the surgical group; p=0.36). As noted in previous analyses of EVEREST II data, most of the additional surgeries in the MitraClip group occurred early, in the first 6 to 12 months postprocedure. Among patients who were event-free at 1 year, there was no significant difference in the composite outcome at 5 years: 69% (60/87) in the MitraClip group and 75% (36/48) in the surgical group (p=0.55).
Nonrandomized Comparative Studies
Several nonrandomized cohort studies have compared outcomes for MR treated with either surgical or TMVR using the MitraClip device. Two studies (Conradi et al., Taramasso et al.) included patients with only FMR, while Paranskaya et al. reported results for a mixed DMR and FMR cohort. These 3 studies were included in the 2013 Wan meta-analysis (described above).

In 2016, De Bonis et al. published a study designed to verify the finding from the EVEREST II trial that, for patients with an initial positive response to MitraClip, results were sustained at long-term follow-up and were similar to surgery. The study included 85 patients with FMR and an initial good result after MitraClip implantation (ie, MR grade ≤1 at hospital discharge). Findings were compared with 58 consecutive surgical patients, treated before MitraClip was an option, who also had MR grade of 1 or less at discharge. Patients were followed prospectively and data were entered into a dedicated database. Patients in the 2 groups were comparable at baseline on most variables (eg, NYHA functional class, proportion with atrial fibrillation, LV dimensions); however, age and logistic EuroSCORE were significantly higher in the MitraClip group.

At 1 year, echocardiographic prevalence of MR grade of 2 or more was 32.5% in the MitraClip group (p<0.001 within group vs hospital discharge). In addition, among patients in the MitraClip group (n=53) with MR grade of 1 or less at 12 months, 8 (19%) of 42 with follow-up data had MR progression at least 1 grade at 2 years and 9 (33%) of 27 with follow-up data had MR grade 2 or more at 3 years. Compared with the surgery group, the 4-year freedom from grade 3+ MR (94% vs 75%) and freedom from grade 2+ MR (82% vs 37%) were significantly higher in the surgery group. Overall survival at 4 years was similar between groups, 74% in MitraClip patients and 77% in surgical patients. This analysis is limited by missing data and lack of randomization. However, it does suggest that, at least in this group of MitraClip patients, an initially successful outcome did not prevent progression of MR over time and that surgery may have greater long-term efficacy for MR control.

Single-Arm Studies
There have been numerous single arm studies of surgical candidates for MitraClip. These studies offer little relevant evidence on the comparative efficacy of MitraClip versus surgery.

Section Summary: MitraClip in Surgical Candidates
The evidence for the use of MitraClip in patients who are considered candidates for open MV repair surgery includes 1 RCT (EVEREST II) and multiple comparative and noncomparative cohort studies. The most rigorous evidence related to MitraClip’s efficacy is from EVEREST II, which found that, MitraClip was noninferior to open surgery in terms of safety and effectiveness at 1-year follow-up. At the 5-year follow-up, efficacy as assessed by a composite outcome, was significantly higher in the surgery group than in the MitraClip group. In EVEREST II, most patients who had persistent MV dysfunction after MitraClip developed it within the first year postprocedure and, among patients event-free at 1 year, 5-year efficacy did not
differ significantly in the MitraClip and surgery groups. EVEREST II had some methodologic limitations. The noninferiority margin of 25% was large, indicating that MitraClip could be somewhat inferior to surgery and the noninferiority margin still met. Crossover to surgery was allowed for patients who had grade 3+ or more MR prior to discharge, and 23% of patients assigned to MitraClip met this criterion. This large rate of crossover would bias results toward the null on intention-to-treat 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. As a result of these factors, this single trial is not definitive in demonstrating improved clinical outcomes with MitraClip compared with surgery and further RCTs are needed to corroborate these results. A subsequent nonrandomized controlled trial, did not find the same low rates of long-term MR control in MitraClip patients with an initially positive response to treatment. This trial was limited by the lack of randomization and high rate of missing data.

**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, Kirkland, WA) and the Monarc device (Edwards Lifesciences, Irvine, CA), have been evaluated. A case series evaluating use of the Carillon device in 53 patients with grade 2+ FMR at 7 European centers was reported in 2012. Of the 53 patients who underwent attempted device implantation, 36 underwent permanent implantation and 17 had the device recaptured due to transient coronary compromise in 8 patients and less than 1 grade of FMR reduction in 9 patients. Echocardiographic measures of FMR improved in the implanted groups up through 12-month follow-up, along with improvements in 6-minute walk distance. An earlier feasibility study of the Carillon device in 48 patients with moderate-to-severe FMR demonstrated successful device placement in 30 patients, with 18 patients unable to be implanted due to access issues, insufficient acute FMR reduction, or coronary artery compromise. The Monarc device has been evaluated in a phase 1 safety trial at 8 European centers. 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 in 91% of patients at 30 days and in 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 and is insufficient to determine the effects of the technology on health outcomes.
Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 2.

Table 2. Summary of Key Trials

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<th>NCT No.</th>
<th>Trial Name</th>
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<th>Completion Date</th>
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<td>NCT02371512</td>
<td>A Multicenter, Randomized, Controlled Study to Assess Mitral Valve reconstruction for advanced Insufficiency of Functional or ischemic Origin (MATTERHORN)</td>
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<tr>
<td>NCT02534155</td>
<td>High and Intermediate Risk Degenerative Mitral Regurgitation Treatment: A Trial Comparing MitraClip® to Surgical Therapy (HiRiDe)</td>
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<tr>
<td>NCT02444338</td>
<td>A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation</td>
<td>380</td>
<td>Sep 2019</td>
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NCT: national clinical trial.

* Denotes industry-sponsored or cosponsored trial.

Summary of Evidence
For individuals who have symptomatic degenerative mitral regurgitation (DMR) or functional mitral regurgitation (FMR) who are at prohibitive risk for open surgery who receive transcatheter mitral valve repair (TMVR) with MitraClip, the evidence includes primarily single-arm cohort studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related morbidity. The evidence for the use of MitraClip among patients who are not considered surgical candidates consists primarily of single-arm cohort studies. The available single-arm studies include the pivotal EVEREST II High Risk Registry (HRR) study and the EVEREST II Real World Expanded Multi-center Study of the MitraClip System (REALISM). These studies have demonstrated that MitraClip implantation is feasible, with high rates (on the order of at least 70% to 90%) of short-term reductions in mitral regurgitation (MR) grade to 2+ or less, and has a reasonable safety profile. A nonrandomized analysis matching patients in the EVEREST registries to similar nonsurgically treated patients found significantly lower 1-year morality rates in MitraClip-treated patients. However, the lack of concurrent control groups, especially in randomized trials, makes it difficult to draw conclusions about whether there is a net health benefit compared with alternative therapies in this population. There are no strong barriers to conducting controlled trials, including RCTs comparing MitraClip to continued medical management. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have symptomatic DMR or FMR who are surgical candidates who receive TMVR with MitraClip, the evidence includes 1 RCT (EVEREST II) and multiple comparative and noncomparative cohort studies.
Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related morbidity. The evidence for the use of MitraClip in patients who are considered candidates for open MV repair surgery includes 1 RCT (EVEREST II) and multiple comparative and noncomparative cohort studies. The most rigorous evidence related to MitraClip’s efficacy is from EVEREST II, which found that, for 1-year outcomes, MitraClip was noninferior to open surgery in terms of safety and effectiveness. At the 5-year follow-up, efficacy as assessed by a composite outcome, was significantly higher in the surgery group than the MitraClip group. In EVEREST II, most patients who had persistent MV dysfunction after MitraClip developed it within the first year postprocedure and, among patients event-free at 1 year, 5-year efficacy was not significantly different in the MitraClip and surgery groups. The EVEREST II trial had some methodologic limitations. The noninferiority margin of 25% was large, indicating that MitraClip could be somewhat inferior to surgery and the noninferiority margin still met. Crossover to surgery was allowed for patients who had grade 3+ or more MR prior to discharge, and 23% of patients assigned to MitraClip met this criterion. This large rate of crossover would bias results toward the null on intention-to-treat 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. As a result of these factors, this single trial is not definitive in demonstrating improved clinical outcomes with MitraClip compared with surgery. Additional RCTs are needed to corroborate these results. A subsequent nonrandomized controlled trial, though not the optimal study design and with missing data, did not find the same low rates of long-term MR control in MitraClip patients who had an initial positive response to treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have DMR or FMR who receive TMVR with 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. The evidence is insufficient to determine the effects of the technology on health outcomes.

Supplemental Information

Clinical Input Received 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.
**2015 Input**
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. The input supported the use of TMVR in patients with DMR 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 and American Heart Association**
The American College of Cardiology (ACC) and American Heart Association released guidelines on the management of valvular heart disease in 2014. The guidelines include the following class IIB recommendation related to the use of TMVR for MR:

Transcatheter mitral valve repair may be considered for severely symptomatic patients (NYHA [New York Heart Association] 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. (Level of Evidence: B.)

**American College of Cardiology, American Association for Thoracic Surgery, et al**
The ACC, American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons released a position statement on transcatheter therapies for MR in 2014. This statement outlines critical components for successful transcatheter MR therapies and recommends 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 2012, the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery released guidelines on the management of valvular heart disease. These guidelines do not address TMVR.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Medicare National Coverage**
In April 2015, the Centers for Medicare and Medicaid Services (CMS) issued a national coverage decision for the use of TMVR.
CMS determined that it would cover TMVR under Coverage with Evidence Development for the treatment of significant symptomatic MR when performed according to a Food and Drug Administration (FDA)–approved indication and when all of the following conditions are met:

1. The procedure is performed with a complete TMVR system that has received FDA 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: a cohesive, multi-disciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care.
4. TMVR must be furnished in a hospital and with the appropriate infrastructure that includes but is not limited to:
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, including 45 Code of Federal Regulations (CFR) Part 46 and 21 CFR Parts 50 & 56.

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.

References


Billing Coding/Physician Documentation Information

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

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

**Additional Policy Key Words**

MitraClip

**Policy Implementation/Update Information**

<table>
<thead>
<tr>
<th>Date</th>
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<tbody>
<tr>
<td>9/1/14</td>
<td>New Policy; considered investigational.</td>
</tr>
<tr>
<td>10/1/15</td>
<td>Notated that CPT 0343T, 0344T were deleted as of 12/31/14. No policy statement changes.</td>
</tr>
<tr>
<td>12/1/15</td>
<td>Transcatheter mitral valve repair considered medically necessary for degenerative mitral regurgitation in patients at prohibitive surgical risk.</td>
</tr>
<tr>
<td>10/1/16</td>
<td>No policy statement changes.</td>
</tr>
</tbody>
</table>

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