2.02.30	Transcatheter Mitral Valve Repair	
Section 2.0 Medicine	**Effective Date** September 30, 20114	
Subsection 2.02 Cardiology	**Original Policy Date** September 30, 2014	**Next Review Date** September 2015

Description

Transcatheter mitral valve (MV) repair is a potential alternative to surgical therapy for mitral regurgitation (MR). MR is a common valvular heart disease that can result from either a primary structural abnormality of the MV complex or a dilated left ventricle due to ischemic or dilated cardiomyopathy, which leads to secondary dilatation of an anatomically normal MV. 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.

Related Policies

- N/A

Policy

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

Policy Guidelines

Effective in 2014, there are CPT category III codes for this procedure:

- 0343T Transcatheter mitral valve repair percutaneous approach including transseptal puncture when performed; initial prosthesis
- 0344T additional prosthesis(es) during same session (List separately in addition to code for primary procedure)
- 0345T Transcatheter mitral valve repair percutaneous approach via the coronary sinus

Benefit Application

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

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

Rationale

Background

MR: Epidemiology and Classification

MR is the second most common valvular heart disease, occurring in 7% of people older than age 75 years and accounting for 24% of all patients with valvular heart disease. (1) MR can result from a heterogeneous set of disease processes that may affect 1 or more parts of the 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 DMR include MV 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 MV.(4) 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.(4) MR can be acute or chronic.(3) 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 lead to reduced forward cardiac output and signs and symptoms of pulmonary congestion. (3)

MR: 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 angiotensin converting enzyme inhibitors, beta blockers, and biventricular pacing can reduce LV pressures, decrease LV dilatation, improve cardiac output, and thus ameliorate clinical symptoms. (3, 4)

Surgical management. In patients with symptoms of MR with preserved LV function (DMR), 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(3):

- 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 <0.30) and/or end-systolic dimension >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 ≥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 MV 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. (2) 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 MV. (2, 5)

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.(6) Fifty-six percent and 32% of patients with DMR and FMR, respectively, did not undergo surgery. Older age, impaired LV ejection fraction (LVEF), 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 U.S., Goel et al found that 53% of patients did not have MV surgery performed. (7) Compared with those who received surgery, patients who did not receive surgery had lower ejection fractions (27 vs 42, p<0.001) and were of higher surgical risk, as judged by a higher Society of 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 MV 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 MV complex and generally are performed on the beating heart without the need for cardiopulmonary bypass. (1, 8) 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 MV replacement via catheter.

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 next). 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 MV. Placement of the MitraClip leads to coapting of the mitral leaflets, thus creating a double-orifice valve.

Additional devices for transcatheter MV 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 Life sciences, 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 Annulus Now) study, with further studies planned. (10) The Monarc system also involves 2 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 Life sciences Percutaneous Mitral Annuloplasty System for the Treatment of Mitral Regurgitation) trial. (11)

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

Several devices are under development for transcatheter MV 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).

Regulatory Status

In October 2013, the MitraClip® Clip Delivery System received U.S. Food and Drug Administration (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)

FDA's approval was based on data from 1 randomized controlled trial (RCT) and 2 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. These studies are described further in the Rationale section.

Rationale

The policy development was based, in part, on a Blue Cross Blue Shield Association (BCBSA) TEC Assessment developed in June 2014, which evaluated the use of transcatheter mitral valve (MV) repair in patients with symptomatic degenerative mitral regurgitation (DMR) who are at prohibitive risk for mortality during open surgery and determined that it does not meet Technology Evaluation Criteria. (13)

The literature search for this policy focused primarily on studies evaluating the MitraClip, but evidence related to other devices is briefly discussed. Assessment of efficacy for therapeutic interventions such as the 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 also 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 the 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 transcatheter MV repair: those who are considered to be at prohibitively high risk for cardiac surgery and those who are surgical candidates. Studies addressing these 2 subsets of patients are outlined separately. Although outcomes and etiology differ for functional MR (FMR) and DMR, studies on the MitraClip most often evaluate the device in mixed populations.

Literature Review

The published evidence related to the efficacy of MitraClip includes 1 industry-sponsored RCT, several nonrandomized comparative studies, and multiple noncomparative registry studies and case series.

<u>MitraClip in Prohibitive Surgical Risk Candidates</u>

The MitraClip device delivery system has FDA approval for use in patients with DMR who are not candidates for open surgery. There are no controlled trials of MitraClip in this population. Available studies include multiple cohort studies and case series, the largest of which are the EVEREST II HRR and the EVEREST II Real World Expanded Multi-center

Study of the MitraClip System (REALISM) studies. Systematic reviews of these uncontrolled studies have also been published.

Systematic Reviews and Meta-Analyses

A 2014 BCBSA TEC Assessment evaluated the evidence on the use of the MitraClip for the U.S. Food and Drug Administration (FDA)-approved indication. (13) 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 higher quality studies, 30-day mortality rates were 6.0% and 6.3%, and 12 to 25 month mortality rates were 17.1% and 23.6%. In evaluable patients at 12 months, the percent of patients who had an MR grade 2 of or less was 83.3% and 74.6%; the percent of patients with New York Heart Association (NYHA) class I/II functional status was 81% and 87%; and improvement of at least 1 NYHA class was present in 68% and 88% of patients. Table 1 (adapted from the BCBSA 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

Study	Original N	MR Grade at 12 Months, % (n/N)	NYHA Class at 12 Months, % (n/N)	Other Pertinent Outcomes Assessed at 12 Months
Lim et al (2013)[1]	127	MR ≤2+ 83.3% (70/84)	NYHA I/II 86.9% (73/84) Improved ≥1 class 86.9% (73/84)	SF-36 PCS score change 6.0 (95% CI, 4.0 to 8.0), n=76 SF-36 MCS score change 5.6 (95% CI, 2.3 to 8.9), n=76
Reichenspurner et al (2013)[2]	117	MR ≤2+ 74.6% (53/71)	NYHA I/II 81% (63/78) Improved ≥1 class 68% (53/78)	Change in MLHFQ from baseline 13.3 points (p=0.03), n=44 Change in 6MWT from baseline 77.4 m (p<0.001), n=52
Estévez-Loureiro et al (2013)[22]	79	NR	NR	
Grasso et al (2013)[23]	28	NR	NR	Kaplan-Meier estimate of freedom from death, surgery, or ≥3+ MR 70% (visual estimate from graph)

Chan et al (2012)[24]	15	MR severity 1.9[a]	NYHA class 2.1 [a]	

Adapted from the BCBSA 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.
[a] 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 the MitraClip in high surgical risk patients. These included 1 published study by Whitlow et al (19) and data presented to FDA as part of the device's premarket approval (PMA) 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 the MitraClip because most patients were either not evaluated for anatomic eligibility for the MitraClip, or were ineligible. As such, the control groups are likely to have higher mortality rates than patients eligible to receive the MitraClip.

Due to the lack of an appropriate control group or clear evidence about the natural history of patients with DMR who are 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.

A systematic review by Munkholm-Larsen et al published in 2013 summarized safety and efficacy results from 12 publications evaluating the efficacy of the MitraClip in surgically high-risk patients. (20) The authors included studies that evaluated high-risk surgical patients with significant MR who underwent transcatheter MR repair with the MitraClip device, and excluded studies that included 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, 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 the 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.

Nonrandomized Studies Evaluating the MitraClip in Prohibitive Surgical Risk Populations.
Evidence on the use of the 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), which included non-high-risk and high-risk arms in the U.S. In addition, several cohort studies have reported experience with the use of the MitraClip in European centers, because the device was CE marked for use in Europe since 2008.

EVEREST High Risk Registries. The EVEREST II RCT, described below, was a pivotal multicenter trial designed to evaluate the efficacy of transcatheter MV repair with the MitraClip compared with open MV repair.(21,22) Concurrently with the EVEREST II RCT, investigators enrolled patients into the EVEREST II HRR Study who were deemed ineligible for surgery due to prohibitively high surgical risks. After completion of the EVEREST II RCT and HRR studies, the MitraClip sponsors performed a continued access study, EVEREST II REALISM, which included a high-risk and a non-high-risk arm. For inclusion in the EVEREST II HRR, patients were considered high surgical risk if either their Society of Thoracic Surgeons (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. These included porcelain aorta or mobile ascending aortic atheroma, postradiation mediastinum, previous mediastinitis, FMR with ejection fraction (EF) less than 40, age older than 75 years with EF less than 40, reoperation with patent grafts, 2 or more prior chest surgeries, hepatic cirrhosis, or 3 or more of the following STS high risk factors: creatinine greater than 2.5 mg/dL, prior chest surgery, age older than 75 years, or EF less than 35.(9) Patients were excluded from the registry if they had LVEF less than 20%, left ventricular end-systolic diameter (LVESD) greater than 60 mm, MV orifice area less than 4 cm^2, 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 2013, Lim et al published outcomes from transcatheter MV repair with the MitraClip among high-surgical-risk patients with DMR who were included in the EVEREST II HRR and REALISM registries.(14) 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" (e.g., 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 REALISM Continued Access 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/IV.

The MitraClip was successfully placed in 95.3% of patients. Thirty-day and 12-month mortality rates were 6.3% and 23.6%, respectively. The 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 3+ MR at baseline and 36.8% of patients with 4+ MR at baseline had MR reduced to 1+. Of 91 patients who had procedural reduction of MR to grade 2+ or less, 64 patients (70.3%) had sustained MR 2+ or less at 1 year, 10 (11.0%) experienced worsening MR to 3+ or 4+, and 17 (18.7%) died. Of 59 patients who had a procedural reduction of MR to grade 1 or less, 21 patients (35.6%) had sustained MR ≤1+ 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+ compared with those the 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, the 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 were 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, as the STS surgical risk calculator changed over time.

In 2012, Whitlow et al reported 12-month results for MitraClip use among patients with severe symptomatic MR and high surgical risk from the EVEREST II HRR study. (19) The authors used a comparator group of retrospectively-identified patients with MR severity ≥3+ and a predicted surgical mortality rate of 12% or higher who were screened for entry into the registry but who did not enroll or who were not anatomically eligible for MitraClip device placement. The HRR MitraClip group included 78 patients, 46 with FMR and 32 with DMR. The MitraClip was successfully placed in 76 patients, of whom 62 (79.5%) achieved at least a 1-grade reduction in MR, and 56 (71.8%) had reduction in MR grade to 2+ or less. By 12-month follow-up, 19 patients died (mortality rate 24.4%). In those who survived, NYHA functional class generally improved. One-year mortality was less than in the concurrent comparator group, but potential differences between the HRR-enrolled patients and the HRR-ineligible patients makes interpretation of this comparison difficult.

Noncomparative cohort studies. Since the publication of the Munkholm-Larsen meta-analysis, several additional noncomparative studies of the use of the MitraClip in high surgical risk patients have been published. Most of these studies included a mix of patients with DMR and FMR, but 1 (Reichenspurner et al (15)) included only patients with DMR and reported outcomes for patients at high risk for surgery. Another cohort study (Estévez-Loureiro et al (16)) reported results separately for patients with DMR considered to be at high surgical risk.

Reichenspurner et al reported procedural and acute safety results at 30 days and survival results at 12 months for patients with DMR enrolled in the ACCESS-EU study, European prospective nonrandomized postapproval study of MitraClip therapy.(15) The authors included 117 patients with DMR (20.6% of the ACCESS-EU cohort at the time of analysis), all of whom had either symptomatic MR or, if asymptomatic, 3+ or 4+ MR, and underwent transcatheter MV repair with the MitraClip from October 2008 to April 2011. Outcomes were analyzed for the entire DMR cohort and stratified for low-risk and high-risk surgical patients (logistic EuroSCORE I<20% or 20% or higher, respectively). Of the 106 patients who were successfully implanted with a MitraClip device and had information on baseline MR severity and hospital discharge available, 88.7% (94/106) had an MR reduction to grade 2+ or less. Fifty six percent had reduction to grade 1+ or less. Thirty-day mortality was 6.0% (7/117) for the entire DMR cohort; 30-day mortality was 9.1% (3/33) for high-risk subgroup patients and 4.8% (4/84) for low-risk subgroup patients. Echocardiographic follow-up data was available for 71 patients at 12 months. The rate of freedom of recurrent/persistent MR greater than grade 3+ was 74.6%, with no statistically significant differences between high- and low-risk subgroups. Most patients (68%) improved by at least 1 NYHA functional class. By 12 months, 13 patients required repeat MV interventions, including MV surgery in 9 cases and a repeat MitraClip placement in 4 cases.

In 2013, Estévez-Loureiro et al reported outcomes for 173 patients who received the MitraClip, 79 of whom had DMR and were judged to be high surgical risk.(16) Procedural success occurred in 76 patients (96.2% of those with DMR), and most patients had

improvement in MR severity. Six-month follow-up data were available for 60 patients, in whom all-cause mortality was 8.3%.

In 2012, Baldus et al reported data from a German registry of patients who underwent transcatheter MV repair with the MitraClip (TRAMI). (23) The TRAMI registry is a 15-center registry that includes a prospective component for patients treated with transcatheter MV repair (for either MR or mitral stenosis) from August 2010 to July 2013, and a retrospective component for patients treated at participating centers from January 2009 to July 2010. At the time of publication, 486 patients had been enrolled in the registry, 177 prospectively and 309 retrospectively. Most of the patients (481/486, or 99%) had undergone transcatheter MV repair with the MitraClip for MR. While this registry was not limited to patients who were not surgical candidates, 76% of patients were described as "high surgical risk." The decision to undergo a transcatheter repair was made by a cardiologist in 63% of cases and by a heart team of cardiologists and cardiovascular surgeons in 35% of cases. One hundred forty-five patients (30%) had degenerative MR. The centers demonstrated right rates of immediate technical success, with 96% of patients demonstrating no, mild or moderate MR. Immediately after MitraClip placement, there was significant improvement in the distribution of MR severity. Twenty-two percent of patients had peri- or postprocedural complications, most commonly need for blood transfusions in 10.4% of cases. Follow-up was obtained for 47% and 78% of patients enrolled retrospectively and prospectively, respectively, at a median of 85 days postprocedure. At follow-up, 21% and 6% of patients enrolled retrospectively and prospectively, respectively, had MR severity above grade 2. This study demonstrates generally good safety and improved MR grade in the short term in an unselected patient population. Compared with the EVEREST registry, patients were older and more likely to have functional MR, and were thus likely sicker at baseline. However, follow-up data were missing for a large proportion of patients, and follow-up occurred a short period after enrollment, so drawing conclusions about longer term durability is difficult.

In 2012, Divchev et al reported short-term, in-hospital outcomes from a prospective cohort of patients with symptomatic MR who were not surgical candidates. (24) Thirty-three patients with symptomatic FMR or DMR were included, all of whom underwent transcatheter MR repair with the MitraClip device from May 2010 to January 2011. Patients were included if they met criteria for MV repair according to European Society of Cardiology guidelines but were determined to be unacceptable for conventional surgical repair and had to have valve anatomy and transfemoral access suitable for the MitraClip. A Logistic EuroSCORE of 20% or higher was "usually" taken as a cutoff. Patients had a mean age of 77.8, and most (81.8%) had a history of decompensated heart failure in the prior month. Seventy percent of patients had FMR. Immediately postprocedure, 81.7% of patients had reduction to MR grade 1+ or less, and 12.1% had reduction to MR grade 2+ or less. NYHA functional class improved from mean 3 preprocedure to 2 on the day of discharge ($p<0.001$). The procedure was generally well-tolerated. One patient required subsequent cardiac surgery for MR. Two patients had minor access site bleedings. Overall, the device appeared to be associated with good short-term safety and effectiveness in a small cohort of patients with significant MR-related symptoms, but longer term follow-up is needed.

Armoiry et al reported data from a prospective registry of patients with severe MR who were judged to be inoperable or at high surgical risk at 7 French centers and treated with transcatheter MV repair with the MitraClip from December 2010 to September 2012. (25) The study was designed to evaluate the feasibility, safety, and efficacy of the MitraClip device implantation. Decisions about surgical risk were made by a heart team that included an interventional cardiologist, a cardiac surgeon, an echocardiography specialist, and an anesthesiologist. Safety was assessed by rates of in-hospital deaths, in-

hospital surgical MV repairs, and other adverse events. Efficacy was assessed by the proportion of patients with residual MR grade 2 or less at discharge and 6 months postprocedure; by NYHA heart failure class at 6 months postprocedure; and by echocardiographic variables. Sixty-two patients were included in the registry, 71.7% men and 73.8 with functional MR. In-hospital death occurred in 2 patients, and surgical MV repair was required in 3 patients (including 1 who died). At discharge 88.2% of patients had MR grade 2 or less. At 6-month follow-up, among the 15 patients for whom data are reported, 80% continued to have MR of grade 2 or less. Among 22 patients for whom functional outcomes are reported, 2 had NYHA class I or II heart failure, compared with 5 at baseline. This study describes good procedural success with the MitraClip device early in its adoption at several centers. However, its generalizability is limited by a significant amount of missing data, its nonrandomized design, and potential bias in selection of patients for the MitraClip given that surgical risk was not determined by a standardized measure.

Section Summary

The evidence related to the use of the MitraClip among patients who are not considered surgical candidates consists primarily of noncomparative cohort studies. In general, these studies demonstrate that MitraClip implantation is feasible and reasonably safe and associated with high rates (on the order of at least 70% to 90%) of short-term reductions in MR grade to 2+ or less. Without intervention, symptomatic MR is likely to follow a worsening course; however, the characteristics of the natural history of DMR and FMR in patients with characteristics similar to those who underwent MitraClip placement are not well-known. Therefore, the lack of concurrent control groups in the reported cohort studies makes drawing conclusions about the net health outcomes of the MitraClip in patients who are not surgical candidates difficult.

MitraClip in Surgical Candidates

Percutaneous repair of MR with the MitraClip has been evaluated in comparison with open surgical repair in patients who are considered surgical candidates. Studies pertaining to this indication include 1 RCT, multiple nonrandomized comparative studies, and multiple noncomparative studies. Similar to publications among nonsurgical candidates, many evaluations of the MitraClip among surgical candidates include mixed populations of FMR and DMR patients.

EVEREST IIRCT. The EVEREST II RCT was a pivotal multicenter trial designed to evaluate the efficacy of transcatheter MV repair with the MitraClip compared with open MV repair.(21,22) Eligible patients had grade 3+ or 4+ MR and were all candidates for MV repair surgery. Symptomatic patients were required to have left ventricular ejection fraction (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 a MV orifice area less than 4.0 cm or leaflet anatomy that may have precluded MitraClip device implantation, proper MitraClip positioning, or sufficient reduction in MR. Two hundred seventy-nine patients were randomized in a 2:1 ratio to transcatheter repair (184 patients) or standard MV surgery (95 patients). There was a composite primary safety end point of major adverse events at 30 days, defined as freedom from death, myocardial infarction, nonelective cardiac surgery for adverse events, renal failure, transfusion of2 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 2+ or more, freedom from cardiac surgery for valve dysfunction, and freedom from death at 12 months.

MitraClip was considered to have acute procedural success if the clip deployed and MR 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 manuscript, crossover to surgery in the immediate post-procedure period if the MitraClip failed to adequately reduce MR is considered a successful treatment strategy. Thus, in the ITT analysis, the efficacy end point was considered met for MitraClip group subjects if they were free from death, *reoperation* for MR, and MR greater than 2+ at 12 months in patients who did not have acute procedural success (and may have undergone open MV repair) and freedom from death, *any* MV surgery for MR, and MR greater than 2+ at 12 months for patients who did have acute procedural success. 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 that in the surgery group (for the ITT analysis).

The treatment groups were generally similar, except for the fact that a higher proportion of those in the MitraClip group had congestive heart failure (167/184 [91%] vs 74/95 [78%], 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, for the study's primary combined efficacy end point, rates of freedom from death, MV surgery, and grade 3+/4+ MR at 12 months, were 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 (23/134 [17.2%] vs 3/74 [4.1%], 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 compared with the surgery group (27/181 [15%] vs 45/89 [48%], 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 compared with those with DMR (p=0.02) in which patients with DMR had more favorable rates of the primary efficacy end point with surgery.

The EVEREST II study suggests that among patients with MR who are surgical candidates for MR repair, the MitraClip has a reasonable safety profile and is not inferior to open surgical repair. Major strengths of this study include its multicenter, randomized design. However, the study was not blinded, and there were higher rates of study dropout for those randomized to the surgery group. The study defined successful reduction of MR relatively liberally (≤2+, rather than to 1+). In addition, the margin by which the MitraClip was considered noninferior was quite broad (25 percentage points). The outcomes for MR severity presented in the ITT analysis may be biased in favor of the MitraClip treatment strategy, as a high proportion (15%) proportion of those randomized to MitraClip who did not have acute procedural success received MV surgery in the immediate postprocedure period. Because of these limitations, the clinical efficacy of the MitraClip for MR among those who are surgical candidates is questionable.

In 2013, Mauri et al reported results from 4-year follow-up of patients enrolled in the EVEREST II trial.(26) Of patients randomized to the percutaneous repair group, 161 (885) 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 evaluated several end points, including freedom from death, surgery for MV dysfunction, and 3+ and 4+ MR at 4 years; freedom from surgery for MV dysfunction; and freedom from death. 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, surgery for MV dysfunction, and 3+ and 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% confidence interval [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 between 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%). These results suggest that outcomes following MitraClip and surgical repair for MR are similar at 4-year follow-up as they are at 1-year follow-up.

In 2012, Glower et al published a follow-up analysis of the EVEREST II study population to evaluate differences in subsequent surgical MV replacement between the MitraClip and open surgery group, to assess specific demographic or valve characteristics that predict MV replacement, and to assess the effect of the MitraClip on the ability to surgically repair the MV.(27) In the 1 year following enrollment, 37 of 178 (21%) of MitraClip patients underwent MV surgery, of whom 54% underwent MV repair (versus 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 of 80 patients (84%) underwent MV repair surgery through the 1 year following enrollment. The authors assessed characteristics that were predictive of MR repair versus replacement, and demonstrated 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 cases (30%) had 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).

Nonrandomized Comparative Studies: MitraClip Versus Surgical Repair. In 2013, Conradi et al published results from a retrospective cohort study that compared outcomes for patients with severe secondary FMR treated with surgical MV repair or transcatheter MV repair with the MitraClip device. (28) They included 76 patients with FMR and 95 patients treated with. Decisions about surgical or transcatheter treatment were made by an interdisciplinary dedicated heart valve team consisting of cardiac surgeons and interventional cardiologists. Surgical and MitraClip candidates differed in that those who received the MitraClip were significantly older (mean, 72.8 vs 64.5 years; p<0.001), had lower LVEF (mean, 36.2 vs 42.1; p=0.014), and had higher logistic EuroSCORE I (indicating

higher risk; 33.7 vs 10.1; p<0.001). Surgical candidates had a greater improvement in MR grade after their procedure, with a mean residual MR grade of 0.2 in the surgical group (vs 1.4 in the MitraClip group, p<0.001). While both groups had similar rates of residual MR of grade 2 or less immediately postprocedure (98.7% vs 95.8% for surgical vs MitraClip, respectively, p=0.383) and similar proportions of patients in NYHA functional class I or II (82.8% vs 69.9% for surgical vs MitraClip, p=0.104), rates of rehospitalization for heart failure up to 180 days postprocedure were higher in MitraClip patients (5.5% vs 22.1% for surgical vs MitraClip, p=0.005). Mortality at 30 days was not significantly different between groups. While this study suggests that MitraClip use may improve MR in patients with severe FMR, the significant differences in treatment groups at baseline make it difficult to draw conclusions about the relative effects of surgical MV repair compared with MitraClip.

In 2012, Taramasso et al reported outcomes from a retrospective single-center cohort patients with FMR treated with either surgery or transcatheter repair with the MitraClip.(29) The study included 143 patients with severe FMR, 63.3% of whom underwent surgical MV repair. Patients who underwent MitraClip implantation were significantly older (mean, 68.4 vs 64.9; p=0.04) and had a higher predicted surgical risk by logistic EuroSCORE (mean, 21.9 vs 10.2; p<0.001), along with a greater prevalence of multiple other medical conditions. In-hospital mortality was 6.6% in the surgical group; no in-hospital deaths occurred in patients treated with the MitraClip. Before hospital discharge, 9.6% of MitraClip group patients had residual MR of 3+ or higher, which occurred in none of the surgical patients. Follow-up occurred at a median 18 months (range, 6.4-45 months) for the surgical group and 8.5 months (range, 4-12 months) for the MitraClip group. Cumulative cardiovascular mortality was 9.9% in the surgical group and 3.8% in the MitraClip group (p=0.2). At follow-up, 94% of the surgical group and 79% of the MitraClip group had freedom from MR of 3+ or more (p=0.01). Overall, this retrospective cohort study demonstrated good safety and short-term improvements in MR in high surgical-risk patients with FMR treated with the MitraClip. Comparisons with high surgical-risk FMR patients treated at their institution suggest that the patients treated with the MitraClip have improved short-term mortality, despite being of higher surgical risk and with more comorbidities at baseline. Limitations to this study include the fact that surgically treated patients treated from 2001 were included, while the MitraClip patients were treated starting in 2008; given improvements in medical management of heart failure over time, this may bias the study in favor of the MitraClip. Timing of follow-up was more variable but, on average, longer for the surgical group, which again may bias mortality results in favor of the MitraClip if deaths occurred later in the observation period. Only patients who had an MV repair with an undersized annuloplasty without other MV repairs were included in the surgical group, which may not be the appropriate comparison group.

In another single-center cohort study, Paranskaya et al retrospectively analyzed outcomes from patients with grade 3+ or 4+ MR treated with transcatheter repair with the MitraClip compared with open surgery.(30) Data on all patients treated with MitraClip or surgical repair for MR were prospectively collected. MR treatment decisions were according to current European Society of Cardiology Task Force guidelines; patients who were considered by an interdisciplinary cardiology-cardiac surgery team to be at high surgical risk were treated with the MitraClip. For the current analysis, the authors included only patients with a EuroSCORE less than 20%, LVEF of 45% or more, and degree of MR 3+ or more. Despite having a EuroSCORE less than 20%, patients in the MitraClip group received transcatheter therapy because of a specific reason not accounted for in the EuroSCORE calculation, including patient refusal of conventional surgical intervention, prior transcatheter aortic valve implantation or complex aortic valve replacement,

extreme frailty, severe pulmonary hypertension, advanced oncologic or autoimmune disease, multiple previous strokes, alcoholism, and significant anemia. Twenty-four patients were treated with the MitraClip and 26 with surgical repair using a variety of techniques. Thirty percent of patients had FMR, with the remainder having DMR or a mixed etiology. Patients who underwent MitraClip implantation were significantly older (mean, 80 vs 63; p<0.001) and had a higher predicted surgical risk by logistic EuroSCORE (mean, 12.3 vs 3.9; p<0.001), and had higher rates of other medical conditions including coronary artery disease, diabetes, hypertension, renal failure, and previous acute decompensated heart failure. Procedural success, is defined as the implantation of at least 1 clip in the MitraClip group and residual MR of grade 2 or less without new mitral stenosis, was achieved in 22 (91.7%) of the MitraClip patients and in 26 (100%) of the surgical patients. Mean follow-up duration was significantly longer for the surgical group (751 vs 284, p<0.001). At follow-up, no patients in the surgical group died, compared with 2 patients in the MitraClip group. There were no differences between groups in rates of freedom from a composite 1-year end point (including death, stroke, major bleeding, MI, and cardiac rehospitalization). No patients in the MitraClip group and 1 patient in the surgical treatment group (3.85, p=0.29) experienced MR grade of 3+ or more at 1-year follow-up.

The 4 studies comparing MitraClip to surgery outlined earlier (Feldman et al, Conradi et al, Taramasso et al, Paranskaya et al) were summarized in a systematic review and meta-analysis by Wan et al in 2013. (31) Across all studies, age was significantly higher in groups receiving the MitraClip compared with 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, it was 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 radio [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 surgical groups. Overall, this study suggested that in spite of baseline higher age and surgical risk, patients receiving the MitraClip for MR have comparable mortality and functional outcomes with those receiving open surgery, but have higher rates of persistent MR. However, as the authors note, the analysis was limited by lack of subgroup analyses comparing outcomes for those with DMR and FMR and lack of consistent definitions of success across studies.

Noncomparative Studies Evaluating the MitraClip in Surgical Candidates. There have been numerous noncomparative studies of MitraClip use in patients who are surgical candidates. (17, 32-36) However, these studies offer little relevant evidence on the comparative efficacy of MitraClip versus surgery and therefore will not be reviewed further here.

Section Summary

The evidence related to the use of the MitraClip among patients who are surgical candidates consists of o1 RCT, the EVEREST II study, along with multiple nonrandomized comparative studies and noncomparative cohort studies and case series. The most rigorous evidence related to the MitraClip's efficacy is from the EVEREST II RCT study, which demonstrated noninferiority of MitraClip to open surgery for safety and effectiveness. About 20% of patients who received the MitraClip required reoperation for persistent MV dysfunction, and the study's per-protocol subanalysis suggests that a larger proportion of patients with grade 1+ or 2+ MR at 12-month follow-up who were analyzed in the MitraClip group had undergone surgical repair. Overall, the RCT and cohort study

evidence suggests that patients who have persistent MV dysfunction after the MitraClip typically develop it within the first year postprocedure.

Outcomes for the MitraClip for Degenerative Versus Functional MR

The MitraClip currently has FDA approval for patients with DMR. Limited evidence exists on differences in outcomes between FMR and DMR patients. Subanalyses from the EVEREST II RCT, described earlier, suggest that DMR patients may demonstrate greater benefit from surgical repair.

Braun et al prospectively compared outcomes for MitraClip placement for DMR and FMR in a cohort of 117 patients with symptomatic MR. (37) Patients were at high risk for open surgery or declined open surgery. At baseline, the 72 patients with DMR differed from the 47 with FMR. The DMR group had a higher proportion of NYHA functional class greater than II, higher end-diastolic and end-systolic volumes, and lower ejection fraction, and a higher incidence of comorbidities. Successful MR reduction by at least 1 grade occurred in 83.3% (60/72) of DMR patients and 89.4% (42/47) of FMR patients (p=0.42). For the study's primary composite efficacy end point (freedom from MR grade 3+ or 4+, reintervention for MV dysfunction, and death 12 months after implantation), rates occurred in 59.7% of the DMR group and 63.8% of the FMR group (p=0.73)

Other Transcatheter MV Repair Devices

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

Several indirect annuloplasty devices, the Carillon® Mitral Contour System™ (Cardiac Dimension Inc., 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 2+ FMR at 7 European centers was reported in 2012. (10) 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. (38) The Monarc device has been evaluated in a phase 1 safety trial at 8 European centers. (11) Among 72 patients enrolled, the device was successfully implanted in 59 patients (82%). 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.

Summary

Transcatheter mitral valve (MV) repair is a potential alternative to surgical therapy for mitral regurgitation (MR). One device, the 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 MV (degenerative MR [DMR]) in patients who are considered at prohibitive risk for surgery.

The evidence on the FDA-approved indication consists of 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). These studies included high-risk and non-high-risk arms in the U.S. 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.

However, the lack of concurrent control groups makes it difficult to draw conclusions about whether there is a net health outcome benefit compared with alternative therapies in this population.

For the use of the MitraClip in patients with DMR or functional MR (FMR) who are considered candidates for open MV repair surgery, the evidence consists of 1 RCT, the EVEREST II trial, and multiple comparative and noncomparative cohort studies. The most rigorous evidence related to the MitraClip's efficacy is from the EVEREST II RCT, which demonstrated noninferiority to open surgery for safety and effectiveness. About 20% of patients who received the MitraClip required reoperation for persistent MV dysfunction, and the study's per-protocol subanalysis suggests that a larger proportion of patients with grade 1+ or 2+ MR at 12-month follow-up who were analyzed in the MitraClip group had undergone surgical repair. Overall, the RCT and cohort study evidence suggests that the device is associated with reasonable short-term safety and results are durable for patients who remain free of recurrent or persistent MR after the first year. However, a high proportion of patients require reoperation during the first year postprocedure. In addition, the most appropriate population of patients in terms of MR etiology for MitraClip therapy (FMR vs DMR) has not been well-established. Ongoing clinical trials are evaluating the MitraClip in subpopulations of patients with MR.

Because of the limitations in the evidence base, transcatheter MV repair is considered investigational for all indications.

Ongoing Clinical Trials

A search of online database ClinicalTrials.gov identified the following RCTs of transcatheter MV repair devices for MR:

- Clinical Outcomes Assessment of the MitraClip Therapy Percutaneous Therapy for High Surgical Risk Patients (COAPT) (NCT01626079): This is a randomized, open-label trial of percutaneous MV repair with the MitraClip among patients with moderate-to-severe functional MR and high surgical risk. Patients with symptomatic functional MR due to cardiomyopathy (ischemic or nonischemic) and who are extremely high risk for open MV surgery due to comorbidities will be randomized to percutaneous MV repair using the MitraClip system or nonsurgical therapy based on standard hospital clinical practice. Primary outcomes are a composite safety end point and an effectiveness end point of recurrent heart failure hospitalizations at 12 months. The planned study enrollment is 420; the study completion date is listed as August 2019.
- A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF) (NCT01772108): This is a randomized, open-label trial of percutaneous MV repair with the MitraClip compared with standard practice among patients with clinically significant functional MR and NYHA functional class III or IV chronic heart failure. The planned study enrollment is 800; the study completion date is listed as August 2016.
- Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR) (NCT01920698): This is a randomized, open-label trial of percutaneous MV repair with the MitraClip. Patients with severe secondary MR will be randomized to MitraClip device placement or optimal medical therapy. The primary outcome is all-cause mortality and unplanned hospitalizations for heart failure in the 1 year following enrollment. The estimated enrollment is 288; the study completion date is listed as October 2017.

Practice Guidelines and Position Statements

The American College of Cardiology (ACC) and American Heart Association (AHA) released guidelines on the management of valvular heart disease in 2014. (39) The guidelines include the following class IIB recommendation related to the use of transcatheter MV repair for MR:

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. (Level of Evidence: B.)

The ACC, American Association for Thoracic Surgery, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons released a position statement on transcatheter therapies for MR in 2014. (40) 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.

In 2012, the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery released guidelines on the management of valvular heart disease.(41) These guidelines do not address transcatheter MV repair.

U.S. Preventive Services Task Force Recommendations

Transcatheter MV repair is not a preventive service.

Medicare National Coverage

The Centers for Medicare and Medicaid Services (CMS) has a proposed decision memo for transcatheter MV repair under Coverage with Evidence Development (CED). (42) As of May 15, 2014, CMS was seeking public comment on the proposed decision.

CMS proposes to cover transcatheter mitral valve repair (TMVR) under CED for the treatment of significant symptomatic MR when performed according to an FDA-approved indication and when all of the following conditions are met:

- The procedure is performed with a complete transcatheter MV repair system that has received FDA premarket approval (PMA) for that system's FDA approved indication.
    - Both a cardiac surgeon experienced in MV surgery and a cardiologist experienced in MV disease have independently examined the patient face-to-face and evaluated the patient's suitability for MV surgery and determination of prohibitive risk; and both physicians have documented the rationale for their clinical judgment and the rationale is available to the heart team.
    - The patient (preoperatively and postoperatively) 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.
    - TMVR must be performed in a hospital and with a surgical program and surgical staff that meet criteria outlined in the proposed decision memo.
    - 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 CFR Part 46 and 21 CFR Parts 50 & 56. The registry must track specific outcomes and answer specific research questions outlined in the proposed decision memo.

- TMVR is covered for 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:
    - The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TMVR.
    - As a fully-described, written part of its protocol, the clinical research study must critically evaluate the following questions:
        - 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 post-procedure as outlined in the proposed decision memo.

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Documentation Required for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.

IE

The following services are considered investigational and therefore not covered for any indication.

Type	Code	Description
CPT®	0343T	Transcatheter mitral valve repair percutaneous approach including transseptal puncture when performed; initial prosthesis
	0344T	additional prosthesis(es) during same session (List separately in addition to code for primary procedure)
	0345T	Transcatheter mitral valve repair percutaneous approach via the coronary sinus
HCPC	None	
ICD-9 Procedure	None	
ICD-10 Procedure	**For dates of service on or after 10/01/2015**	
	02QG4ZZ	Repair, mitral valve, percutaneous endoscopic, no device
	02RG4JZ	Replacement, mitral valve, percutaneous endoscopic, synthetic substitute
	02UG4JZ	Supplement, mitral valve, percutaneous endoscopic, synthetic substitute
ICD-9 Diagnosis	All Diagnoses	
ICD-10 Diagnosis	**For dates of service on or after 10/01/2015**	
	All Diagnoses	

Policy History

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

Effective Date	Action	Reason
9/30/2014	BCBSA medical policy adoption	Medical Policy Committee

Definitions of Decision Determinations

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

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

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

Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.