Medical Coverage Policy | Transcatheter Mitral Valve Repair

EFFECTIVE DATE:
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OVERVIEW

Transcatheter mitral valve (MV) repair is a potential alternative to surgical therapy for mitral regurgitation (MR) in patients who are considered at prohibitive risk for surgery. 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. Patients with multiple comorbidities could benefit from less invasive procedures for MV repair utilizing the MitraClip.

MEDICAL CRITERIA

BlueCHiP for Medicare and Commercial Products
Not Applicable

PRIOR AUTHORIZATION

Not Applicable

POLICY STATEMENT

BlueCHiP for Medicare
Transcatheter mitral valve repair with a device cleared by the U.S. Food and Drug Administration may be considered **medically necessary** for patients enrolled in an approved Clinical Trail.

Original Medicare (also referred to as Medicare "fee for service") covers most of the routine costs for BlueCHiP for Medicare members participating in qualified Medicare clinical trials. All claims for services as part of a clinical trial must be submitted to Original Medicare first. Please refer to the following policy for more detail Clinical Trial Mandates

Commercial Products:
Transcatheter mitral valve repair with a device cleared by the U.S. Food and Drug Administration may be considered **medically necessary** for patients with symptomatic, degenerative mitral regurgitation who are considered at prohibitive risk for open surgery.

COVERAGE

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Commercial Products:
Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable surgery benefits/coverage

BACKGROUND

Mitral Regurgitation: Epidemiology and Classification

Mitral regurgitation (MR) is the second most common valvular heart disease, occurring in 7% of people older than age 75 years and accounting for 24% of all patients with valvular heart disease. MR can result from a heterogeneous set of disease processes that may affect 1 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. 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 mitral regurgitation (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. In contrast, in functional mitral regurgitation (FMR), the primary abnormality is a dilated LV due to ischemic or dilated cardiomyopathy, which leads to secondary dilatation of an anatomically normal MV. 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, it 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.

The evidence for the use of MitraClip in patients with severe symptomatic DMR or functional mitral regurgitation (FMR) who are considered at prohibitive risk for open surgery includes single-arm cohort studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment related morbidity. The evidence for the use of transcatheter mitral valve repair devices other than the MitraClip for patients with MR 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.

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 because the underlying pathophysiology is related to LV dysfunction and dilatation. Primary treatment of the LV systolic dysfunction with angiotensin-converting enzyme inhibitors, β-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 (DMR), surgery is the main 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 and the American Heart Association 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 <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.

Standard open MV repair includes 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 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 MV.2,5

However, there are limitations to the standard approaches for MV surgery. While surgical MV repair is durable, its use is limited by the requirement for thoracotomy and cardiopulmonary bypass, which is 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, 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 United States, 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%, $p<0.001$) 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. Approaches to MV repair include direct leaflet repair, repair of the mitral annulus via direct annuloplasty, or indirect repair based on the annulus's proximity to the coronary sinus. There are also devices in development to counteract ventricular remodeling, and systems designed for complete MV replacement via catheter.

Direct Leaflet Approximation

One device that undertakes direct leaflet repair, the MitraClip® Clip Delivery System (Abbott Vascular, Menlo Park, CA), has approval through the U.S. Food and Drug Administration premarket approval process for use in certain patients with symptomatic MR (see Regulatory Status section). Of the transcatheter MV repair devices under investigation, MitraClip has the largest body of evidence evaluating its use and has been in use in Europe since 2008. 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. MitraClip is deployed via a transfemoral approach, with transseptal puncture used to access the left side of the heart and the MV. Placement of MitraClip leads to coapting of the mitral leaflets, thus creating a double-orifice valve.

Other MV Repair Devices

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, 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 was 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. 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 Lifesciences Percutaneous Mitral Annuloplasty System for the Treatment of Mitral Regurgitation) trial.

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 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, 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, Or-Yehuda, Israel), an implantable annuloplasty band with a transfemoral venous delivery system.

Transcatheter MV Replacement

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

REGULATORY STATUS

In October 2013, the MitraClip® Clip Delivery System (Abbott Vascular, Menlo Park, CA) was approved by the U.S. Food and Drug Administration (FDA) through the premarket approval process for treatment of "significant symptomatic mitral regurgitation (MR ≥3+) due to primary abnormality of the mitral apparatus (degenerative MR) in patients who have been determined to be at a prohibitive risk for mitral valve surgery by a heart team."12 FDA product code: NKM. FDA's approval was based on data from 1 randomized controlled trial (RCT) and 2 patient registry databases. These studies are described further in the Rationale section.

RATIONALE

This evidence review was created in July 2014 based, in part, on a 2014 Blue Cross Blue Shield Association (BCBSA) TEC Assessment that 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 the procedure did not meet Technology Evaluation Criteria (TEC). The evidence review has been updated periodically with literature reviews through searches of the Medline database. The most recent update covered the period through June 1, 2015.

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 transcatheter MV repair: 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.

MitraClip in Prohibitive Surgical Risk Candidates

The MitraClip device delivery system was approved by the U.S. Food and Drug Administration (FDA) 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 High Risk Registry (HRR) and the EVEREST II Real World Expanded Multicenter 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 MitraClip for 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/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 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 (2014)[14]	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)[15]	117	MR ≤2+, 74.6% (53/71)	• NYHA I/II, 81% (63/78) • Improved ≥1 class, 68% (53/78)	• Change in MLHFQ from baseline, 13.3points (p=0.03), n=44 • Change in 6MWT from baseline, 77.4 m (p<0.001), n=52
Estévez-Loureiro et al (2013)[16]	79	NR	NR	
Grasso et al (2013)[17]	28	NR	NR	Kaplan-Meier estimate of freedom from death, surgery, or ≥3+ MR, 70% (visual estimate from graph)
Chan et al (2012)[18]	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 MitraClip in high surgical risk patients. The evidence included 1 published study by Whitlow et al19 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 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).20 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 was limited to 47 patients and 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 transcatheter MR repair 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.

Nonrandomized Studies Evaluating MitraClip in Prohibitive Surgical Risk Populations
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 HRR study and the EVEREST II REALISM study, which included non-high-risk and high-risk arms in the United States. In addition, several cohort studies have reported experience with MitraClip in European centers, because the device has been 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 MitraClip compared with open MV repair.22,23 Concurrent 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. 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.9 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 transcatheter MV repair 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/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 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 of 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.24 Seventy percent of patients had FMR. Following MitraClip implantation, 325 patients (86%) had MR reduced 2+ or less. At 12 months, 225 patients (84%) had MR of 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.

An earlier (2012) analysis of 78 EVEREST II HRR study subjects with high surgical risk, who were compared with a historical cohort of high surgical risk patients who did not receive MitraClip, was published Whitlow et al.19 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.

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 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 lower. In addition, heart failure–related symptoms and quality of life have been shown to improve. Without intervention, symptomatic MR is likely to worsen. However, the natural history of DMR and FMR in patients with characteristics similar to those who underwent MitraClip

placement are not clearly defined, which limits conclusions drawn about the net health outcomes of MitraClip in patients who are not surgical candidates.

MitraClip in Surgical Candidates
Percutaneous repair of MR with MitraClip has been compared 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 studies of nonsurgical candidates, many evaluations of MitraClip among surgical candidates include mixedpopulations of FMR and DMR patients.

Other Transcatheter MV Repair Devices
Several devices other than MitraClip are being investigated for transcatheter MV repair, although none is FDA approved for use in the United States.

Summary of Evidence
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 abnormalityof 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. 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 MV (degenerative mitral regurgitation [DMR]) in
patients who are considered at prohibitive risk for surgery.

The evidence for the use of MitraClip in patients with severe symptomatic DMR or functional mitral regurgitation (FMR) who are considered at prohibitive risk for open surgery includes single-arm cohort studies. Relevant outcomes are overall survival, morbid events, functional outcomes, and treatment related morbidity. The available single-arm cohort 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 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 benefit compared with alternative therapies in this population. The body of evidence consists of single-arm studies, even though there are no strong barriers to controlled trials that compare MitraClip with continued medical management. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of MitraClip in patients with DMR or FMR who are considered candidates for open MV repair surgery 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 most rigorous evidence related to 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 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 in the MitraClip group had undergone surgical repair. Overall, the RCT and cohort study evidence suggests that the device is associated with lower rates of major complications than open repair and that results are durable for patients who remain free of recurrent or persistent MR after the first year. However, this trial has some methodologic limitations. The noninferiority margin of 25% was is 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 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. In addition, the most appropriate population of patients in terms of MR etiology for MitraClip therapy (FMR vs DMR) has not been well-established. The evidence is insufficient to determine the effects of the technology on health outcomes.

The evidence for the use of transcatheter mitral valve repair devices other than the MitraClip for patients with MR 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.

Clinical input supported the use of transcatheter MV repair in patients with DMR who are considered to be a prohibitive risk for open surgery, which is the Food and Drug Administration–approved indication for the MitraClip device. Given the lack of other treatment options for this population, the suggestive clinical evidence, and the support from clinical input, transcatheter MV repair with the MitraClip may be considered medically necessary for this patient population.

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 2014.49 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 [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 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. These guidelines do not address transcatheter MV repair.

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 transcatheter mitral valve repair (TMVR). CMS determined that it would cover TMVR under Coverage with Evidence Development (CED) 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:

- 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.
  - o 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.
  - o 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.
  - o TMVR must be performed in a hospital and with a surgical program and surgical staff that meet criteria outlined in the proposed decision memo.
  - o 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 an FDA-approved randomized clinical trial that fulfills all of the following:
  - o The heart team's interventional cardiologist(s) and cardiac surgeon(s) must jointly participate in the intra-operative technical aspects of TMVR.
  - o As a fully-described, written part of its protocol, the clinical research study must critically evaluate the following questions:
  - o What is the patient's post-TMVR quality of life (compared to pre-TMVR) at one year?
  - o 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.

CODING

BlueCHiP for Medicare

The following codes are considered medically necessary when billed with the correct modifier, (Q0 or Q1) as part of an approved Clinical Trial

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)

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

Commercial Products

The following codes are considered medically necessary;

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)

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

RELATED POLICIES
Clinical Trial Mandate

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