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| 2.02.30 | Transcatheter Mitral Valve Repair | | |
| Original Policy Date: | September 30, 2014 | Effective Date: | July 1, 2023 |
| Section: | 2.0 Medicine | Page: | Page 1 of 33 |

Policy Statement

- I. Transcatheter mitral valve repair (TMVR) with a device approved by the U.S. Food and Drug Administration (FDA) for use in mitral valve repair may be considered **medically necessary** for individuals with symptomatic, primary mitral regurgitation (MR) who are considered at prohibitive risk for open surgery (see Policy Guidelines section).
- II. TMVR with a device approved by the U.S. FDA may be considered **medically necessary** for individuals with heart failure and moderate-to-severe or severe symptomatic secondary MR despite the use of maximally tolerated guideline-directed medical therapy (see Policy Guidelines section).
- III. TMVR is considered **investigational** in all other situations.

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

Policy Guidelines

"Prohibitive risk" for open surgery may be determined based on:

- Presence of a Society for Thoracic Surgeons predicted mortality risk of 12% or greater and/or
- Presence of a logistic EuroSCORE of 20% or greater.

Moderate to severe or severe mitral regurgitation (MR) may be determined by:

- Grade 3+ (moderate) or 4+ (severe) MR confirmed by echocardiography
- New York Heart Association (NYHA) functional class II, III, or IVa (ambulatory) despite the use of stable maximal doses of guideline-directed medical therapy and cardiac resynchronization therapy (if appropriate) administered in accordance with guidelines of professional societies.

Optimal medical therapy may be determined by guidelines from specialty societies (e.g., American Heart Association/American College of Cardiology Guideline for the Management of Patients with Valvular Heart Disease, European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines for the Management of Valvular Heart Disease, American Heart Association/American College of Cardiology/Heart Failure Society of America Guideline for the Management of Heart Failure (refer to supplemental materials for guideline citations).

Coding

The following are category I CPT codes for this procedure:

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

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

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

Description

Transcatheter mitral valve repair (TMVR) is an alternative to surgical therapy for mitral regurgitation (MR). MR is a common valvular heart disease that can result from a primary structural abnormality of the mitral valve (MV) complex or a secondary dilatation of an anatomically normal MV due to a dilated left ventricle caused by ischemic or dilated cardiomyopathy. Surgical therapy may be underutilized, particularly in patients with multiple comorbidities, suggesting that there is an unmet need for less invasive procedures for MV repair. One device, MitraClip, has approval from the U.S. Food and Drug Administration for the treatment of severe symptomatic MR due to a primary abnormality of the MV (primary MR) in patients considered at prohibitive risk for surgery and for patients with heart failure and moderate-to-severe or severe symptomatic secondary MR despite the use of maximally tolerated guideline-directed medical therapy.

Related Policies

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

Benefit Application

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

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

Regulatory Status

In October 2013, the MitraClip Clip Delivery System (Abbott Vascular) was approved by the FDA through the premarket approval process for treatment of "significant symptomatic mitral regurgitation (MR $\geq 3+$) due to primary abnormality of the mitral apparatus (degenerative MR) in patients who have been determined to be at a prohibitive risk for mitral valve surgery by a heart team."¹⁹

In March 2019, the FDA approved a new indication for MitraClip, for "treatment of patients with normal mitral valves who develop heart failure symptoms and moderate-to-severe or severe mitral regurgitation because of diminished left heart function (commonly known as secondary or functional mitral regurgitation) despite being treated with optimal medical therapy. Optimal medical therapy includes combinations of different heart failure medications along with, in certain patients, cardiac resynchronization therapy and implantation of cardioverter defibrillators."

In September 2022, the FDA approved the PASCAL Precision Transcatheter Valve Repair System through the premarket approval process for treatment of "significant, symptomatic mitral regurgitation (MR $\geq 3+$) due to primary abnormality of the mitral apparatus (degenerative MR) in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team."²⁰

FDA product code for MitraClip and PASCAL: NKM.

Rationale

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

Patients with MR generally fall into 2 categories: primary (also called degenerative) and secondary (also called functional) MR. Primary MR results from a primary structural abnormality in the valve, which causes it to leak. This leak may result from a floppy leaflet (called prolapse) or a ruptured cord that caused the leaflet to detach partially (called flail).⁴ Because the primary cause is a structural abnormality, most cases of primary MR are surgically corrected. Secondary MR results from LV dilatation due to ischemic or dilated cardiomyopathy. This causes the mitral valve (MV) leaflets not to coapt or meet in the center.³ Because the valves are structurally normal in secondary MR, correcting the dilated LV using medical therapy is the primary treatment strategy used in the U.S.

Standard Management

Surgical Management

In symptomatic patients with primary MR, surgery is the main therapy. In most cases, MV repair is preferred over replacement, as long as the valve is suitable for repair and personnel with appropriate surgical expertise are available. The American College of Cardiology and the American Heart Association have issued joint guidelines on the surgical management of MV (See Supplemental Information).⁵

The use of standard open MV repair is limited by the requirement for thoracotomy and cardiopulmonary bypass, which may not be tolerated by elderly or debilitated patients due to their underlying cardiac disease or other conditions. In a single-center evaluation of 5737 patients with severe MR in the U.S., Goel et al (2014) found that 53% of patients did not have MV surgery performed, suggesting an unmet need for such patients.⁶

Isolated MV surgery (repair or replacement) for severe chronic secondary MR is not generally recommended because there is no proven mortality reduction and an uncertain durable effect on symptoms. Recommendations from major societies^{7,8} regarding MV surgery in conjunction with coronary artery bypass graft surgery or surgical aortic valve replacement are weak because the current evidence is inconsistent on whether MV surgery produces a clinical benefit.^{9,10,11,12}

Transcatheter Mitral Valve Repair

Transcatheter approaches have been investigated to address the unmet need for less invasive MV repair, particularly among inoperable patients who face prohibitively high surgical risks due to age or comorbidities. MV repair devices under development address various components of the MV complex and generally are performed on the beating heart without the need for cardiopulmonary bypass.^{1,13} Approaches to MV repair include direct leaflet repair,¹⁴ 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

Devices currently approved by the FDA for transcatheter mitral valve repair (TMVR) undergo direct mitral leaflet repair (also referred to as transcatheter edge-to-edge repair). Of the TMVR devices under investigation, MitraClip has the largest body of evidence evaluating its use; it has been in use in Europe since 2008.¹⁴ The MitraClip system is deployed percutaneously and approximates the open Alfieri edge-to-edge repair approach to treating MR. The delivery system consists of a catheter, a steerable sleeve, and the MitraClip device, which is a 4-mm wide clip fabricated from a cobalt-chromium alloy and polypropylene fabric. MitraClip is deployed via a transfemoral approach, with transseptal puncture used to access the left side of the heart and the MV. Placement of MitraClip leads to coaptation of the mitral leaflets, thus creating a double-orifice valve.

The PASCAL (PAddles Spacer Clasps ALfieri) Mitral Repair System (Edwards Lifesciences) is also a direct coaptation device and works in a similar manner to the MitraClip system.¹⁵ PASCAL has been in clinical use since 2016 and was approved for use in Europe in 2019.¹⁶ The delivery system consists of a 10-mm central spacer that attaches to the MV leaflets by 2 paddles and clasps.

Other Mitral Valve Repair Devices

Devices for TMVR that use different approaches are in development. Techniques to repair the mitral annulus include those that target the annulus itself (direct annuloplasty) and those that tighten the mitral annulus via manipulation of the adjacent coronary sinus (indirect annuloplasty). Indirect annuloplasty devices include the Carillon Mitral Contour System (Cardiac Dimension) and the Monarc device (Edwards Lifesciences). The CE-marked Carillon Mitral Contour System is comprised of self-expanding proximal and distal anchors connected with a nitinol bridge, with the proximal end coronary sinus ostium and the distal anchor in the great cardiac vein. The size of the connection is controlled by a manual pull back on the catheter. The Carillon system was evaluated in the Carillon Mitral Annuloplasty Device European Union Study and the follow-up Tighten the Annulus Now study, with further studies planned.¹⁷ The Monarc system also involves 2 self-expanding stents connected by a nitinol bridge, with one end implanted in the coronary sinus via the internal jugular vein and the other in the great cardiac vein. Several weeks after implantation, the biologically degradable coating over the nitinol bridge degrades, allowing the bridge to shrink and the system to shorten. It has been evaluated in the Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for the Treatment of Mitral Regurgitation trial.¹⁸

Direct annuloplasty devices include the Mitralign Percutaneous Annuloplasty System (Mitralign) and the AccuCinch[®] System (Guided Delivery Systems), both of which involve transcatheter placement of anchors in the MV; they are cinched or connected to narrow the mitral annulus. Other transcatheter direct annuloplasty devices under investigation include the enCorTC[™] device (MiCardia), which involves a percutaneously insertable annuloplasty ring that is adjustable using radiofrequency energy, a variation on its CE-marked enCor_{sq} Mitral Valve Repair System, and the Cardioband Annuloplasty System (Valtech Cardio), an implantable annuloplasty band with a transfemoral venous delivery system.

Transcatheter Mitral Valve Replacement

Permavalve (Micro Interventional Devices), under investigation in the U.S., is a transcatheter MV replacement device that is delivered via the transapical approach. On June 5, 2017, the SAPIEN 3 Transcatheter Heart Valve (Edwards Lifesciences) was approved by the FDA as an MV replacement device. These replacement valves are outside the scope of this evidence review.

Medical Management

The standard treatment for patients with chronic secondary MR is medical management. Patients with chronic secondary MR should receive standard therapy for heart failure with reduced ejection fraction; standard management includes angiotensin-converting enzyme inhibitor (or angiotensin II receptor blocker or angiotensin receptor-neprilysin inhibitor), beta-blocker and mineralocorticoid receptor antagonist, and diuretic therapy as needed to treat volume overload.^{4,3} Resynchronization

therapy may provide symptomatic relief, improve LV function, and in some patients, lessen the severity of MR.

Literature Review

This review was informed, in part, by a TEC Assessment (2014) that evaluated the use of transcatheter mitral valve repair (TMVR) in patients with symptomatic primary mitral regurgitation (MR) at prohibitive risk for mortality during open surgery.²¹

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

MitraClip and PASCAL

Primary Mitral Valve Regurgitation at Prohibitive Surgical Risk

Clinical Context and Therapy Purpose

The purpose of TMVR using MitraClip or PASCAL in patients who have primary MR and are at prohibitive risk for open surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

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

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

Intervention

The therapy being considered is TMVR using MitraClip or PASCAL.

Comparators

Comparators of interest are medical management. Given that primary MR is a mechanical problem and there is no effective medical therapy, an RCT comparing MitraClip or PASCAL with medical management is not feasible or ethical.

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Randomized Controlled Trials

The ongoing CLASP IID/IIF pivotal trial for the PASCAL device is enrolling adults with MR (3+ to 4+) into 1 of 3 cohorts, 2 of which have undergone interim analyses and were evaluated by the FDA for pre-marketing approval. The main cohort constituted a randomized, multicenter noninferiority study comparing PASCAL and MitraClip in patients with primary MR. The second cohort constituted a single-arm registry study (the PASCAL IID registry, described in the Non-Randomized Studies section) that enrolled patients with primary MR who were eligible for treatment in the study with PASCAL but were ineligible for randomization due to complex mitral valve anatomy (rendering them unsuitable for treatment with MitraClip).^{20,22} The third cohort constituted a randomized, multicenter study comparing PASCAL and MitraClip in patients with functional (secondary) MR receiving guideline-directed medical therapy, results of which have not yet been reported.²³

In the main CLASP IID cohort, eligible patients were randomized 2:1 to TMVR with PASCAL or MitraClip.²⁰ The primary safety endpoint was a composite of major adverse events at 30-day follow-up, including cardiovascular death, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding, and/or non-elective mitral valve re-intervention. The primary effectiveness endpoint was the proportion of patients with MR $\leq 2+$ at 6-month follow-up. The noninferiority margins for the primary safety and effectiveness endpoints were absolute differences between groups of 15% and 18%, respectively. The first planned interim analysis was performed after 180 patients were randomized and had undergone the study procedure attempt. Mean age was approximately 81 years; most participants were male (67% of PASCAL and 68% of MitraClip patients) and White (72% and 76% of PASCAL and MitraClip patients, respectively; 4.3% and 1.6% were Asian and 2.6% and 3.2% were Black or African American, respectively). All 180 patients randomized at the time of analysis underwent the procedure attempt. No differences between groups in New York Heart Association (NYHA) functional class, operative risk scores, or other baseline characteristics were identified. The most common reasons for prohibitive surgical risk were frailty (>84% in both groups) and a predicted mortality risk for mitral valve replacement $\geq 8%$ (>14% in both groups). In the primary analyses, PASCAL was noninferior to MitraClip for safety and effectiveness. The proportion of patients in the PASCAL (n=117) and MitraClip groups (n=63) who experienced a major adverse event at 30 days was 3.4% and 4.8% (upper bound of 95% confidence interval [CI] for between-group difference, 5.1%), respectively. The most common major adverse event was severe bleeding in both

PASCAL and MitraClip groups (2.6% and 3.2%, respectively). In the PASCAL group, 2 patients died prior to 30-day follow-up and 1 patient had missing 30-day and 6-month data. In the MitraClip group, 1 patient died prior to 30-day follow-up. The proportion of patients in the PASCAL (n=114) and MitraClip groups (n=62) with MR $\leq 2+$ at 6 months was 96.5% and 96.8%, respectively (lower bound of 95% CI for between-group difference, -6.2%). At 6 months, 6.1% of PASCAL recipients and 11.1% of MitraClip recipients had experienced a major adverse event, and all-cause mortality was 5.1% and 6.3%, respectively. Functional status, exercise capacity, and quality-of-life measures improved from baseline at comparable rates in both groups. No interactions between the primary outcomes and sex or age were identified in either group.

Non-Randomized Studies

A TEC Assessment (2014) evaluated the evidence on the use of MitraClip for primary MR, a U.S. Food and Drug Administration (FDA) approved indication.²¹ The Assessment included 5 case series reporting outcomes of patients with primary MR considered at high-risk of surgical mortality who underwent MitraClip placement. Three of the 5 case series were rated as poor because of low or unknown follow-up rates and are not discussed further. Tables 1 and 2 summarize patient characteristics and health outcomes of the case series by Reichenspurner et al (2013)²⁴, and Lim et al (2013),²⁵ which were considered higher quality. The Reichenspurner et al (2013) study reported data on 117 patients with primary MR who were enrolled in a European postmarketing registry. The Lim et al (2013) study reported data on 127 patients enrolled in the Endovascular Valve Edge-to-Edge REpair STudy (EVEREST II) High Risk Registry (HRR) and the Real World Expanded Multicenter Study of the MitraClip System (REALISM) registry and then retrospectively identified as meeting the definition of prohibitive risk and were followed for 1 year. The 30-day mortality rates were 6.0% and 6.3%, and 12- and 25-month mortality rates were 17.1% and 23.6%, respectively.^{24,26} In evaluable patients at 12 months, the percentages of patients who had an MR severity grade of 2 or less were 83.3% and 74.6% in the 2 studies; the percentages with NYHA class I or II functional status were 81% and 87%; and the percentages who improved at least 1 NYHA class level were 68% and 88%, respectively.

Table 1. Key MitraClip Case Series Characteristics

| Study; Trial | Country | Participants | Treatment Delivery | Follow-Up |
|---|---------|--|--------------------|-----------------|
| Reichenspurner et al (2013) ²⁴ ; ACCESS-EU | Europe | N=117 EF <40% or mean EF: 9.4% NYHA class ≥ 3 : 74% MR severity $\geq 3+$: 96.6% Mean EuroSCORE: 15.5% | MitraClip | 71 had 1-y data |
| Lim et al (2014) ²⁶ ; subset of patients at prohibitive risk of open surgery from EVEREST II HRR and REALISM | U.S. | N=127 EF <40% or Mean EF: 61% NYHA class ≥ 3 : 87% MR severity $\geq 3+$: 100% Mean STS score: 13.2% | MitraClip | 1.47 y |

Adapted from the TEC Assessment (2014).²¹

EF: ejection fraction; MR: mitral regurgitation; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons surgical risk score.

Table 2. 12-Month Outcomes for Key Case Series of MitraClip for Primary Mitral Valve Disease

| Study; Trial | Original N | MR Grade at 12 Months, % (n/N) | NYHA Class at 12 Months, % (n/N) | Other Pertinent Outcomes at 12 Months |
|--|------------|---------------------------------------|----------------------------------|---|
| Reichenspurner et al (2013) ²⁴ ; ACCESS-EU | 117 | MR severity $\leq 2+$: 74.6% (53/71) | Class I/II: 81% (63/78) | Change in MLHFQ from baseline, 13.3 points (p=.03), n=44 |
| Lim et al (2014) ²⁶ ; subset of patients at | 127 | MR severity $\leq 2+$: 83.3% (70/84) | Class I/II: 86.9% (73/84) | Improved ≥ 1 class: 68% (53/78) Change in 6MWT from baseline, 77.4 m (p<.001), n=52 SF-36 PCS score change, 6.0 (95% CI, 4.0 to 8.0), n=76 |

| Study; Trial | Original N | MR Grade at 12 Months, % (n/N) | NYHA Class at 12 Months, % (n/N) | Other Pertinent Outcomes at 12 Months |
|--|------------|--------------------------------|--|--|
| prohibitive risk of open surgery from EVEREST II HRR and REALISM | | | Improved ≥ 1 class: 86.9% (73/84) | SF-36 MCS score change, 5.6 (95% CI, 2.3 to 8.9), n=76 |

Adapted from the TEC Assessment (2014).²¹

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

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

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

The FDA, on the contrary, concluded that the totality of the evidence demonstrated reasonable assurance of safety and effectiveness of MitraClip to reduce MR and provide patient benefit in this discreet and specific patient population based on the following¹⁹:

- It is broadly accepted that primary MR is a mechanical problem in which there is a primary abnormality of the mitral apparatus and the "leaflets are broken". There is no medical therapy for reducing primary MR, which must be treated with mechanical correction of the mitral valve (MV).
- The observed procedural mortality rate with MitraClip was 6.4% (95% confidence interval [CI], 2.8% to 12.0%) at 30 days. This rate was lower than the predicted mortality rate of 13.2% (95% CI, 11.9% to 14.5%) using STS Replacement Risk Score or 9.5% (95% CI, 11.3% to 13.7%) using STS Repair Score for the Lim et al (2014) cohort.
- While acknowledging the pitfalls of using historical controls from the Duke Registry, the FDA found no elevated risk of mortality in MitraClip cohort patients over nonsurgical management and both immediate and long-term improvement in MR severity. MR severity grade of 2+ or less and of 1+ or less was observed in 82% and 54% of surviving patients at

discharge, respectively. This improvement was sustained at 12 months, with the majority (83.3%) of surviving patients reporting MR severity grade of 2+ or less and 36.9% reporting MR severity grade of 1+ or less. At 12 months, freedom from death and MR severity grade greater than 2+ was 61.4%, and freedom from death and MR severity grade greater than 1+ was 27.2%.

- Quality of life was assessed using the 36-Item Short-Form Health Survey (SF-36). The mean difference in the Physical Component Summary and Mental Component Summary scores from baseline to 12 months improved by 6 and 5.6 points, respectively, which is above the 2- to 3-point minimally important difference threshold reported in the literature.²⁷ Sensitivity analyses showed that these effectiveness results were robust to missing data.
- The commercial post registry data of over 8300 patients (one-third primary MR and two-thirds secondary MR) outside the U.S. suggests that mortality rates reported in patients at prohibitive risk of surgery undergoing the MitraClip procedure do not appear to be elevated and are not unexpected given the age and burden of comorbidities of the patients treated. Reported mortality ranges were: in-hospital mortality, 0% to 4%; 30-day mortality, 0% to 9.1%; and 6- to 12-month mortality, 8% to 24%. Reported clinical benefits were: improvement in MR severity grade of 2+ or less after MitraClip in more than 75% of patients; improvement in 6-minute walk distance of 60 to >100 meters (the generally accepted threshold is >40 m), and percentages of patients who improved to an NYHA class of I or II ranged from 48% to 97%.
- The probable adverse event risks of the MitraClip included procedure-related complications such as death (6.3%), stroke (3.4%), prolonged ventilation (3.1%), and transfusion greater than 2 units (12.6%), major vascular complications (5.4%), noncerebral thromboembolism (1.6%), new onset of atrial fibrillation (3.9%), and atrial septal defect (1.6%).

Table 3. Key Observational Comparative Study Characteristics

| Study | Design | Country | Dates | Participants | Treatment | Treatment | Follow-up |
|--------------------------|--|---------|---------|--|-----------|------------------------|-----------|
| FDA (2013) ¹⁹ | Single cohort with historical comparator | U.S. | Unclear | MitraClip cohort N=127 Age: 82.4 y >75 y: 84% NYHA class ≥III: 87% STS predicted mortality: 13.2% LVEF: 61% Duke cohort N=65 Age: 76.8 y >75 y: 68% NYHA class ≥III: 44% STS predicted mortality: 13.3% LVEF: 44% | MitraClip | Nonsurgical management | 1 y |

FDA: Food and Drug Administration; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons.

Table 4. Key Observational Comparative Study Results

| Study | Percent Event Free (95% CI), % | | | Freedom From Death and MR >2+ | Freedom From Death and NYHA Class III/IV |
|--------------------------|--------------------------------|---------------------|---------------------|-------------------------------|--|
| | At 30 Days | At 6 Months | At 12 Months | | |
| FDA (2013) ¹⁹ | N=192 | N=192 | N=192 | N range, 114-124 | N range, 114-124 |
| MitraClip | 93.6 (87.6 to 96.8) | 84.8 (77.2 to 90.0) | 75.2 (66.1 to 82.1) | Baseline: 10% | Baseline: 13% |

| Percent Event Free (95% CI), % | | | |
|--------------------------------|---------------------|---------------------|---------------------|
| | | | |
| | | | 30 d: 82% |
| | | | 30 d: 76% |
| | | | 12 mo: 61% |
| | | | 12 mo: 64% |
| Duke cohort | 89.1 (78.5 to 94.7) | 79.6 (67.4 to 87.6) | 69.4 (56.3 to 79.3) |

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

Subsequent to the FDA approval of MitraClip in 2013, patients who received MitraClip under Medicare coverage were required to enroll in the joint STS and American College of Cardiology Transcatheter Valve Therapy Registry as part of coverage under evidence development (see the Medicare National Coverage section). Initial results from this U.S.-based registry were reported in 2016 (short-term outcomes) and in 2017 (long-term outcomes) and summarized in Table 5.^{28,29} In the initial results of 564 patients enrolled between 2013 to 2014 from 561 U.S. centers, the median STS predicted risk of mortality scores for MV repair and replacement were 7.9% (range, 4.7% to 12.2%) and 10.0% (range, 6.3% to 14.5%), respectively.²⁸ The in-hospital mortality rate was 2.3% and the 30-day mortality rate was 5.8%. These results are consistent with those reported in the cohort by Lim et al (2014) used by the FDA for approval²⁶ and supports that a favorable benefit-risk ratio is attainable outside a clinical trial setting in appropriately selected patients. At 1 year, the proportion of patients who died was 25.8%, had a repeat hospitalization for heart failure (HF) was 20.2%, and cumulative incidence of mortality or rehospitalization for HF was 37.9%.²⁹ Higher age, lower baseline LV ejection fraction, worse postprocedural MR, moderate or severe lung disease, dialysis, and severe tricuspid regurgitation were associated with higher mortality or rehospitalization for HF. The persistency of mortality (25.8%) and heart failure rehospitalization (20.2%) at 1 year despite the effectiveness of MitraClip remains a concern. However, the results observed in the Transcatheter Valve Therapy Registry at 1 year were comparable with the 1-year rates observed in the analysis of high-risk patients in the EVEREST II (23.8%) and REALISM (18.0%) studies.³⁰

An open-label head-to-head trial by Gercek et al (2021) evaluated the efficacy of the PASCAL system versus the MitraClip system in patients with severe primary MR.³¹ During the study time frame, 38 patients with primary MR underwent percutaneous edge-to-edge MV repair; 22 received the PASCAL device and 16 received MitraClip intervention. The decision of the device used was made at the discretion of the interventionalist. All patients were in NYHA functional class III or IV and had MR severity scores of 3+ or 4+. Procedural success was achieved in 95.5% of patients who had PASCAL implantation versus 87.5% of patients with MitraClip implantation. In 86.4% of patients who received the PASCAL device, a residual MR severity grade $\leq 1+$ was achieved, whereas, reduction to MR severity grade $\leq 1+$ with MitraClip was achieved in 62.5% of patients ($p=.039$). No patients in either group had any periprocedural major adverse events.

The second cohort of patients who were enrolled in the single-arm PASCAL IID registry cohort included: patients with primary MR enrolled in the CLASP IID/IIF trial comparing PASCAL and MitraClip who were eligible for use of PASCAL but ineligible to undergo randomization due to complex mitral valve anatomy precluding use of MitraClip.^{20,32} Outcomes of the initial analysis of this registry study are summarized in Table 5. Among 92 patients who underwent successful PASCAL implantation (6 patients did not receive the device due to inability to grasp leaflets, increased transmitral valve gradient, or insufficient MR reduction), mean age was 81 years; most were male (62%) and White (73%; 3.3% were Asian and 4.3% were Black or African American). At 30-day follow-up, 8.7% of patients in the registry cohort had experienced a major adverse event, the most common of which was severe bleeding (4.3%); at 6-month follow-up, 12% had experienced a major adverse event and all-cause mortality was 6.5%. Severity of MR was $\leq 2+$ in 91% of patients at 6 months.

Table 5. Summary of U.S.-Based Transcatheter Valve Therapy Registry Data

| | No. of Patients | Primary MR, % | Secondary MR, %Study | Postimplantation MR Grade ≤ 2 , % | In-Hospital Death, % | 30-Day Death, % | 6-Month Death, % | 1-Year Death, % |
|--------------------------------------|-----------------|---------------|----------------------|--|----------------------|-----------------|------------------|-----------------|
| Sorajja et al (2016) ²⁸ , | 564 | 86 | 14 | 93 | 2.3 | 5.8 | NR | NR |
| Sorajja et al (2017) ²⁹ , | 2952 | 86 | 9 | 92 | 2.7 | 5.2 | NR | 25.8 |
| FDA (2022) ²⁰ , | 92 | 100 | 0 | 91 | NR | 2.2 | 6.5 | NR |

MR: mitral regurgitation; NR: not reported

Other multiple subgroup analyses and systematic reviews have been reported using the EVEREST II HRR, REALISM, CLASP IID/IIF, and other European/Non-European studies/registries but are not discussed further because they did not report results stratified by MR etiology (primary MR or secondary MR) or were of poor quality or did not add substantial clarity to the evidence already discussed herein.^{30,33,-47}

Section Summary: Primary Mitral Valve Regurgitation at Prohibitive Surgical Risk

The evidence for the use of MitraClip and PASCAL in patients with primary MR at prohibitive surgical risk consists of 1 RCT, and otherwise primarily of single-arm prospective cohort and registry studies. Included are the pivotal EVEREST II HRR and EVEREST II REALISM studies and the Transcatheter Valve Therapy Registry studies. These studies have demonstrated that MitraClip implantation is feasible, with a procedural success rate greater than 90%, 30-day mortality rates ranging from 2.3% to 6.4% (less than predicted STS mortality score for MR repair or replacement [range, 9.5% to 13.2%]), MR severity of 2+ or less in 82% to 93% patients, and clinically meaningful gains in quality of life (5- to 6-point gain in SF-36 scores). However, the 1-year mortality or HF hospitalization rates remained considerably high (38%) compared with U.S.-based registry data thereby raising uncertainty about the long-term benefits. The randomized cohort of the CLASP IID/IIF trial demonstrated noninferiority of PASCAL to MitraClip for safety and effectiveness in reducing MR severity to 2+ or less, and findings from the single-arm PASCAL IID registry cohort of this study further indicate that PASCAL is safe and effective in patients with complex mitral valve anatomy precluding the use of MitraClip.

Heart Failure and Secondary Mitral Valve Regurgitation

Clinical Context and Therapy Purpose

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

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with HF and moderate-to-severe or severe symptomatic SMR despite the use of maximally tolerated guideline-directed medical therapy.

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

Intervention

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

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Reviews

A systematic review and meta-analysis by Kumar et al (2020)⁴⁸, evaluated the comparison of MitraClip plus medical therapy to medical therapy alone in patients with SMR (N=1130) using data from the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) and the Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) RCTs discussed below, as well as 2 preceding small propensity score-matched observational studies. Pooled analyses that included the RCT's and the observational studies found that compared to medical therapy alone, at 2 years of follow-up, MitraClip plus medical therapy significantly reduced the risk of all-cause mortality (relative risk [RR], 0.72; 95% CI, 0.55 to 0.95; $I^2=55%$), readmission events for HF (RR, 0.62; 95% CI, 0.42 to 0.92 ; $I^2=90%$), but not cardiovascular mortality (RR, 0.69; 95% CI, 0.47 to 1.02 ; $I^2=68%$). Further, results of fixed-effect meta-regression suggest that baseline LV end-diastolic volume and age are associated with all-cause mortality and cardiovascular mortality outcomes. However, the interpretation of these pooled analyses is limited by their considerable heterogeneity and the potential for increased risk of selection bias due to the inclusion of the nonrandomized studies.

Randomized Controlled Trials

Limited experience using PASCAL in patients with SMR has been reported.⁴⁹ This use is being investigated in a randomized cohort of the CLASP IID/IIF trial; analysis of this cohort has not yet been reported.²³

The evidence for the use of MitraClip in patients with SMR consists of 2 RCTs, the COAPT^{50,51}, and the MITRA-FR^{52,53} (Tables 6 and 7). Both trials compared MitraClip plus medical therapy to medical therapy alone in patients with SMR and heart failure, but they differed in their eligibility criteria and primary outcome measures. COAPT enrolled 614 patients at 78 centers in the U.S. and Canada.⁵⁰ MITRA-FR enrolled 304 patients at 37 centers in France.^{52,53}

COAPT found a significant benefit for Mitraclip on the primary efficacy outcome (all HF hospitalizations within 24 months) and the primary safety outcome (freedom from device-related complications at 12 months).⁵⁰ Improvements in MR severity, quality-of-life measures, and functional capacity persisted to 36 months in patients who received TMVR.⁵¹ In the final analysis of COAPT through 5-year follow-up, rates of all-cause death (hazard ratio [HR] 0.72, 95% CI 0.58 to 0.89) and cardiovascular death (HR 0.71, 95% CI 0.56 to 0.90), hospitalization for any reason (HR 0.75, 95% CI 0.63 to 0.89) and for cardiovascular reason (HR 0.64, 95% CI 0.53 to 0.77), death or hospitalization for heart failure (HR 0.53, 95% CI 0.44 to 0.64), and unplanned mitral valve intervention or surgery (HR 0.09, 95% CI 0.05 to 0.17) were significantly lower in the MitraClip arm.⁵⁴ The 5-year rate of freedom from device-related complications was 89.2%; severe mitral stenosis was reported in 7.6% of MitraClip patients, none of whom underwent surgery for severe mitral stenosis. No patients in the control group developed mitral stenosis. Crossover TMVR had been performed in 21.5% of patients in the control group at median 26 months after randomization; in a post hoc analysis, crossover TMVR was independently associated with lower risk of subsequent death or hospitalization for heart failure (HR 0.53, 95% CI 0.36 to 0.78).

In contrast, the MITRA-FR investigators found no significant differences between Mitra-Clip plus medical therapy and medical therapy alone on the composite primary outcome (death from any cause or unplanned HF hospitalization at 12 months) or any secondary outcome, including all-cause mortality at 12 and 24 months and cardiovascular death at 12 and 24 months (See Table 7).^{52,53}

Although the reasons for these discrepant results are not entirely clear, differences in the studies' design and conduct have been proposed as possible explanations.^{55,56,57} The severity of MR and HF among the patients in the trials differed. COAPT participants had more severe MR at baseline (effective regurgitant orifice area, 41 vs. 31 mm²) and remained symptomatic despite the use of maximal doses of guideline-directed medical therapy.^{7,58,57} In both trials, eligible patients had to be symptomatic despite the use of optimal medical therapy. In COAPT, however, a central eligibility committee confirmed that the patient was using maximal doses of guideline-directed medical therapy prior to enrollment, and patients who improved with medical therapy were excluded. MITRA-FR had less stringent eligibility criteria and patients had more changes in medical therapy during the trial, indicating their treatment might not have been optimized. Additionally, patients in MITRA-FR had further progressed HF as indicated by LV dilation and may have been less likely to benefit from MR treatment.

There is some evidence that technical success and procedural safety differed between the trials.⁵⁷ Procedural complications were higher in MITRA-FR than in COAPT, and more patients in MITRA-FR experienced residual MR class >3+ post-procedure (both acutely and at 12 months).

Table 6. Summary of Key Randomized Controlled Trial Characteristics

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|--|---------------|-------|-----------|---|---|--------------------------------|
| | | | | | Active | Comparator |
| Stone et al (2018); ⁵⁰]COAPT | US and Canada | 78 | 2012-2017 | Ischemic or nonischemic cardiomyopathy with LVEF 20% to 50%; moderate-to-severe (grade 3+) or severe (grade 4+) secondary MR; symptomatic (NYHA functional class II, III, or IVa) despite the use of stable maximal doses of guideline-directed medical therapy and cardiac resynchronization therapy | N=302 MitraClip plus medical therapy | N=312 Medical therapy alone |

| Study; Trial | Countries | Sites | Dates | Participants | Interventions |
|---|-----------|-------|-----------|---|---|
| Obadia et al (2018); ⁵² MITRA-FR | France | 37 | 2013-2017 | Severe SMR with a regurgitant volume of greater than 30ml per beat or an EROA \geq 20 mm ² ; NYHA functional class II, III, or IV despite optimal standard of care therapy for heart failure according to investigator LVEF between 15% and 40%; not appropriate for MV surgery by local heart team assessment | N=152 N=152 MitraClip plus medical therapy Medical therapy alone |

COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; EROA: effective regurgitant orifice area; LVEF: left ventricular ejection fraction; MITRA-FR: Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation; MR: mitral regurgitation; MV: mitral valve; NYHA: New York Heart Association; SMR: secondary mitral regurgitation.

Table 7. Summary of Key Randomized Controlled Trial Results

| Study | Primary Outcome: HF hospitalizations within 24 months | Primary Outcome: Death from any cause or unplanned HF hospitalization at 12 months | All-cause mortality at 12 months | Cardiovascular death at 12 months | All-cause mortality at 24 months | Cardiovascular death at 24 months | MR grade 2+ or lower at 12 months | NYHA class I or II at 12 months | Primary Safety Outcome: Freedom from device-related complications at 12 months ¹ | Serious Adverse events at 1 year ² | Periprocedural complications during device implantation |
|---|---|--|----------------------------------|-----------------------------------|----------------------------------|-----------------------------------|-----------------------------------|---------------------------------|---|---|---|
| Stone et al (2018); ⁵⁰ COAPT | | | | | | | | | | | |
| Sample size | 612 | | 612 | | 612 | 612 | 385 | 469 | 302 | | |
| Medical therapy alone | 283/416.8 (67.9%) | | 57 (19.1%) | | 121/312 (46.1%) | 97 (38.2%) | 82/175 (46.9%) | 115/232 (49.6%) | | | |
| MitraClip + medical therapy | 160/446.5 (35.8%) | | 70 (23.2%) | | 80/302 (29.1%) | 61 (23.5%) | | 171/237 (72.2%) | 96.6% (94.8%) | | |
| HR (95% CI); p-value | 0.53 (0.40 to 0.70); p<.001 | | 0.81 (95% CI 0.57 to 1.15); | | 0.62 (0.46 to 0.81); | 0.59 (90.43 to 0.81); p=.001 | p<.001 | p<.001 | | | |

| Study | Primary Outcome: HF hospitalizations within 24 months | Primary Outcome: Death from any cause or unplanned HF hospitalization at 12 months | All-cause mortality at 12 months | Cardiovascular death at 12 months | All-cause mortality at 24 months | Cardiovascular death at 24 months | MR grade 2+ or lower at 12 months | NYHA functional class I or II at 12 months | Primary Safety Outcome: Freedom from device-related complications at 12 months ¹ | Serious Adverse events at 1 year ² | Periprocedural complications during device implantation |
|---|---|--|----------------------------------|-----------------------------------|----------------------------------|-----------------------------------|-----------------------------------|--|---|---|---|
| | | | p<.001 for noninferiority | | 0.82); p<.001 | | | | Kaplan-Meier estimate of event-free rate (lower 95% confidence limit) | | |
| NNT 3.1 | | | | | | | | | | | |
| Obadia et al (2018); 12-month results ⁵² ;lung et al (2019) 24-month results ⁵³ ;MITRA-FR | | | | | | | | | | | |
| Sample size | 304 | 304 | 304 | 304 | 304 | 304 | | | | 304 | |
| Medication therapy alone | 94/152 (62.3%) | 78/152 (51.3%) | 34/152 (22.4%) | 31/152 (20.4%) | 52/152 (34.2%) | 48/152 (31.6%) | | | | 121/152 (79.6%) | |
| MitraClip + medication therapy | 85/152 (55.9%) | 83/152 (54.6%) | 37/152 (24.3%) | 33/152 (21.7%) | 53/152 (34.9%) | 47/152 (31.0%) | | | | 125/152 (82.2%) | 21/144 (14.6%) |
| HR (95% CI); p-value | 0.97 (0.72 to 1.30) | 1.16 (0.73 to 1.84); p=.53 | 1.11 (0.69 to 1.77) | 1.09 (0.67 to 1.78) | 1.02 (0.70 to 1.50) | 0.99 (0.66 to 1.48) | | | | p-values not reported because no adjustment was made for multiple testing | |

CI: confidence interval; COAPT: Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; HF: heart failure; HR: hazard ratio; MITRA-FR: Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation; MR: mitral regurgitation; NNT: number needed to treat; NYHA: New York Heart Association.

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

² includes prespecified adverse events heart transplantation or mechanical cardiac assistance, ischemic or hemorrhagic stroke, myocardial infarction, need for renal-replacement therapy, severe hemorrhage, and infections

Tables 8 and 9 display notable gaps identified in COAPT and MITRA-FR. Patients enrolled in MITRA-FR had less severe MR and more severe HF than those who are likely to benefit from MV treatment. Design and conduct gaps in both trials include their open-label design and lack of information on allocation concealment. Lack of blinding is less of a concern with objective outcome measures but could impact the validity of measures of symptoms and quality of life. At baseline, more patients in the intervention group in MITRA-FR had a previous myocardial infarction. Otherwise, there were no significant differences between groups at baseline.

Table 8. Study Relevance Limitations

| Study | Population ^a | Intervention ^b | Comparator ^c | Outcomes ^d | Follow-Up ^e |
|---|-------------------------|---------------------------|-------------------------|-----------------------|------------------------|
| Stone et al (2018); ⁵⁰ COAPT | | | | | |
| Obadia et al (2018); ⁵² MITRA-FR | 4 | | 2 | | 1 |

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

^a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

^b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

^c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

^d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

^e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 9. Study Design and Conduct Limitations Gaps

| Study | Allocation ^a | Blinding ^b | Selective Reporting ^c | Data Completeness ^d | Power ^e | Statistical ^f |
|---|-------------------------|-----------------------|----------------------------------|--------------------------------|--------------------|--------------------------|
| Stone et al (2018); ⁵⁰ COAPT | 3 | 1,2 | | | | |
| Obadia et al (2018); ⁵² MITRA-FR | 3 | 1,2 | | | | |

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

^a Allocation key: 1. Participants not randomly allocated; 2. Allocation not concealed; 3. Allocation concealment unclear; 4. Inadequate control for selection bias.

^b Blinding key: 1. Not blinded to treatment assignment; 2. Not blinded outcome assessment; 3. Outcome assessed by treating physician.

^c Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.

^d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

^e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

^f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p values not reported; 4. Comparative treatment effects not calculated.

Non-Randomized Studies

EXPAND was a prospective, multicenter, post-marketing observational study designed to evaluate safety outcomes (as a composite of major adverse events, including all-cause death, myocardial infarction, stroke, or non-elective surgery for device-related complications, at 30 days) in patients treated with MitraClip.⁵⁹ A total of 1041 patients from 22 sites in the U.S. and 35 sites in Europe were enrolled in EXPAND, 413 of whom received MitraClip for SMR. Among these patients, mean age was 75 years and most were male (58%) with class III NYHA functional status (66%). The acute procedural success rate was 97%, and 99% had MR \leq 2+ at hospital discharge. At 30-day follow-up, 3.6% of patients had experienced a major adverse event, most of which were cardiovascular deaths (2.7%). At 1-year follow-up, 99.6% of patients had MR maintained at \leq 2+ and 1-year rates of all-cause death

and hospitalization for heart failure were 17.7% and 26% (representing a 65% reduction from baseline in annualized heart failure hospitalizations; $p < .001$), respectively; repeat MV intervention and MV replacement each occurred in 1.4% of patients.

Section Summary: Heart Failure and Secondary Mitral Regurgitation

The evidence for the use of MitraClip in patients with SMR consists of a systematic review, 2 RCTs, and observational studies. The trials had discrepant results, but the larger trial, with patients selected for nonresponse to maximally tolerated therapy, found a significant benefit for MitraClip after up to 5 years compared to medical therapy alone, including improvements in OS and hospitalization for heart failure. Improvements in MR severity, quality of life measures, and functional capacity persisted to 36 months in patients who received TMVR. The systematic review confirmed the benefit of MitraClip found in the larger RCT, but had important methodological limitations.

Primary or Secondary Mitral Regurgitation in Surgical Candidates

Clinical Context and Therapy Purpose

The purpose of TMVR using MitraClip in patients who have symptomatic primary or SMR and are surgical candidates is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The following PICO was used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is TMVR using MitraClip.

Comparators

Relevant comparators are open MV repair and open MV replacement.

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

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Systematic Review

A systematic review by Takagi et al (2017) identified 1 RCT and 6 nonrandomized comparative studies evaluating MitraClip and surgery.⁶⁰ The RCT (EVEREST II) is described below. The systematic review conducted several pooled analyses. The meta-analysis did not detect a statistically significant difference in early (30-day or in-hospital) mortality between the MitraClip and surgery groups (pooled odds ratio [OR], 0.54; 95% CI, 0.27 to 1.08; $p=.08$). Similarly, a pooled analysis of late survival (≥ 6 months) did not find a statistically significant difference between the MitraClip and surgery groups (pooled OR/hazard ratio [HR], 1.17; 95% CI, 0.77 to 1.78; $p=.46$). However, there was a significantly higher incidence of recurrent MR in the MitraClip than in the surgery group (pooled OR/HR, 4.80; 95% CI, 2.58 to 8.93; $p<.001$).

Randomized Controlled Trial

Feldman et al (2011) reported on the results of EVEREST II, an RCT that evaluated symptomatic or asymptomatic patients with grade 3+ or 4+ chronic MR who had SMR or primary MR etiology ; patients were randomized to MitraClip or open MV repair/replacement (see Table 10).^{61,62} Most patients (73%) had primary MR. Patients were excluded if they had an MV orifice area less than 4.0 cm or leaflet anatomy that precluded MitraClip device implantation, proper MitraClip positioning, or sufficient reduction in MR. MitraClip was considered to have acute procedural success if the clip deployed and MR grade was reduced to less than 3+.

Trial results are summarized in Table 11. In the intention-to-treat (ITT) analysis, for patients who did not have acute procedural success with MitraClip and subsequently underwent open MV repair, the efficacy endpoint was considered met for MitraClip group subjects if they were free from death, reoperation for MR, and MR grade greater than 2+ at 12 months. The trial had a predetermined efficacy endpoint of noninferiority of the MitraClip strategy, with a margin of 25% for the ITT analysis and 31% for prespecified per-protocol analyses. This implies that the MitraClip strategy would be noninferior to surgery at 12 months if the upper bound of difference in the proportion of patients achieving the primary efficacy endpoint between the 2 groups did not exceed 25 percentage points for the ITT analysis and 31 percentage points for the per-protocol analysis. Results showed that TMVR was less effective at reducing MR than conventional surgery before hospital discharge. MitraClip group subjects were more likely to require surgery for MV dysfunction, either immediately post-MitraClip implantation or in the 12 months following. Twenty percent (37/181) of the MitraClip group and 2% (2/89) of the surgery group required reoperation for MV dysfunction ($p<.001$). Although in the ITT analysis rates of MR severity grades of 3+ or 4+ at 12 months were similar between groups, in the published per-protocol analysis, patients in the MitraClip group were more likely to have severity grades of 3+ or 4+ (17.2% [23/134] vs. 4.1% [3/74] ; $p=.01$), which would suggest that a larger proportion of patients with grade 1+ or 2+ MR in the MitraClip group had surgical repair. As expected, rates of major adverse events at 30 days were lower in the MitraClip group (15% [27/181]) than in the surgery group (48% [45/89]; $p<.001$). 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; $p<.001$) of the surgery group. Long-term follow-up at 4 years⁶³ and 5 years⁶⁴ showed that significantly more MitraClip patients required surgery for MV dysfunction during the follow-up period.

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

The REPAIR MR RCT is comparing TMVR with MitraClip to surgical MV repair in surgical candidates who are older (age ≥ 75 years) or at moderate surgical risk; results have not yet been reported.⁶⁵

Table 10. Key Randomized Controlled Trial Characteristics

| Study; Trial | Countries | Sites | Dates | Participants | Interventions | |
|---|--------------|-------|-----------|---|---------------|--------------------------------------|
| | | | | | Active | Comparator |
| Feldman et al (2011) ⁶¹ ; EVEREST II | U.S., Canada | 37 | 2005-2008 | N=279 Grade 3+ or 4+ chronic MR Symptomatic (LVEF \geq 25% and LVESD \leq 55 mm) or asymptomatic (LVEF 25%-60% or LVESD 40-55 mm or new AF or pulmonary hypertension) | TMVR (n=184) | Open MV repair or replacement (n=95) |

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

Table 11. Key Randomized Controlled Trial Results

| Study; Trial | Freedom From Death, Surgery for MR Dysfunction, and Grade 3+ or 4+ MR | Major AE at 30 Days ^a | Surgery for MV Dysfunction ^b | Death | Grade 3+ or 4+ MR |
|---|---|----------------------------------|---|--------------|-------------------|
| Feldman et al (2011) ⁶¹ ; EVEREST II ^c (1 year) | 270 | 274 | 270 | 270 | 270 |
| TMVR | 100/181 (55%) | 27/180 (15%) | 37/181 (20%) | 11/181 (6%) | 38/181 (21%) |
| Open repair | 65/89 (73%) | 45/94 (48%) | 2/94 (2%) | 5/94 (6%) | 18/94 (20%) |
| p | .007 | <.001 | <.001 | 1.00 | 1.00 |
| FDA (2013) ¹⁹ ; EVEREST II (1 year) | Range, 156-208 | 274 | - | - | - |
| TMVR | 97/134 (72%) ^d | 27/180 (15%) | NR | NR | NR |
| Open repair | 37/82 (45%) ^e 65/74 (88%) ^d | 45/94 (48%) | NR | NR | NR |
| p | 51/74 (69%) ^e .001 ^{d,f} | <.001 | NR | NR | NR |
| Mauri et al (2013) ⁶³ ; EVEREST II (4 years) | .169 ^{e,f} NR | NR | 234 | 234 | 234 |
| TMVR | NR | NR | 40/161 (25%) | 28/161 (17%) | 35/161 (22%) |
| Open repair | NR | NR | 4/73 (6%) | 13/73 (18%) | 18/73 (25%) |
| p | NR | NR | <.001 | .914 | .745 |
| Feldman et al (2015) ⁶⁴ ; EVEREST II(5 years) | | | 197 | 197 | 197 |
| TMVR | NR | NR | 43/154 (28%) | 32/154 (21%) | 19/154 (19%) |
| Open repair | NR | NR | 5/56 (9%) | 15/56 (27%) | 1/56 (2%) |
| p | NR | NR | .003 | .36 | .02 |

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

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

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

^b The rate of the first MV surgery in the percutaneous repair group and the rate of reoperation for MV dysfunction in the surgery group

^c Crossover to surgery in the immediate postprocedure period if MitraClip failed to adequately reduce MR was

considered a successful treatment strategy.

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

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

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

Observational Studies

Buzzatti et al (2019) reported on the results of a retrospective, propensity-weighted analysis that compared 5-year outcomes between low-intermediate risk individuals aged ≥ 75 years with degenerative MR who underwent treatment with MitraClip or surgical mitral repair (see Tables 12 and 13).⁶⁶ Preoperative variables included in the model were age at operation, sex, body mass index categorized as normal (20 to 30) or not normal (<20 or >30), serum creatinine, atrial fibrillation, NYHA class III, ejection fraction, systolic pulmonary artery pressure, isolate P2 prolapse, and STS Predicted Risk of Mortality (STS-PROM). Although MitraClip was associated with improved 1-year survival and a lower rate of all acute complications, longer-term survival and MR recurrence were significantly worse with MitraClip.

Table 12. Summary of Observational Comparative Study Characteristics

| Study | Study Type | Country | Dates | Participants | Treatment | Treatment | Follow-Up |
|-------------------------------------|----------------------|--------------------|-----------|---|-------------------|-------------------------|-----------|
| Buzzatti et al (2019) ⁶⁶ | Retrospective Cohort | Italy, Switzerland | 2005-2017 | Individuals aged 75 years and older with degenerative mitral regurgitation and STS-PROM <8% | MitraClip (N=100) | Surgical repair (N=206) | 5 years |

STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

Table 13. Summary of Observational Comparative Study Results

| Study | Survival at 1 year | Survival at 5 years | All Postoperative complications | MR >3+ recurrence at 5 years |
|-------------------------------------|-------------------------|-------------------------|---|------------------------------|
| Buzzatti et al (2019) ⁶⁶ | | | | |
| MitraClip | 97.6% | 34.5% | NR | 36.9% |
| Surgical Repair | 95.3% | 82.2% | NR | 3.9% |
| HR or OR (95% CI) | HR, 0.09 (0.02 to 0.37) | HR, 4.12 (2.31 to 7.34) | "Risk significantly reduced, but data NR" | OR, 11.4 (4.40 to 29.68) |

CI: confidence interval; HR: hazard ratio; MR: Mitral Regurgitation; NR: Not Reported; OR: Odds Ratio.

Section Summary: MitraClip in Surgical Candidates

The evidence for the use of MitraClip in patients considered candidates for open MV repair surgery includes an RCT (EVEREST II) and a systematic review. The RCT found that MitraClip did not reduce MR as often or as completely as the surgical control, although it could be safely implanted and was associated with fewer adverse events at 1 year. Long-term follow-up of the RCT showed that significantly more MitraClip patients required surgery for MV dysfunction than conventional surgery. EVEREST II had some methodologic limitations. The noninferiority margin of 25% (ITT) or 31% (per-protocol) was large, indicating that MitraClip could be somewhat inferior to surgery and, yet, the test for noninferiority margin would be met. Crossover to surgery was allowed for patients who had an MR severity grade of 3+ or higher prior to discharge, and 23% of patients assigned to MitraClip met this criterion. This large crossover rate would bias results toward the null on ITT analysis, thus increasing the likelihood of meeting the noninferiority margin. In an analysis by treatment received, this crossover would result in a less severely ill population in the MitraClip group and bias the results in favor of MitraClip. A high proportion of patients required open MV replacement or repair during the first year of postprocedure, thus limiting the number of patients who had long-term success without surgical intervention. For these reasons, this single trial is not definitive in demonstrating improved clinical outcomes using MitraClip compared with surgery. Further RCTs are needed to

corroborate these results. Similarly, in the retrospective study that compared 5-year propensity-weighted outcomes between low-intermediate risk individuals aged ≥ 75 years with degenerative MR who underwent treatment with MitraClip or surgical mitral repair, although MitraClip was associated with improved 1-year survival and a lower rate of all acute complications, it had lower longer-term survival and greater MR recurrence.

Other Transcatheter Mitral Valve Repair Devices

Clinical Context and Therapy Purpose

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

The following PICO was used to select literature to inform this review.

Populations

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

Interventions

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

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

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

Indirect Annuloplasty Devices

Randomized Controlled Trial

Several indirect annuloplasty devices, including the Carillon Mitral Contour System (Cardiac Dimension) and the Monarc device (Edwards Lifesciences), have been evaluated. The Carillon Mitral Contour System for Reducing Functional Mitral Regurgitation (REDUCE-FMR) study by Witte et al (2019) was a multicenter, double-blind, sham-controlled randomized trial to report outcomes with the Carillon device in patients with functional SMR.⁶⁷ Patients included were taking optimally tolerated doses of guideline-directed medication therapy. Of note, 29.7% of patients included were classified as having mild MR (severity class 1+) based on echocardiographic evaluation. Patients were randomized to Carillon device (n=87) or sham (n=33). In the treatment group, 73 (84%) of patients had the device implanted. At 1 year, patients with the Carillon device had a statistically significant reduction in MR volume (decrease of 7.1 mL/beat; 95% CI, -11.7 to -2.5) compared to the sham group (decrease of 3.3 mL/beat; 95% CI, -6.0 to 12.6; p=.049). Additionally, the Carillon device significantly

reduced LV volumes in symptomatic patients with MR receiving optimal medical therapy (LV end-diastolic volume decrease of 10.4 mL; 95% CI, -18.5 to -2.4; LV end-systolic volume decrease of 6.2 mL; 95% CI, -12.8 to 0.4) compared to sham (LV end-diastolic volume increase of 6.5 mL; 95% CI, -5.1 to 18.2; $p=.03$; LV end-systolic volume increase of 6.1 mL; 95% CI, -1.42 to 13.6; $p=.04$). Patient-centered outcomes, including 6-minute walk test and quality of life scores, did not differ between groups. A post-hoc analysis by Khan et al (2021) assessed patient-centered outcomes only in patients with SMR severity 2+ to 4+.⁶⁸ Of the 83 patients included in this analysis, 62 (75%) were randomized to the Carillon device group and 21 (25%) were randomized to sham procedure. A minimally clinically important difference for the outcomes was defined as a ≥ 30 m increase in 6-minute walk test, an NYHA decrease in ≥ 1 class, and a ≥ 3 point increase in KCCQ score at 1 year follow-up. All outcomes at 1 year favored the Carillon group over sham, but the only significant difference was in the 6-minute walk test scores (59% vs. 23%; $p=.029$; number needed to treat, 2.8). This analysis was not adequately powered to evaluate clinical endpoints. Further studies are needed to determine actual benefit and long-term outcomes beyond 1 year.

Case Series

A case series evaluating the use of the Carillon device in 53 patients with an SMR severity grade of 2+ at 7 European centers was reported by Siminiak et al (2012).¹⁷ Of the 53 patients who underwent attempted device implantation, 36 underwent permanent implantation and 17 had the device removed due to transient coronary compromise in 8 patients and less than 1 severity grade reduction in SMR in 9 patients. Echocardiographic measures of SMR improved in the implanted groups through 12-month follow-up, along with improvements in 6-minute walk distance. An earlier feasibility study of the Carillon device reported by Schoder et al (2009) who evaluated 48 patients with moderate-to-severe SMR; it demonstrated successful device placement in 30 patients, with 18 patients unable to be implanted due to access issues, insufficient acute SMR reduction, or coronary artery compromise.⁶⁹ The Monarc device has been evaluated in a phase 1 safety trial at 8 European centers, as reported by Harnek et al (2011).¹⁸ Among 72 patients enrolled, the device was successfully implanted in 59 (82%) patients. The primary safety endpoint (freedom from death, tamponade, or myocardial infarction at 30 days) was met by 91% of patients at 30 days and by 82% at 1 year.

Section Summary: Other Transcatheter Mitral Valve Repair Devices

The evidence for the use of TMVR devices other than MitraClip and PASCAL for patients with MR includes a randomized study, nonrandomized prospective studies, and small case series and case reports. The randomized, sham-controlled trial for the indirect annuloplasty device Carillon offers promising safety data, however further studies are needed to determine efficacy and long-term outcomes.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Clinical Input From Physician Specialty Societies and Academic Medical Centers

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

2015 Input

In response to requests, input was received from 4 academic medical centers, 1 of which provided 4 responses, for a total of 7 responses, while this policy was under review in 2015. Input supported the use of transcatheter mitral valve repair (TMVR) in patients with primary (degenerative) mitral regurgitation (MR) at prohibitive risk of open surgery. The greatest consensus for selection criteria to determine "prohibitive risk" was for the use of the Society of Thoracic Surgeons predictive operative risk of 12% or higher, or a logistic EuroSCORE of 20% or higher.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Cardiology and American Heart Association

In 2020, the American College of Cardiology and American Heart Association presented updated expert consensus on the management of mitral regurgitation (MR).⁷⁰ The recommendations are as follows: "At present, transcatheter mitral repair using an edge-to-edge clip device can be considered for the treatment of patients with primary MR and severe symptoms who are felt to be poor surgical candidates. Surgical or transcatheter treatment for secondary MR is undertaken only after appropriate medical and device therapies have been instituted and optimized, as judged by the multidisciplinary team with input from a cardiologist with experience managing heart failure and MR."

Also in 2020, the American College of Cardiology and American Heart Association released updated guidelines on the management of valvular heart disease.⁵ The guidelines state that TMVR is of benefit to patients with severely symptomatic primary MR who are at high or prohibitive risk for surgery, and to a subset of patients with secondary MR who remain severely symptomatic despite guideline-directed management and therapy for heart failure. Relevant recommendations on interventions for primary and secondary MR are shown in Table 14.

Table 14. Recommendations on Interventions for Primary and Secondary Mitral Regurgitation

| Recommendation | COR | LOE |
|--|--------------------|-------------------|
| <i>Primary MR</i> | | |
| In symptomatic patients with severe primary MR (Stage D), mitral valve intervention is recommended irrespective of LV systolic function | 1 (Strong) | B-NR ¹ |
| In asymptomatic patients with severe primary MR and LV systolic dysfunction (LVEF \leq 60%, LVESD \geq 40 mm) (Stage C2), mitral valve surgery is recommended | 1 (Strong) | B-NR ¹ |
| In patients with severe primary MR for whom surgery is indicated, mitral valve repair is recommended in preference to mitral valve replacement when the anatomic cause of MR is a degenerative disease, if a successful and durable repair is possible | 1 (Strong) | B-NR ¹ |
| In asymptomatic patients with severe primary MR and normal LV systolic function (LVEF \geq 60% and LVESD \geq 40 mm) (Stage C1), mitral valve repair is reasonable when the likelihood of a successful and durable repair without residual MR is $>$ 95% with an expected mortality rate of $<$ 1% when it can be performed at a Primary or Comprehensive Valve Center | 2a (Moderate) | B-NR ¹ |
| In asymptomatic patients with severe primary MR and normal LV systolic function (LVEF $>$ 60% and LVESD $<$ 40 mm) (Stage C1) but with a progressive increase in LV size or decrease in EF on \geq 3 serial imaging studies, mitral valve surgery may be considered irrespective of the probability of a successful and durable repair | 2b (Weak) | C-LD ² |
| In severely symptomatic patients (NYHA class III or IV) with primary severe MR and high or prohibitive surgical risk, TEER is reasonable if mitral valve anatomy is favorable for the repair procedure and patient life expectancy is at least 1 year | 2a (Moderate) | B-NR ¹ |
| In symptomatic patients with severe primary MR attributable to rheumatic valve disease, mitral valve repair may be considered at a Comprehensive Valve Center by an experienced team when surgical treatment is indicated, if a durable and successful repair is likely | 2b (Weak) | B-NR ¹ |
| In patients with severe primary MR where leaflet pathology is limited to less than one half the posterior leaflet, mitral valve replacement should not be performed unless mitral valve repair has been attempted at a Primary or Comprehensive Valve Center and was unsuccessful | 3:Harm (Strong) | B-NR ¹ |
| <i>Secondary MR</i> | | |
| In patients with chronic severe secondary MR related to LV systolic dysfunction (LVEF $<$ 50%) who have persistent symptoms (NYHA class II, III, or IV) while on optimal GDMT | 2a (Moderate) | B-R ³ |

| Recommendation | COR | LOE |
|--|------------------|-------------------|
| for HF (Stage D), TEER is reasonable in patients with appropriate anatomy as defined on TEE and with LVEF between 20% and 50%, LVESD \leq 70 mm, and pulmonary artery systolic pressure \leq 70 mmHg | | |
| In patients with severe secondary MR (Stages C and D), mitral valve surgery is reasonable when CABG is undertaken for the treatment of myocardial ischemia | 2a (Moderate) | B-NR ¹ |
| In patients with chronic severe secondary MR from atrial annular dilation with preserved LV systolic function (LVEF \geq 50%) who have severe persistent symptoms (NYHA class III or IV) despite therapy for HF and therapy for associated AF or other comorbidities (Stage D), mitral valve surgery may be considered | 2b (Weak) | B-NR ¹ |
| In patients with chronic severe secondary MR related to LV systolic dysfunction (LVEF $<$ 50%) who have persistent severe symptoms (NYHA class III or IV) while on optimal GDMT for HF (Stage D), mitral valve surgery may be considered | 2b (Weak) | B-NR ¹ |
| In patients with CAD and chronic severe secondary MR related to LV systolic dysfunction (LVEF $<$ 50%) (Stage D) who are undergoing mitral valve surgery because of severe symptoms (NYHA class III or IV) that persist despite GDMT for HF, chordal-sparing mitral valve replacement may be reasonable to choose over downsized annuloplasty repair | 2b (Weak) | B-R ³ |

Source: Adapted from Otto et al (2020)⁵.

¹Moderate, nonrandomized; ²Limited data; ³Moderate, randomized.

AF: atrial fibrillation; CABG: coronary artery bypass graft; CAD: coronary artery disease; COR: class of recommendation; EF: ejection fraction; GDMT: guideline-directed medical therapy; HF: heart failure; LOE: level of evidence; LV: left ventricular; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameters; MR: mitral regurgitation; MV: mitral valve; NYHA: New York Heart Association; TEE: transesophageal echocardiogram; TEER: transcatheter edge-to-edge repair

American College of Cardiology, American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons

The American College of Cardiology, American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons (2014) issued a position statement on transcatheter therapies for MR.⁷¹ This statement outlined critical components for successful transcatheter MR therapies and recommended ongoing research and inclusion of all patients treated with transcatheter MR therapies in a disease registry.

National Institute for Health and Care Excellence

The NICE guideline on heart valve disease management (2021) makes the following recommendations related to TMVR:⁷²

- "1.5.10 - Consider transcatheter edge-to-edge repair, if suitable, for adults with severe primary mitral regurgitation and symptoms, if surgery is unsuitable.
- 1.5.14 - Consider transcatheter mitral edge-to-edge repair for adults with heart failure and severe secondary mitral regurgitation, if surgery is unsuitable and they remain symptomatic on medical management."

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicaid Services issued a national coverage decision for the use of TMVR in 2015, which was updated in 2021.⁷³

The Centers for Medicare & Medicaid Services determined that it would cover TMVR under Coverage with Evidence Development for the treatment of symptomatic moderate-to-severe or severe functional (secondary) MR or significant symptomatic degenerative (primary) MR when all of the following conditions are met:

1. The procedure is furnished with a [TMVR] system that has received FDA [Food and Drug Administration] premarket approval (PMDA).
2. The patient (preoperatively and postoperatively) is under the care of a heart team...

3. Each patient's suitability for surgical mitral valve repair, [TMVR], or palliative therapy must be evaluated, documented...
4. An interventional cardiologist or cardiac surgeon from the heart team must perform the mitral valve [TMVR]...
5. Mitral valve [TMVR] must be furnished in a hospital with appropriate infrastructure and experience...
6. The heart team and hospital are participating in a prospective, national, audited registry...
7. The registry shall collect all data necessary and have a written executable analysis plan..."

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 15.

Table 15. Summary of Key Trials

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|--|-----------------------------------|--|
| <i>Ongoing</i> | | | |
| NCT02444338 | A RandomizEd Study of tHe MitrACliP DEvice in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF) | 650 | June 2024 |
| NCT04009434 | Treatment of Concomitant Mitral Regurgitation by Mitral Valve Clipping in Patients With Successful Transcatheter Aortic Valve Implantation | 1162 | Aug 2023 |
| NCT01626079 ^a | Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (The COAPT Trial) and COAPT CAS (COAPT) | 614 in COAPT and 162 in COAPT CAS | July 2024 (5-year follow-up per protocol) ^b |
| NCT04198870 ^a | Percutaneous MitraClip Device or Surgical Mitral Valve REpair in PATients With PrImaRy MIttral Regurgitation Who Are Candidates for Surgery (REPAIR MR) | 500 | Feb 2032 |
| NCT05090540 | Transcatheter Edge to Edge Mitral Valve Repair Versus Standard Surgical Mitral Valve Operation for Secondary Mitral Regurgitation | 600 | Dec 2023 |
| NCT05051033 | Percutaneous or Surgical Repair In Mitral Prolapse And Regurgitation for ≥ 65 Year-Olds (PRIMARY) | 450 | Jan 2032 |
| NCT05021614 ^a | Evaluation of the Efficacy and Safety of the Transcatheter Mitral Valve Repair System in Patients With Moderate and Above Degenerative Mitral Regurgitation at High Surgical Risk | 150 | Sep 2027 |
| NCT04734756 ^a | A Prospective, Multicenter, Objective Performance Criteria Study to Evaluate the Safety and Effectiveness of Dragonfly Transcatheter Mitral Valve Repair System for the Treatment of Degenerative Mitral Regurgitation (DMR) Subjects | 120 | May 2027 |
| NCT04733404 ^a | A Prospective, Multicenter, Objective Performance Criteria Study to Evaluate the Safety and Effectiveness of Dragonfly Transcatheter Mitral Valve Repair System for the Treatment of Functional Mitral Regurgitation (FMR) Subjects | 120 | Sep 2027 |
| NCT04430075 ^a | Transcatheter Repair of Mitral Regurgitation With Edwards PASCAL Transcatheter Valve Repair System: A European Prospective, Multicenter Post Market Clinical Follow-Up (PMFC) | 500 | June 2028 |
| NCT03706833 ^a | Edwards PASCAL TrAnScatheter Valve RePAir System Pivotal Clinical Trial (CLASP IID/IIF): A Prospective, Multicenter, Randomized, Controlled Pivotal Trial to Evaluate the Safety and Effectiveness of Transcatheter Mitral Valve Repair With the Edwards PASCAL Transcatheter Valve Repair System Compared to Abbott MitraClip in Patients With Mitral Regurgitation | 1275 | Jan 2028 |
| NCT05332782 | Outcomes of Patients tReated with Mitral Transcatheter Edge-to-edge Repair for Primary Mitral Regurgitation Registry (PRIME-MR) | 2000 | Jan 2026 |

| NCT No. | Trial Name | Planned Enrollment | Completion Date |
|--------------------------|---|--------------------|-----------------|
| NCT05496998 ^a | Transcatheter Mitral Valve Replacement With the Medtronic Intrepid™ TMVR Transfemoral System in Patients With Severe Symptomatic Mitral Regurgitation - APOLLO-EU Trial | 360 | Nov 2026 |
| NCT05417945 ^a | A Prospective, Multicenter Study to Evaluate the JensClip Transcatheter Valve Repair System | 124 | Dec 2024 |
| NCT05455489 | GISE Registry of Transcatheter Treatment of Mitral Valve Regurgitation With the MitraClip G4 | 264 | Aug 2029 |

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

^b Primary results have been published, long-term follow-up ongoing

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Documentation for Clinical Review

Please provide the following documentation:

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

Post Service (in addition to the above, please include the following):

- Procedure report

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

| Type | Code | Description |
|------|-------|---|
| CPT® | 0345T | Transcatheter mitral valve repair percutaneous approach via the coronary sinus |
| | 0544T | Transcatheter mitral valve annulus reconstruction, with implantation of adjustable annulus reconstruction device, percutaneous approach including transeptal puncture |
| | 33418 | Transcatheter mitral valve repair, percutaneous approach, including transeptal puncture when performed; initial prosthesis |

| Type | Code | Description |
|-------|-------|--|
| | 33419 | Transcatheter mitral valve repair, percutaneous approach, including transseptal puncture when performed; additional prosthesis(es) during same session (List separately in addition to code for primary procedure) |
| HCPCS | None | |

Policy History

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

| Effective Date | Action |
|----------------|--|
| 09/30/2014 | BCBSA Medical Policy adoption |
| 01/01/2015 | Coding update |
| 12/04/2015 | Policy revision with position change |
| 07/01/2016 | Policy revision without position change |
| 07/01/2017 | Policy revision without position change |
| 07/01/2018 | Policy revision without position change |
| 08/01/2019 | Policy revision without position change Coding update |
| 07/01/2023 | Policy reactivated. Previously archived from 07/01/2020 to 06/30/2023. |

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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 and Feedback (as applicable to your plan)

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

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

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

Appendix A

| POLICY STATEMENT | |
|--|---|
| BEFORE | AFTER <i>Blue font: Verbiage Changes/Additions</i> |
| <p>Reactivated Policy</p> <p>Policy Statement: N/A</p> | <p>Transcatheter Mitral Valve Repair 2.02.30</p> <p>Policy Statement:</p> <ul style="list-style-type: none"> I. Transcatheter mitral valve repair (TMVR) with a device approved by the U.S. Food and Drug Administration (FDA) for use in mitral valve repair may be considered medically necessary for individuals with symptomatic, primary mitral regurgitation (MR) who are considered at prohibitive risk for open surgery (see Policy Guidelines section). II. TMVR with a device approved by the U.S. FDA may be considered medically necessary for individuals with heart failure and moderate-to-severe or severe symptomatic secondary MR despite the use of maximally tolerated guideline-directed medical therapy (see Policy Guidelines section). III. TMVR is considered investigational in all other situations. |