Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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(See policy history boxes for previous effective dates)

Title: Transcatheter Mitral Valve Procedures

Description/Background

Repair Versus Replacement

Transcatheter mitral valve repair is an alternative to surgical therapy for mitral regurgitation (MR) in native/primary mitral valves that have not been surgically altered in the past. Transcatheter mitral valve replacement is being investigated as a less invasive means of replacing a valve by implanting a catheter based artificial heart valve (bioprosthesis valve) into an existing valve (valve-in-valve), when there is mitral regurgitation, mitral stenosis, and complications of a previously placed mitral valve prosthesis.

Mitral regurgitation (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.

MITRAL REGURGITATION

Epidemiology and Classification

Mitral regurgitation 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 two 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 value (MV) leaflets not to co-apt 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 United States (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 for 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 a high risk procedure and can have uncertain durable effects on symptoms. Recommendations from major societies (7,8) regarding MV surgery in the setting of severe chronic secondary MR in conjunction with coronary artery bypass graft surgery or surgical aortic valve replacement remain fluid because the current evidence is inconsistent on whether MV surgery produces a clinical benefit.(9-12)

TRANSCATHETER MV REPAIR AND REPLACEMENT

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 transcatheter MV repair devices under investigation, MitraClip has the largest body of evidence evaluating its use; it has been in use in Europe since 2008.(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 coapting 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 MV Repair Devices

Devices for transcatheter MV repair that use different approaches are in development. Techniques to repair the mitral annulus include those that target the annulus itself (direct annuloplasty) and those that tighten the mitral annulus via manipulation of the adjacent coronary sinus (indirect annuloplasty). Indirect annuloplasty devices include the Carillon Mitral Contour System (Cardiac Dimension) and the Monarc™ device (Edwards Lifesciences). The CE-marked Carillon Mitral Contour System is comprised of self-expanding proximal and distal anchors connected with a nitinol bridge, with the proximal end coronary sinus ostium and the distal anchor in the great cardiac vein. The size of the connection is controlled by manual pullback on the catheter. The Carillon system was evaluated in the Carillon Mitral Annuloplasty Device European Union Study (AMADEUS) and the follow-up Tighten the Annulus Now study, with further studies planned.(17) The Monarc system also involves 2 self-expanding stents connected by a nitinol bridge, with 1 end implanted in the coronary sinus via internal jugular vein and the other in the great cardiac vein. Several weeks after implantation, the biologically degradable coating over the nitinol bridge degrades, allowing the bridge to shrink and the system to shorten. It has been evaluated in the Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for the Treatment of Mitral Regurgitation (EVOLUTION I) trial.(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 transcutaneous 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.

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.(3,4) Resynchronization therapy may provide symptomatic relief, improve LV function, and in some patients, lessen the severity of MR.

Regulatory Status

In October 2013, the MitraClip® Clip Delivery System (Abbott Vascular) was approved by FDA through the premarket approval process for treatment of “significant symptomatic mitral regurgitation (MR ≥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 ≥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 MitrClip and PASCAL: NKM.

Permavalve™ (MicroInterventional Devices), under investigation in the United States, is a transcatheter MV replacement device that is delivered via the transapical approach.

In 2017, the SAPIEN 3 Transcatheter Heart Valve (Edwards Lifesciences) FDA PMA approval was extended by the FDA to include use as a mitral valve replacement device in patients with symptomatic heart disease due to failure of a surgical bioprosthetic…mitral valve, who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality ≥ 8% at 30 days, based on the STS risk score and other clinical co-morbidities unmeasured by the STS risk calculator).

In 2020 the FDA expanded the PMA to include the Sapien 3 Ultra Transcatheter Heart Valve System (Edwards Lifesciences) for replacement of a failing (narrowed, leaky, or both) previously implanted surgical artificial…mitral heart valve in patients who are too high risk for open-heart surgery.

Medical Policy Statement

The safety and effectiveness of transcatheter mitral valve repair[a] (e.g., MitraClip®) has been established and may be considered a useful option when performed via the devices FDA-approved labeling and specified criteria are met.

The safety and effectiveness of transcatheter mitral valve implantation (replacement[a]) (e.g., Edwards Sapien 3 Transcatheter Heart Valve, Sapien 3 Ultra Transcatheter Heart Valve) has

been established and may be considered a useful option when performed via the devices FDA-approved labeling and specified criteria are met.

The safety and efficacy of transcatheter implantable mitral valve annulus reshaping devices for the treatment of mitral valve regurgitation are under clinical trial evaluation. Therefore, this service is experimental/investigational.

Inclusionary and Exclusionary Guidelines

Inclusions:

Transcatheter mitral valve repair[a] with an FDA-approved mitral valve repair system (i.e., Mitraclip®) is indicated when all of the following criteria are met:

- Significant symptomatic mitral regurgitation (MR ≥ 3+) due to one of the following:
  - Primary abnormality of the mitral apparatus (degenerative MR)
  - Heart failure and secondary mitral regurgitation despite the use of maximally tolerated guideline-directed medical therapy
- Individuals who have been determined to be at prohibitive risk for open mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease
- Existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.

Percutaneous transcatheter mitral valve-in-valve implantation (replacement[a]) using an FDA-approved device (i.e., Edwards Sapien 3 Transcatheter Heart Valve System, Sapien 3 Ultra Transcatheter Heart Valve System) when all of the following are met:

- Symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic mitral valve or a prosthetic ring from a prior repair
- Determination by a heart team, including a cardiac surgeon, that the individual is at high or greater risk for open surgical therapy (i.e., predicted risk of surgical mortality greater than or equal to 8% at 30 days, based on the Society of Thoracic Surgeons risk score and other clinical co-morbidities

Exclusions:

- Transcatheter mitral valve repair[a] or transcatheter mitral valve-in-valve implantation (replacement[a]) procedures when one of the following apply:
  - Individuals who cannot tolerate procedural anticoagulation or post procedural antiplatelet regimen
  - Active endocarditis of the mitral valve
  - Rheumatic mitral valve disease
  - Evidence of intracardiac, inferior vena cava (IVC) or femoral venous thrombus
  - The individual is an appropriate candidate for the standard, open surgical approach but has refused
- Transcatheter mitral valve annulus reshaping devices
- Non-FDA approved systems or approaches including:
  - Permavalve™ system

[a]Repair (MitraClip) and replacement (Edwards Sapien 3. Sapien 3 Ultra Transcatheter Heart Valve) are separate procedures and involve different devices

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure.)*

Established codes:

33418 33419 0345T 0483T* 0484T

Other codes (investigational, not medically necessary, etc.):

0543T 0544T

** Per American Academy of Professional Coders, 0483T is billed when the procedure comprises of implantation/replacement of a mitral valve with mitral regurgitation, mitral stenosis, and complication of a previously placed mitral valve prosthesis.*

Rationale

This review was informed, in part, by a TEC Assessment (2014) that evaluated the use of transcatheter mitral valve repair in patients with symptomatic primary mitral regurgitation (MR) at prohibitive risk for mortality during open surgery.(19)

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

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent 1 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.

MITRACLIP REPAIR AND PASCAL

Primary Mitral Valve Regurgitation at Prohibitive Surgical Risk

Clinical Context and Therapy Purpose
The purpose of transcatheter mitral valve repair 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 PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are 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 3-4+ 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 transcatheter mitral valve repair 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 ≤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 ≥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 ≤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, the 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 2 and 3 summarizes 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 post marketing registry. The Lin 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 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 one 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 two studies; the percentages with New York Heart Association (NYHA) class I or II functional status were 81% and 87%; and the percentages who improved at least 1 NYHA class level were 68% and 88%, respectively.

Table 1. Key MitraClip Case Series Characteristics

Study; Trial	Country	Participants	Treatment Delivery	Follow-Up
Reichenspurner et al (2013) ACCESS-EU	Europe	• N=117 • EF <40% or mean EF: 9.4% • NYHA class ≥3: 74% • MR severity ≥3+: 96.6% • Mean EuroSCORE: 15.5%	MitraClip	71 had 1-y follow-up data
Lim et al (2014) 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 ≥3+: 100% • Mean STS score: 13.2% • Mean STS score: 13.2%	MitraClip	1.47 y

Adapted from the TEC Assessment (2014).
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) ACCESS-EU	117	MR severity ≤2+: 74.6% (53/71)	• Class I/II: 81% (63/78) • Improved ≥1 class: 68%(53/78)	• Change in MLHFQ from baseline, 13.3 points (p=0.03), n=44 • Change in 6MWT from baseline, 77.4 m (p<0.001), n=52
Lim et al (2014) subset of patients at prohibitive risk of open surgery from EVEREST II HRR and REALISM	127	MR severity ≤2+: 83.3% (70/84)	• Class I/II: 86.9% (73/84) • Improved ≥1 class: 86.9% (73/84)	• SF-36 PCS score change, 6.0 (95% CI, 4.0 to 8.0), n=76 • SF-36 MCS score change, 5.6 (95% CI, 2.3 to 8.9), n=76

Adapted from the TEC Assessment (2014).
CI: confidence interval; MCS: Mental Component Summary; MLHFQ: Minnesota Living with Heart Failure 10 Questionnaire; MR: mitral regurgitation; NYHA: New York Heart Association; PCS: Physical Component Summary; 6MWT: 6-minute walk test; SF-36: 36-Item Short-Form Health Survey.

In reviewing data for MitraClip, the FDA compared the cohort reported by Lin et al (2014, discussed above) with a historical cohort (n=65) generated from the patient-level data Duke Registry of primary MR patients with MR of 3+ or more. The Duke cohort of 65 patients with primary MR was derived from a dataset of 953 patients with an MR severity grade of 3+ or 4+ who were retrospectively identified as being at a prohibitively high risk for surgery based on the

same high-risk criteria as those in the EVEREST II HRR and REALISM studies (i.e., Society of Thoracic Surgeons (STS) mortality risk calculation of 12% or higher or protocol-specified surgical risk factors). For the cohort described by Lin et al (2014), compliance to follow-up visits in continuing patients was 98%, 98%, and 95% at 30 days, 12 months, and two 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 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 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 totality of the evidence demonstrated reasonable assurance of safety and effectiveness of MitraClip to reduce MR and provide patient benefit in this discreet and specific patient population based on the following:(19)

- It is broadly accepted that primary MR is a mechanical problem in which there is a primary abnormality of the mitral apparatus and the “leaflets are broken”. There is no medical therapy for reducing primary MR, which must be treated with mechanical correction of the mitral valve.
- The observed procedural mortality rate with MitraClip was 6.4% (95% CI, 2.8% to 12.0%) at 30 days. This rate was lower than the predicted mortality rate of 13.2% (95% CI, 11.9% to 14.5%) using STS Replacement Risk Score or 9.5% (95% CI, 11.3% to 13.7%) using STS Repair Score for the Lin cohort.
- While acknowledging the pitfalls of using historical controls from the Duke Registry, FDA found no elevated risk of mortality in MitraClip cohort patients over nonsurgical management and both immediate and long-term improvement in MR severity. MR severity grade of 2+ or less and of 1+ or less was observed in 82% and 54% of surviving patients at discharge, respectively. This improvement was sustained at 12 months, with the majority (83.3%) of surviving patients reporting MR severity grade of 2+ or less and 36.9% reporting MR severity grade of 1+ or less. At 12 months, freedom from death and MR severity grade greater than 2+ was 61.4%, and freedom from death and MR severity grade greater than 1+ was 27.2%.
- Quality of life was assessed using the 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 United States suggests that mortality rates reported in patients at prohibitive risk of surgery undergoing the MitraClip procedure do not appear to be elevated and are not unexpected given the age and burden of comorbidities of the patients treated. Reported mortality ranges were: in-hospital mortality, 0% to 4%; 30-day mortality, 0% to 9.1%; and 6- to 12-month mortality, 8% to 24%. Reported clinical benefits were: improvement in MR severity grade of 2+ or less after MitraClip in more than 75% of patients; improvement in 6-minute walk distance of 60 to >100 meters (the generally accepted threshold is >40 m), and percentages of patients who improved to a NYHA class of I or II ranged from 48% to 97%.
- The probable adverse event risks of the MitraClip included procedure-related complications such as death (6.3%), stroke (3.4%), prolonged ventilation (3.1%), and transfusion greater than 2 units (12.6%), major vascular complications (5.4%), noncerebral thromboembolism (1.6%), new onset of atrial fibrillation (3.9%), and atrial septal defect (1.6%).

Table 3. Key Observational Comparative Study Characteristics

Study	Design	Country	Dates	Participants	Treatment	Treatment	FU
FDA (2013)	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 yr

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

Table 4. Key Observational Comparative Study Results

	Percent Event Free (95% CI), %				
Study	**At 30 Days**	**At 6 Months**	**At 12 Months**	**Freedom From Death and MR >2+**	**Freedom From Death and NYHA Class III/IV**
FDA (2013)	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% 30 d: 82% 12 mo: 61%	Baseline: 13% 30 d: 76% 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 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%-12.2%) and 10.0% (range, 6.3%-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 FDA for approval (26) and supports that a favorable benefit-risk ratio is attainable outside a clinical trial setting in appropriately selected patients. At 1 year, the proportion of patients who died was 25.8%, had a repeat hospitalization for heart failure was 20.2%, and cumulative incidence of mortality or rehospitalization for heart failure was 37.9%.(29) Higher age, lower baseline left ventricular ejection fraction, worse postprocedural MR, moderate or severe lung disease, dialysis, and severe tricuspid regurgitation were associated with higher mortality or rehospitalization for heart failure. The persistency of mortality (25.8%) and heart failure rehospitalization (20.2%) at 1 year despite of the effectiveness of MitraClip remains a concern. However, the results observed in the Transcatheter Valve Therapy Registry at 1 year were comparable with the 1-year rates observed in the analysis of high-risk patients in the EVEREST II (23.8%) and REALISM (18.0%) studies.(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 <1+ was achieved, whereas, reduction to MR severity grade <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 ≤2+ in 91% of patients at 6 months.

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

Study	No. of Patients	Primary MR, %	Secondary MR, %	Post implantation MR Grade ≤2, %	In-Hospital Death, %	30-Day Death, %	6-Month Death %	1-Year Death, %
Sorajja et al (2016)	564	86	14	93	2.3	5.8	NR	NR

Sorajja et al (2017)	2952	86	9	92	2.7	5.2	NR	25.8
FDA (2022)	92	100	0	91	NR	2.2	NR	NR

MR: mitral regurgitation

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 MV 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 procedural success rate greater than 90%, 30- day mortality rates ranging from 2.3% to 6.4% (less than predicted STS mortality score for MR repair or replacement [range, 9.5%-13.2%]), MR severity of 2+ or less in 82% to 93% patients, and clinically meaningful gains in quality of life (5- to 6-point gain in SF-36 scores). However, the one-year mortality or heart failure hospitalization rates remained considerably high (38%) compared with U.S.-based registry data thereby raising uncertainty about the long-term benefits. 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 transcatheter mitral valve repair using MitraClip in patients who have heart failure, 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 PICOs were used to select literature to inform this review.

Populations
The relevant population of interest are patients with heart failure 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. [Abbott] 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 transcatheter mitral valve repair using MitraClip. transcatheter mitral valve repair 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 heart failure 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 principles listed above.

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) RCT's discussed below, as well as two 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 two years of follow-up, MitraClip plus medical therapy significantly reduced the risk of all-cause mortality (relative risk, 0.72; 95% CI, 0.55 to 0.95; I^2=55%), readmission events for heart failure (relative risk, 0.62; 95% CI, 0.42-0.92; I^2=90%), but not cardiovascular mortality (relative risk, 0.69; 95% CI, 0.47-1.02; I^2=68%). Further, results of fixed-effect meta-regression suggest that baseline left ventricular end diastolic volume and age are associated with all-cause mortality and cardiovascular mortality outcomes. However, interpretation of these pooled analyses are 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 two 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.(42) 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 transcatheter mitral valve repair.(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 transcatheter mitral valve repair had been performed in 21.5% of patients in the control group at median 26 months after randomization; in a post hoc analysis, crossover transcatheter mitral valve repair 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.(55-57) The severity of MR and heart failure among the patients in the trials differed. COAPT participants had more severe MR at baseline (effective regurgitant orifice area 41 vs 31 mm^2) and remained symptomatic despite the use of maximal doses of guideline-directed medical therapy.(7,57,58) 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 heart failure 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 RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	Comparator
Stone et al (2018);	US and Canada	78	2012-2017	Ischemic or nonischemic cardiomyopathy with LVEF	N=302	N=312

COAPT				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	MitraClip plus medical therapy	Medical therapy alone
Obadia et al (2018); MITRA-FR	France	37	2013-2017	Severe SMR with a regurgitant volume of greater than 30ml per beat or an EROA ≥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 MitraClip plus medical therapy	N=152 Medical therapy alone

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

Table 7. Summary of Key RCT 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 mon	NYHA functional class I or II at 12 months	Primary Safety Outcome: Freedom from device-related complications at 12 months1 Kaplan-Meier estimate of event-free rate (lower 95% confidence limit)	Serious Adverse events at 1 year	Periprocedural complications during device implantation
Stone et al (2018); 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); p <.001 for noninferiority		0.62 (0.46 to 0.82) ; p <.001	0.59 (90.43 to 0.81); p =.001	p <.001	p <.001			
NNT	3.1										
Obadia et al (2018); 12-month											

results lung et al (2019) 24-month results MITRA-FR								
Sample size	304	304	304	304	304	304	304	
Medical therapy alone	94/152 (62.3%)	78/152 (51.3%)	34/152 (22.4%)	31/152 (20.4%)	52/152 (22.8%)	48/152 (21.1%)	121/152 (79.6%)	
MitraClip + medical therapy	85/152 (55.9%)	83/152 (54.6%)	37/152 (24.3%)	33/152 (21.7%)	53/152 (23.1%)	47/152 (20.5%)	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, eft 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 heart failure than those who are likely to benefit from MV treatment, and the trial duration may not have been sufficient to show a benefit for the intervention. 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) COAPT					
Obadia et al (2018) 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) COAPT	3	1,2				
Obadia et al (2018); 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 ≤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 ≤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, two RCTs, and observational studies. The trials had discrepant results, but the larger trial, with a longer duration and patients selected for nonresponse to maximally tolerated therapy, found a significant benefit for MitraClip 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 transcatheter mitral valve repair . 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 transcatheter mitral valve repair 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 PICOs were used to select literature to inform this review.

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

Interventions
The therapy being considered is transcatheter mitral valve repair 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
Methodologically credible studies were selected using the principles described above.

Review of Evidence

Systematic Review
A systematic review by Takagi et al (2017) identified one RCT and six 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=0.08). 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, 1.17; 95% CI, 0.77 to 1.78; p=0.46). However, there was a significantly higher incidence of recurrent MR in the MitraClip than in the surgery group (pooled OR/hazard ratio, 4.80; 95% CI, 2.58 to 8.93; p<0.001).

Randomized Controlled 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 secondary MR 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 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 end point was considered met for MitraClip group subjects if they were free from death, reoperation for MR, and MR grade greater than 2+ at 12 months. The trial had a predetermined efficacy end point of noninferiority of the MitraClip strategy, with a margin of 25% for the ITT analysis and 31% for prespecified per-protocol analyses. This implies that the MitraClip strategy would be noninferior to surgery at 12 months if the upper bound of difference in the proportion of patients achieving the primary efficacy end point between the 2 groups did not exceed 25 percentage points for the ITT analysis and 31% percentage points for the per-protocol analysis. Results showed that transcatheter mitral valve repair was less effective at reducing MR than conventional surgery before hospital discharge. MitraClip group subjects were more likely to require surgery for MV dysfunction, either immediately post-MitraClip implantation or in the 12 months following. Twenty percent (37/181) of the MitraClip group and 2% (2/89) of the surgery group required reoperation for MV dysfunction ($p<0.001$). Although in the ITT analysis rates of MR severity grades of 3+ or 4+ at 12 months were similar between groups, in the published per-protocol analysis, patients in the MitraClip group were more likely to have severity grades of 3+ or 4+ (17.2% [23/134] vs 4.1% [3/74], $p=0.01$), which would suggest that a larger proportion of patients with grade 1+ or 2+ MR in the MitraClip group had had surgical repair. As expected, rates of major adverse events at 30 days were lower in the MitraClip group (15% [27/181]) than in the surgery group (48% [45/89]; $p<0.001$). Rates of transfusion of more than 2 units of blood were the largest component of major adverse events in both groups, occurring in 13% (24/181) of the MitraClip group and 45% (42/89; $p<0.001$) of the surgery group. Long-term follow-up at 4 years (63) and 5 years (64) showed that significantly more MitraClip patients required surgery for MV dysfunction during the follow-up period.

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

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 RCT Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Feldman et al (2011) EVEREST II	U.S., Canada	37	2005-2008	• N=279 • Grade 3+ or 4+ chronic MR • Symptomatic (LVEF ≥25% and LVESD ≤55 mm) or asymptomatic (LVEF 25%-60% or LVESD 40-55 mm or new AF or pulmonary hypertension)	transcatheter mitral valve repair (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; transcatheter mitral valve repair : transcatheter mitral valve repair.

Table 11. Key RCT 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) EVEREST II[c] (1 year)	270	274	270	270	270
transcatheter mitral valve repair	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	0.007	<0.001	<0.001	1.00	1.00
FDA (2013) EVEREST II (1 year)	Range, 156-208	274	-	-	-
transcatheter mitral valve repair	97/134 (72%)[d] 37/82 (45%)[e]	27/180 (15%)	Not reported	Not reported	Not reported
Open repair	65/74 (88%)[d] 51/74 (69%)[e]	45/94 (48%)	Not reported	Not reported	Not reported
p	0.001[d,f] 0.169[e,f]	<0.001	Not reported	Not reported	Not reported
Mauri et al (2013) EVEREST II (4 years)	NR	NR	234	234	234
transcatheter mitral valve repair	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	<0.001	0.914	0.745
Feldman et al (2015) EVEREST II (5 years)			197	197	197
transcatheter mitral valve repair	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	0.003	0.36	0.02

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

AE: adverse event; FDA: Food and Drug Administration; MR: mitral regurgitation; MV: mitral valve; NR: not reported; RCT: randomized controlled trial; transcatheter mitral valve repair : 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 ≥2 units of blood, reoperation for failed surgery, stroke, gastrointestinal complications requiring surgery, ventilation for ≥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 five-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 (20-30) or not normal (<20 or >30), serum creatinine, atrial fibrillation, New York Heart Association class III, ejection fraction, systolic pulmonary artery pressure, isolate P2 prolapse, and Society of Thoracic Surgeons 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 was significant 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)	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)				
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 (0.02-0.37)	HR 4.12 (2.31-7.34)	"Risk significantly reduced, but data NR"	OR 11.4 (4.40-29.68)

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

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 post-procedure, 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 five-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 one-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 transcatheter mitral valve repair 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 PICOs were used to select literature to inform this review.

Populations

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

Interventions

The therapy being considered is transcatheter mitral valve repair 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 principles listed above.

Review of Evidence

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

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 use of the Carillon device in 53 patients with a secondary MR severity grade of 2+ at 7 European centers was reported by Siminiak et al (2012).(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 secondary MR in 9 patients. Echocardiographic measures of secondary MR improved in the implanted groups through 12-month follow-up, along with improvements in SIX-minute walk distance. An earlier feasibility study of the Carillon device reported by Schoder et al (2009) who evaluated 48 patients with moderate-to-severe secondary MR; it demonstrated successful device placement in 30 patients, with 18 patients unable to be implanted due to access issues, insufficient acute secondary MR reduction, or coronary artery compromise.(69) The Monarc device has been evaluated in a phase I 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 end point (freedom from death, tamponade, or myocardial infarction at 30 days) was met by 91% of patients at 30 days and by 82% at 1 year.

Section Summary: Other Transcatheter MV Repair Devices

The evidence for the use of transcatheter mitral valve repair devices other than MitraClip and PASCAL for patients with MR includes an RCT, 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

MITRAL VALVE REPLACEMENT (MITRAL VALVE, VALVE-IN-VALVE)

Transcatheter valve-in-valve implantation procedures are being investigated as less invasive alternatives to redo open heart surgery in selected patients deemed at high surgical risk.(74)

Transcatheter mitral valve replacement consists of using a transcatheter device with a balloon to advance a bioprosthesis, usually made out of bovine pericaridal tissue, to a failing post-operative soft tissue mitral valve (valve-in-valve). The bioprosthesis is then anchored to the failing valve to encourage blood to flow in the correct direction.

The current standard of care for degenerated bioprosthetic valves is open heart surgery. The large number of patients who are not eligible for open mitral valve surgery has driven the field of percutaneous transcatheter mitral valve replacement. Transcatheter valve-in-valve replacement continues to be explored as a less invasive method for patients who suffer from surgical bioprosthesis dysfunction.

The combination of a decrease in rheumatic valve disease and increased life expectancy has led to a high prevalence of degenerative mitral regurgitation. Older patient populations result in comorbidities that increase operative mortality and morbidity risks. High surgical risk and deference of patients from the standard care has encouraged providers to seek alternatives for mitral valve replacement. Less invasive procedures are preferred when significant health outcomes can be achieved.

Del Val et al (2019) reported on a systemic review of transcatheter mitral valve replacement as an alternative option for the treatment of severe mitral regurgitation in patients with prohibitive or high surgical risk.(75) A total of 16 publications describing 308 patients were analyzed. Most patients (65.9%) were men, with a mean age of 75 years (range: 69-81 years) and Society for Thoracic Surgery Predicted Risk of Mortality score of 7.7% (range: 6.1-8.6%). The etiology of mitral regurgitation was predominantly secondary or mixed (87.1%), and 81.5% of the patients were in New York Heart Association class III or IV. A transapical approach was used in 81.5% of patients, and overall technical success was high (91.7%). Post-procedural mean transmitral gradient was 3.5 mm Hg (range: 3-5.5 mm Hg), and only 4 cases (1.5%) presented residual moderate to severe mitral regurgitation. Procedural and all-cause 30-day mortality were 4.6% and 13.6%, respectively. Left ventricular outflow obstruction and conversion to open heart surgery were reported in 0.3% and 4% of patients, respectively. All-cause and cardiovascular-related mortality rates were 27.6% and 23.3%, respectively, after a mean follow-up of 10 (range: 3 to 24) months. Authors concluded that although transcatheter mitral valve replacement was associated with a high rate of successful valve implantation, periprocedural complications and all-cause mortality were relatively high.

Many challenges still need to be addressed when targeting the most complex of the hearts 4 valves.(76-77) Access to the left atrium or left ventricle require a multidimensional, highly curved catheter. Large delivery systems limit the precision with which tension and traction are transmitted to the operating end of the system. Multiple approaches (percutaneous, transfemoral, transapical, transthoracic, transseptal, transatrial, etc.) are still being explored. The anatomy of the mitral valve is an asymmetrical saddle-shape making it difficult to effectively reproduce. There is no stable calcified structure available for anchoring, which can prove fatal if the prosthesis migrates into the aortic arch. In some patients with mitral valve stenosis, it is possible to anchor the device to the severely calcified mitral annulus. The mitral valve is a complex structure composed of irregular geometric leaflets, annulus, chordae tendineae and papillary muscles. Preservation of the subvalvular apparatus is mandatory to preserve left ventricular geometry. Due to dynamic changes of the annular area and circumference during the cardiac cycle, a device should be balanced with radial stiffness to resist the changes but needs to be gentle enough not to cause perforation of adjacent structures. The device should not obstruct the left ventricular outflow tract, occlude the

circumflex coronary artery, compress the coronary sinus or cause major conduction system disruption. Valve materials should be durable enough to withstand the generated loads. Paravalvular leaks should be minimized because regurgitation is poorly tolerated in the mitral position as a result of the higher-pressure gradient across the valve. Ultimately, the possibility of reoperation or transcatheter mitral valve replacement in transcatheter mitral valve replacement is still unclear.

Summary: Mitral Valve Replacement
Transcatheter mitral valve replacement may have the potential to become an alternative treatment for patients who are a high surgical risk and have severe mitral regurgitation. Currently, data on transcatheter mitral valve-in-valve replacement remains scarce and questions are abundant. Available sources of literature contain very small case studies and case reports. Comparisons of transcatheter valve-in-valve with open mitral valve replacement and long-term durability studies of transcatheter valves following valve-in-valve procedures are lacking. FDA approvals for mitral valve replacement device(s) are beginning to emerge. Randomized control trials and long-term evaluations are needed to assess the safety and efficacy of transcatheter mitral valve replacement. The evidence is sufficient to determine that the technology may result an improvement in the net health outcome.

Summary of Evidence
For individuals who have symptomatic primary mitral regurgitation (MR) and are at prohibitive risk for open surgery who receive transcatheter mitral valve repair using MitraClip or PASCAL, the evidence includes a noninferiority randomized controlled trial and single-arm prospective cohort with historical cohort and registry studies. The relevant outcomes are overall survival, morbid events, functional outcomes, and treatment-related morbidity. The primary evidence includes the pivotal EVEREST II HRR and EVEREST II REALISM studies, the Transcatheter Valve Therapy Registry study and the CLASP IID/IIF study. Studies evaluating MitraClip have demonstrated that MitraClip implantation is feasible with a procedural success rate greater than 90%, 30- day mortality ranging from 2.3% to 6.4% (less than predicted Society of Thoracic Surgeons [STS] mortality risk score for MR repair or replacement; range, 9.5%-13.2%), post implantation MR severity grade of 2+ or less in 82% to 93% of patients, and a clinically meaningful gain in quality of life (5- to 6-point gains in 36-Item Short-Form Health Survey scores). At 1 year, freedom from death and MR more than 2+ was achieved in 61% of patients but the 1-year mortality or heart failure hospitalization rates remain considerably high (38%). Conclusions related to the treatment effect on mortality based on historical controls cannot be made because the control groups did not provide unbiased or precise estimates of the natural history of patients eligible to receive MitraClip. Given that primary MR is a mechanical problem and there is no effective medical therapy, a randomized controlled trial (RCT) comparing MitraClip with medical management is not feasible or ethical. The post marketing data from the United States is supportive that MitraClip surgery is being performed with short-term effectiveness and safety in select patient population. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome. The CLASP IID/IIF randomized cohort demonstrated that PASCAL is noninferior to MitraClip in safety and effectiveness for patients with primary MR at prohibitive surgical risk, and the single-arm registry cohort demonstrated that PASCAL is safe and effective in patients with complex mitral valve (MV) anatomy precluding the use of MitraClip.

For individuals who have heart failure and symptomatic secondary MR despite the use of maximally tolerated guideline-directed medical therapy who receive transcatheter mitral valve repair using MitraClip, the evidence includes a systematic review, 2 RCTs and multiple

observational studies. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. The trials had conflicting results, but the larger trial, with a longer duration and patients selected for nonresponse to maximally tolerated therapy, found a significant benefit for MitraClip up to 5 years compared to medical therapy alone, including benefits in overall survival and hospitalization for heart failure. Improvements in MR severity, quality of life measures, and functional capacity persisted to 36 months in patients who received transcatheter mitral valve repair . The systematic review confirmed the benefit of MitraClip found in the larger RCT but had important methodological limitations. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have symptomatic primary or secondary MR and are surgical candidates who receive transcatheter mitral valve repair using MitraClip, the evidence includes 1 RCT and a retrospective comparative observational study in individuals aged ≥ 75 years. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. The RCT found that MitraClip did not reduce MR as often or as completely as the surgical control, although it could be safely implanted and was associated with fewer adverse events at one year. Long-term follow-up from the RCT showed that significantly more MitraClip patients required surgery for MV dysfunction than conventional surgery patients. For these reasons, this single trial is not definitive in demonstrating improved clinical outcomes with MitraClip compared with surgery. Additional RCTs are needed to corroborate these results. The observational study in individuals aged ≥ 75 years found that although MitraClip was associated with improved 1-year survival and a lower rate of all acute complications compared with surgical repair, it had lower 5-year survival and greater MR recurrence. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have symptomatic primary or secondary MR who receive transcatheter mitral valve repair using devices other than MitraClip or PASCAL, the evidence includes and RCT, nonrandomized prospective studies, and noncomparative feasibility studies. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. 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.

For individuals who have severe mitral valve regurgitation and are a high surgical risk, data regarding transcatheter mitral valve replacement remains scarce and questions are abundant. Evidence in the peer reviewed literature is limited to case studies and registry data. Many challenges still need to be addressed including approach, device designs, anchoring techniques and 30-day perioperative mortality. FDA approvals for mitral valve replacement device(s) have been issued. Continued approval is contingent upon the submission of periodic reports which include the frequency and prevalence of adverse events; allowing the FDA to evaluate the continued safety and effectiveness of the approved device. Large, long term studies are needed to determine device durability, the ideal candidates for mitral valve replacement and comparisons of transcatheter valve-in-valve with open mitral valve replacement. The evidence is sufficient to determine that the technology may result an improvement in the net health outcome.

Supplemental Information

CLINICAL INPUT RECEIVED FROM PHYSICIAN SPECIALTY SOCIETIES AND ACADEMIC MEDICAL CENTERS

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

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. The input supported the use of transcatheter MV repair in patients with DMR at prohibitive risk of open surgery. The greatest consensus for selection criteria to determine "prohibitive risk" was for the use of the Society of Thoracic Surgeons predictive operative risk of 12% or higher, or a logistic EuroSCORE of 20% or higher.

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Cardiology and American Heart Association

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 transcatheter mitral valve repair is of benefit to patients with severely symptomatic primary mitral regurgitation who are at high or prohibitive risk for surgery, and to a subset of patients with secondary mitral regurgitation 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. They note that several transcatheter mitral valve repair systems focusing on leaflet modification (such as leaflet ablation and space occupation between leaflets) or annular reduction, as well as transcatheter mitral valve replacement platforms, are in various stages of development and not available outside of clinical trials.

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

Recommendation	COR	LOE
Primary MR		
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 ≤60%, LVESD ≥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 ≥60% and LVESD ≥40 mm) (Stage C1), mitral valve repair is reasonable when the likelihood of a successful and durable repair without residual MR is >95%	2a (Moderate)	B-NR[1]

with an expected mortality rate of <1% when it can be performed at a Primary or Comprehensive Valve Center		
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 ≥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]
Secondary MR		
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 for HF (Stage D), TEER is reasonable in patients with appropriate anatomy as defined on TEE and with LVEF between 20% and 50%, LVESD ≤70 mm, and pulmonary artery systolic pressure ≤70 mmHg	2a (Moderate)	B-R[3]
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 ≥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].
[1]Moderate, nonrandomized; [2]Limited data; [3]Moderate, 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 the Society of Thoracic Surgeons (2014) released 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.

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
Ongoing			
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 MItral 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	Jun 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
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

Government Regulations
National Coverage Determination:

Centers for Medicare and Medicaid Services (2021) issued a National Coverage Determination for the use of transcatheter edge-to-edge repair (TEER) for mitral valve regurgitation; 100-3 Version 1 (20.33).(66) Effective date: 1/19/21; Implementation date: 10/08/21

A. General

Transcatheter Edge-to-Edge Repair (TEER) of the mitral valve is used in the treatment of mitral regurgitation. TEER approximates the anterior and posterior mitral valve leaflets by grasping them with a clipping device in an approach similar to a treatment developed in cardiac surgery called the Alfieri stitch.

Indications and Limitations of Coverage

B. Nationally Covered Indications

The Centers for Medicare & Medicaid Services (CMS) covers *TEER of the mitral valve* under Coverage with Evidence Development (CED) with the following conditions:

A. For the treatment of symptomatic moderate-to-severe or severe functional mitral regurgitation (MR) when the patient remains symptomatic despite stable doses of maximally tolerated guideline-directed medical therapy (GDMT) plus cardiac resynchronization therapy, if appropriate, or for the treatment of significant symptomatic degenerative MR when furnished according to a Food and Drug Administration (FDA)-approved indication and when ALL of the following conditions are met:
   1. The procedure is furnished with a mitral valve TEER system that has received FDA premarket approval (PMA).
   2. The patient (preoperatively and postoperatively) is under the care of a heart team: a cohesive, multidisciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care… *(See NCD for more information)*
   3. Each patient's suitability for surgical mitral valve repair, TEER, or palliative therapy must be evaluated, documented, and made available to other heart team members. Additionally, for patients with functional MR, the heart team heart failure cardiologist must document that the patient has persistent symptoms despite maximally tolerated GDMT and cardiac resynchronization therapy, if appropriate... *(See NCD for more information)*

4. An interventional cardiologist or cardiac surgeon from the heart team must perform the mitral valve TEER and an interventional echocardiographer from the heart team must perform transesophageal echocardiography during the procedure. The interventional echocardiographer may not also furnish anesthesiology during the same procedure. The interventional cardiologist and cardiac surgeon may jointly participate in the intra-operative technical aspects of TEER as appropriate. All physicians who participate in the procedure must have device-specific training as required by the manufacturer.
5. Mitral valve TEERs must be furnished in a hospital with appropriate infrastructure and experience… *(See NCD for more information)*
6. The heart team and hospital are participating in a prospective, national, audited registry that: 1) comprehensively enrolls TEER patients; 2) accepts all manufactured devices; 3) follows the patient for at least one year; and 4) complies with relevant regulations relating to protecting human research subjects, including 45 Code of Federal Regulations (CFR) Part 46 and 21 CFR Parts 50 & 56.

The following outcomes must be tracked by the registry, and the registry must be designed to permit identification and analysis of patient, practitioner, and facility level variables that predict each of these outcomes:

a. Stroke;
b. All-cause mortality;
c. Repeat *TEER* or other mitral procedures;
d. Transient Ischemic *Attacks* (TIAs);
e. Major vascular events;
f. Renal complications;
g. Functional capacity; *and*
h. Quality of Life (QoL).

(See determination for further information regarding hospital, institutional and operator requirements)

Mitral valve TEERs are covered for uses that are not expressly listed as an FDA-approved indication when performed within a clinical study that fulfills specific criteria. (See determination for more information).

Local Coverage Determination:

There is no local coverage determination for transcatheter mitral valve repair.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

Closure Devices for Patent Foramen Ovale and Atrial Septal Defects
Transcatheter Aortic Valve Implantation for Aortic Stenosis

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through February 8, 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
3/1/11	1/25/11	1/4/11	Joint policy established
7/1/12	4/10/12	5/18/12	Routine maintenance
5/1/14	2/24/14	3/3/14	Routine maintenance
1/1/15	10/21/14	11/3/14	Routine maintenance; title changed from “Percutaneous Mitral Valve Repair” to current title. Added CMS Decision Memo for Transcatheter Mitral Valve Repair dated 8/7/14.
7/1/15	4/21/15	5/11/15	Policy position changed from E/I to “established” for transcatheter mitral valve repair ; new codes for 2015, 33418 and 33419, replace 0343T and 0344T, respectively; CMS information updated to reflect NCD
7/1/16	4/19/16	4/19/16	Routine maintenance
11/1/16	8/16/16	8/16/16	Routine maintenance
11/1/17	8/15/17	8/15/17	Routine maintenance
11/1/18	9/7/18	8/21/18	Permavalve and 0483T and 0484T added as EI (replacement) per code update
11/1/19	9/9/19		• Routine maintenance • 0543T and 0544T added per code update • Added inclusion regarding secondary MVR per FDA update for MitraClip use.
3/1/20	12/17/19		• Routine maintenance
5/1/21	2/16/21		• Routine maintenance
5/1/22	3/11/22		• Routine maintenance • Updated NCD • Title Changed from: Transcatheter Mitral Valve Repair • FDA approved products are covered

5/1/23	2/21/23		• Routine maintenance (slp) • Vendor Managed: N/A
5/1/24	2/20/24		• Routine maintenance (slp) • Vendor managed: N/A

Next Review Date: 1st Qtr, 2025

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: TRANSCATHETER MITRAL VALVE PROCEDURES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered, criteria apply
BCNA (Medicare Advantage)	Refer to the Medicare information under the Government Regulations section of this policy.
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.