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Transcatheter Mitral Valve Procedures

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Related Policies (if applicable)
SUR707.028: Transcatheter Aortic-Valve Implantation for Aortic Stenosis

Disclaimer

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Coverage

Transcatheter Mitral Valve Repair
Transcatheter mitral valve repair with a device approved by the United States (U.S.) Food and Drug Administration (FDA) for use in mitral valve repair **may be considered medically necessary** for individuals with:

- Symptomatic, primary mitral regurgitation who are considered at prohibitive risk for open surgery (see **NOTE 1**); or
- Heart failure and moderate-to-severe or severe symptomatic secondary mitral regurgitation (see **NOTE 2**) despite the use of maximally tolerated guideline-directed medical therapy (see **NOTE 3**).

NOTE 1: Prohibitive risk for open surgery may be determined based on:

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

NOTE 2: Moderate to severe or severe mitral regurgitation (MR) may be determined by:

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

NOTE 3: Optimal medical therapy may be determined by guidelines from specialty societies (e.g., American Heart Association/American College of Cardiology Guideline for the Management of Patients with Valvular Heart Disease, European Society of Cardiology/European Association for Cardio-Thoracic Surgery Guidelines for the Management of Valvular Heart Disease, American Heart Association/American College of Cardiology/Heart Failure Society of America Guideline for the Management of Heart Failure).

Transcatheter mitral valve repair **is considered experimental, investigational and/or unproven** in all other situations.

Transcatheter Mitral Valve-in-Valve Replacement

Transcatheter mitral valve-in-valve replacement (TMViVR) with a device approved by the U.S. FDA **may be considered medically necessary** for individuals when all of the following conditions are present:

- Failure (stenosed, insufficient, or combined) of a surgical bioprosthetic mitral valve; AND
- New York Heart Association heart failure class II, III, or IV symptoms; AND
- One of the following (see **NOTE 4**):
    - Individual is not an operable candidate for open surgery, as documented by at least 2 cardiovascular specialists (including a cardiac surgeon); **OR**
    - Individual is an operable candidate but is considered at increased surgical risk for open surgery, as documented by at least 2 cardiac specialists (including a cardiac surgeon); **OR**
    - Individual is considered at increased surgical risk for open surgery (e.g., repeat sternotomy) due to a history of congenital vascular anomalies **AND/OR** has a complex intrathoracic surgical history, as documented by at least 2 cardiovascular specialists (including a cardiac surgeon).

NOTE 4: The FDA definition of high risk for open surgery is:

- Society of Thoracic Surgeons (STS) predicted operative risk score of 8% or higher; **OR**
- Judged by a heart team, which includes an experienced cardiac surgeon and a cardiologist, to have an expected mortality risk of 15% or higher for open surgery.

Transcatheter mitral valve repair using percutaneous annuloplasty **is considered experimental, investigational, and/or unproven** for the treatment of mitral valve regurgitation (insufficiency).

Policy Guidelines

None.

Description

Transcatheter mitral valve repair (TMVR) is an alternative to surgical therapy for mitral regurgitation (MR). MR is a common valvular heart disease that can result from a primary structural abnormality of the mitral valve (MV) complex or a secondary dilatation of an anatomically normal MV due to a dilated left ventricle caused by ischemic or dilated cardiomyopathy. Surgical therapy may be underutilized, particularly in patients with multiple comorbidities, suggesting that there is an unmet need for less invasive procedures for MV repair. Two devices, MitraClip™ and PASCAL™, have 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. MitraClip is also approved for patients with heart failure and moderate-to-severe or severe symptomatic secondary MR despite the use of maximally tolerated guideline-directed medical therapy. The Edwards SAPIEN 3 transcatheter heart valve has been approved by the U.S. Food and Drug Administration for transcatheter mitral valve-in-valve replacement (TMViVR) in patients with a failing surgical bioprosthetic mitral valve who are at high or greater risk for repeat surgery.

Mitral Regurgitation (MR)

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 present in patients with valvular dysfunction. (3) MR severity is classified into mild, moderate, and 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 leaflets not to coapt or meet in the center. (3) Because the valves are structurally normal in secondary MR, correcting the dilated LV using medical therapy is the primary treatment strategy used in the U.S.

Standard Management

Surgical Management

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

The use of standard open MV repair is limited by the requirement for thoracotomy and cardiopulmonary bypass, which may not be tolerated by patients who are elderly or debilitated due to their underlying cardiac disease or other conditions. In a single-center evaluation of 5,737 patients with severe MR in the U. S., Goel et al. (2014) found that 53% of patients did not have MV surgery performed, suggesting an unmet need for such patients. (6)

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

Transcatheter MV Repair

Transcatheter approaches have been investigated to address the unmet need for less invasive MV repair, particularly among inoperable patients who face prohibitively high surgical risks due to age or comorbidities. MV repair devices under development address various components of the MV complex and generally are performed on the beating heart without the need for cardiopulmonary bypass. (1, 13) Approaches to MV repair include direct leaflet repair, (14) repair of the mitral annulus via direct annuloplasty, or indirect repair based on the annulus's proximity to the coronary sinus. There are also devices in development to counteract ventricular remodeling, and systems designed for complete MV replacement via catheter.

Direct Leaflet Approximation

Devices currently approved by the FDA for transcatheter mitral valve repair (TMVR) undergo direct mitral leaflet repair (also referred to as transcatheter edge-to-edge repair). Of the TMVR devices under investigation, MitraClip has the largest body of evidence evaluating its use; it has been in use in Europe since 2008. (14) The MitraClip system is deployed percutaneously and approximates the open Alfieri edge-to-edge repair approach to treating MR. The delivery system consists of a catheter, a steerable sleeve, and the MitraClip device, which is a 4-mm wide clip fabricated from a cobalt-chromium alloy and polypropylene fabric. MitraClip is deployed via a transfemoral approach, with transseptal puncture used to access the left side of the heart and the MV. Placement of MitraClip leads to 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 Mitral Valve Repair Devices

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

Direct annuloplasty devices include the Mitralign Percutaneous Annuloplasty System (Mitralign) and the AccuCinch® System (Guided Delivery Systems), both of which involve transcatheter placement of anchors in the MV; they are cinched or connected to narrow the mitral annulus. Other 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.

Transcatheter Mitral Valve-in-Valve Replacement

Mitral valve-in-valve replacement is a minimally invasive procedure designed to treat patients with failing surgical bioprosthetic mitral valves who are at high risk for complications with repeat open-heart surgery. The Edwards SAPIEN 3 Transcatheter Heart Valve received FDA approval in June 2017 (PMA# P140031) for patients with a failing surgical bioprosthetic mitral valve who are at high or prohibitive risk for repeat surgery. The procedure involves deploying the replacement valve within the failing bioprosthetic valve using a catheter-based transapical or transseptal approach. Once in position, the replacement valve is expanded, pushing the leaflets of the failing bioprosthetic valve aside and taking over the valve function.

<u>Medical Management</u>

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 inhibitors (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 the FDA through the PMA 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 MV surgery by a heart team." (19)

In June 2017, the Edwards SAPIEN 3 Transcatheter Heart Valve received FDA approval through the premarket approval process for the treatment of patients with a "failing surgical bioprosthetic mitral valve who have been determined to be at high or greater risk for open-heart surgery by a heart team."

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." (97)

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 MitraClip and PASCAL: NKM

FDA product code for Edwards SAPIEN 3: NPV

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or

worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

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

MitraClip and PASCAL

Primary Mitral Valve Regurgitation at Prohibitive Surgical Risk

Clinical Context and Therapy Purpose

The purpose of for transcatheter mitral valve repair (TMVR) using MitraClip or PASCAL in individuals who have primary mitral regurgitation (MR) and are at prohibitive risk for open surgery is to provide a treatment option that is an alternative to or an improvement on existing therapies.

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

Populations

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

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

Intervention

The therapy being considered is TMVR using MitraClip or PASCAL.

Comparators

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

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

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

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

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, 21) 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. (22)

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.

Zahr et al. (2023) reported 1-year outcomes of the CLASP IID trial, which compared the safety and effectiveness of the PASCAL device (n=204) with the MitraClip device (n=96) for the treatment of MR in the full cohort of 300 patients. (23) The study population was well-balanced between the 2 groups, with the majority of participants in each group deemed to be at prohibitive surgical risk due to frailty. At 1-year follow-up, data were available for 91.5% and 94.3% of participants in the PASCAL and MitraClip groups, respectively. The primary safety endpoint, the proportion of patients experiencing a major adverse event at 30 days, was similar between the PASCAL (4.6%) and MitraClip (5.4%) groups (upper bound of 95% CI for between-group difference, 4.6%). Severe bleeding was the most common major adverse event in both groups (PASCAL: 3.6%; MitraClip: 2.2%), with 1 cardiovascular death (0.5%) in the PASCAL group and 2 (2.2%) in the MitraClip group. Freedom from major adverse events remained comparable between groups at 1 year (PASCAL: 84.7%; MitraClip: 88.3%; p=.471). The primary effectiveness endpoint, the proportion of patients with MR ≤2+ at 6 months, was achieved by 97.9% and 95.7% of patients in the PASCAL and MitraClip groups, respectively (absolute difference, 2.2%), meeting the prespecified noninferiority margin. At 1 year, MR reduction to ≤2+ was sustained in both groups (PASCAL: 95.8%; MitraClip: 93.8%), with no significant differences observed. Both groups experienced significant improvements in functional (NYHA functional class) and quality of life (Kansas City Cardiomyopathy Questionnaire Score, EQ-5D-5L, mean 6-minute walk distance) from baseline to 1 year (p<.05 for all), with no differences between groups. Study limitations included unblinded treatment allocation, the use of multiple generations of PASCAL and MitraClip devices, and loss to follow-up for time-to-event outcomes. The findings suggest that the PASCAL device is non-inferior to the MitraClip device for the reduction of MR severity and the rate of major adverse events at 1 year, consistent with the interim analysis.

Non-Randomized Studies

Tables 1 and 2 summarize patient characteristics and health outcomes of the case series by Reichenspurner et al. (2013) (24) and Lim et al. (2013), (25) which were considered higher quality. The Reichenspurner et al. (2013) study reported data on 117 patients with primary MR who were enrolled in a European postmarketing registry. The Lim et al. (2013) study reported data on 127 patients enrolled in the Endovascular Valve Edge-to-Edge REpair Study (EVEREST II)

High Risk Registry (HRR) and the Real World Expanded Multicenter Study of the MitraClip System (REALISM) registry and then retrospectively identified as meeting the definition of prohibitive risk and were followed for 1 year. The 30-day mortality rates were 6.0% and 6.3%, and 12-and 25-month mortality rates were 17.1% and 23.6%, respectively. (24, 26) In evaluable patients at 12 months, the percentages of patients who had an MR severity grade of 2 or less were 83.3% and 74.6% in the 2 studies; the percentages with NYHA class I or II functional status were 81% and 87%; and the percentages who improved at least 1 NYHA class level were 68% and 88%, respectively.

Table 1. Key MitraClip Case Series Characteristics

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

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

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

Study; Trial	Original N	MR Grade at 12 Months, % (n/N)	NYHA Class at 12 Months, % (n/N)	Other Pertinent Outcomes at 12 Months
Reichenspurner et al. (2013) (24); ACCESS-EU	117	MR severity ≤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=.03), n=44 Change in 6MWT from baseline, 77.4 m (p<.001), n=52
Lim et al. (2014) (26); subset of patients at	127	MR severity ≤2+: 83.3% (70/84)	Class I/II: 86.9% (73/84)	SF-36 PCS score change, 6.0

prohibitive risk of open surgery from EVEREST II HRR and REALISM			Improved ≥1 class: 86.9% (73/84)	(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

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

In reviewing data for MitraClip, the FDA compared the cohort reported by Lim et al. (2014; discussed above) with a historical cohort (n=65) generated from the patient-level data Duke Registry of primary MR patients with MR of 3+ or more. The Duke cohort of 65 patients with primary MR was derived from a dataset of 953 patients with an MR severity grade of 3+ or 4+ who were retrospectively identified as being at a prohibitively high risk for surgery based on the same high-risk criteria as those in the EVEREST II HRR and REALISM studies (i.e., Society of Thoracic Surgeons [STS] mortality risk calculation of12% or higher or protocol-specified surgical risk factors). For the cohort described by Lim et al. (2014), compliance to follow-up visits in continuing patients was 98%, 98%, and 95% at 30 days, 12 months, and 2 years, respectively. Cohort characteristics and results are summarized in Tables 3 and 4. There were no intraprocedural deaths and the MitraClip was implanted successfully in 95% of patients. Eight patients died within 30 days of the procedure or discharge post-procedure, resulting in a procedural mortality rate of 6.4% that increased to 24.8% at 12 months. Comparative mortality rates in the Duke cohort at 30 days and 12 months were 10.9% and 30.6%, respectively.

The FDA 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 MV.
- 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 Lim et al. (2014) cohort.
- While acknowledging the pitfalls of using historical controls from the Duke Registry, the FDA found no elevated risk of mortality in MitraClip cohort patients over nonsurgical management and both immediate and long-term improvement in MR severity. MR severity grade of 2+ or less and of 1+ or less was observed in 82% and 54% of surviving patients at discharge, respectively. This improvement was sustained at 12 months, with the majority (83.3%) of surviving patients reporting MR severity grade of 2+ or less and 36.9% reporting

MR severity grade of 1+ or less. At 12 months, freedom from death and MR severity grade greater than 2+ was 61.4%, and freedom from death and MR severity grade greater than 1+ was 27.2%.

- Quality of life was assessed using the 36-Item Short-Form Health Survey (SF-36). The mean difference in the Physical Component Summary and Mental Component Summary scores from baseline to 12 months improved by 6 and 5.6 points, respectively, which is above the 2- to 3-point minimally important difference threshold reported in the literature. (27) Sensitivity analyses showed that these effectiveness results were robust to missing data.
- The commercial post-registry data of over 8300 patients (one-third primary MR and two-thirds secondary MR) outside the U. S. suggests that mortality rates reported in patients at prohibitive risk of surgery undergoing the MitraClip procedure do not appear to be elevated and are not unexpected given the age and burden of comorbidities of the patients treated. Reported mortality ranges were: in-hospital mortality, 0% to 4%; 30-day mortality, 0% to 9.1%; and 6- to 12-month mortality, 8% to 24%. Reported clinical benefits were: improvement in MR severity grade of 2+ or less after MitraClip in more than 75% of patients; improvement in 6-minute walk distance of 60 to >100 meters (the generally accepted threshold is >40 m), and percentages of patients who improved to 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) (19)	Single cohort with historical comparator	U.S.	Unclear	**MitraClip cohort** • N=127 • Age: 82.4 y • >75 y: 84% • NYHA class ≥III: 87% • STS predicted mortality: 13.2% • LVEF: 61% **Duke cohort** • N=65 • Age: 76.8 y • >75 y: 68%	MitraClip	Nonsurgical management	1 y

				• NYHA class ≥III: 44% • STS predicted mortality: 13.3% • LVEF: 44%			

FDA: Food and Drug Administration; FU: follow-up; LVEF: left ventricular ejection fraction; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons; U.S.: United States; y: year(s).

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) (19)	N=192	N=192	N=192	N range, 114-124	N range, 114-124
MitraClip	93.6 (87.6 to 96.8)	84.8 (77.2 to 90.0)	75.2 (66.1 to 82.1)	Baseline: 10% 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; d: day(s); FDA: Food and Drug Administration; mo: month(s); MR: mitral regurgitation; N: total number; NYHA: New York Heart Association.

Subsequent to the FDA approval of MitraClip in 2013, patients who received MitraClip under Medicare coverage were required to enroll in the joint STS and American College of Cardiology Transcatheter Valve Therapy Registry as part of coverage under evidence development. 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 the 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 LV 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 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 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 CLASPIID/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

	Number of Patients	**Primary MR, %**	**Secondary MR, % Study**	**Post-implant-ation MR Grade ≤2, %**	**In-Hospital Death, %**	**30-Day Death, %**	**6-Month Death, %**	**1-Year Death, %**
Sorajja et al. (2016) (28)	564	86	14	93	2.3	5.8	NR	NR
Sorajja et al. (2017) (29)	2952	86	9	92	2.7	5.2	NR	25.8
FDA (2022)	92	100	0	91	NR	2.2	6.5	NR

(20)								

MR: mitral regurgitation; NR: not reported.

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

Section Summary: Primary Mitral Valve Regurgitation at Prohibitive Surgical Risk

The evidence for the use of MitraClip and PASCAL in patients with primary MR at prohibitive surgical risk consists of 1 RCT, and otherwise primarily of single-arm prospective cohort and registry studies. Included are the pivotal EVEREST II HRR and EVEREST II REALISM studies and the Transcatheter Valve Therapy Registry studies. The 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 (5-6 point gain in SF-36 scores). However, the 1-year mortality or heart failure hospitalization rates remained considerably high (38%) compared with the 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 MV Regurgitation

Clinical Context and Therapy Purpose

The purpose of TMVR 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 PICO was used to select literature to inform this policy.

Populations

The relevant population of interest is individuals 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. MR severity is classified as mild,

moderate, or severe disease on the basis of echocardiographic and/or angiographic findings (1+, 2+, and 3+ to 4+ angiographic grade, respectively).

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

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

Outcomes
The general outcomes of interest are overall survival, 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 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.

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 (total N=1,130) using data from the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) and the Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) RCTs discussed below, as well as 2 preceding small propensity score-matched observational studies. Pooled analyses that included the RCT's and the observational studies found that compared to medical therapy alone, at 2 years of follow-up, MitraClip plus medical therapy significantly reduced the risk of all-cause mortality (relative risk [RR], 0.72; 95% CI, 0.55 to 0.95; I^2=55%), readmission events for heart failure (RR, 0.62; 95% CI, 0.42 to 0.92, I^2=90%), but not cardiovascular mortality (RR, 0.69; 95% CI, 0.47 to 1.02, I^2=68%). Further, results of fixed-effect meta-regression suggest that baseline left ventricular end-diastolic volume and age are associated with all-cause mortality and cardiovascular mortality outcomes. However, the interpretation of these pooled analyses is limited by their considerable

heterogeneity and the potential for increased risk of selection bias due to the inclusion of the nonrandomized studies.

Randomized Controlled Trials

Limited experience using PASCAL in patients with SMR has been reported. (49) This use is being investigated in a randomized cohort of the CLASP IID/IIF trial; analysis of this cohort has not yet been reported. (22)

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

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

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

Although the reasons for these discrepant results are not entirely clear, differences in the studies' design and conduct have been proposed as possible explanations. (55-57) 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 Randomized Controlled Trial Characteristics

Study; Trial	Countries	Sites	Dates	Participants	Interventions	
					Active	**Comparator**
Stone et al. (2018); (50) COAPT	US and Canada	78	2012-2017	Ischemic or nonischemic cardiomyopathy with LVEF 20% to 50%; moderate-to-severe (grade 3+) or severe (grade 4+) secondary MR; symptomatic (NYHA functional class II, III, or IVa) despite the use of stable maximal doses of guideline-directed medical therapy and cardiac resynchronization therapy	N=302 MitraClip plus medical therapy	N=312 Medical therapy alone
Obadia et al. (2018); (52) MITRA-FR	France	37	2013-2017	Severe SMR with a regurgitant volume of greater than 30ml per beat or an EROA ≥20 mm^2; NYHA functional class II, III, or IV despite optimal standard of care	N=152 MitraClip plus medical therapy	N=152 Medical therapy alone

				therapy for heart failure according to investigator LVEF between 15% and 40%; not appropriate for MV surgery by local heart team assessment		

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

Table 7a. Summary of Key Randomized Controlled Trial Results

Study	Primary Outcomes: HF hospitalizations within 24 months	Primary Outcomes: Death from any cause or unplanned HF hospitalization at 12 months	All-cause mortality at 12 months	CV death at 12 months	All-cause mortality at 24 months	CV death at 24 months
Stone et al. (2018); (50) COAPT						
Sample size	612		612		612	612
Medical therapy alone	283/416.8 (67.9%)		57 (19.1%)		121/312 (46.1%)	97 (38.2%)
MitraClip + medical therapy	160/446.5 (35.8%)		70 (23.2%)		80/302 (29.1%)	61 (23.5%)
HR (95% CI); p-value	0.53 (0.40 to 0.70); p<0.001		0.81 (95% CI 0.57 to 1.15); p<0.001 for noninferiority		0.62 (0.46 to 0.82); p<0.001	0.59 (90.43 to 0.81); p=0.001
NNT	3.1					
Obadia et al. (2018); 12-month results (52) Iung et al. (2019) 24-month results (53) MITRA-FR						
Sample size	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%)
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%)
HR (95% CI); p-value	0.97 (0.72 to 1.30)	1.16 (0.73 to 1.84); p=0.53	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)

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

Table 7b. Summary of Key Randomized Controlled Trial Results

Study	**MR grade 2+ or lower at 12 months**	**NYHA functional class I or II at 12 months**	**Primary Safety Outcome: Freedom from device-related complications at 12 months[1]** **Kaplan-Meier estimate of event-free rate (lower 95% confidence limit)**	**Serious adverse events at 1 year[2]**	**Periprocedural complications during device implantation**
Stone et al. (2018); (50) COAPT					
Sample size	385	469	302		
Medical therapy alone	82/175 (46.9%)	115/232 (49.6%)			
MitraClip + medical therapy		171/237 (72.2%)	96.6% (94.8%)		
HR (95% CI); p-value	P<0.001	P<0.001			
NNT					
Obadia et al. (2018); 12-month results (52) **Iung et al. (2019) 24-month results (53) MITRA-FR**					
Sample size				304	

Medical therapy alone				121/152 (79.6%)	
MitraClip + medical therapy				125/152 (82.2%)	21/144 (14.6%)
HR (95% CI); p-value				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; HR: hazard ratio; MITRA-FR: Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation; MR: mitral regurgitation; NYHA: New York Heart Association.

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

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

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

Table 8. Study Relevance Limitations

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

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

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

[b] Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.
[c] Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.
[d] Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.
[e] Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 9. Study Design and Conduct Limitations Gaps

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

The evidence gaps stated in this table are those notable in the current literature 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 1,041 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, 2 RCTs, and observational studies. The trials had discrepant results, but the larger trial, with patients selected for nonresponse to maximally tolerated therapy, found a significant benefit for MitraClip after up to 5 years compared to medical therapy alone, including improvements in OS and hospitalization for heart failure. Improvements in MR severity, quality of life measures, and functional capacity persisted to 36 months in patients who received TMVR. The systematic review confirmed the benefit of MitraClip found in the larger RCT but had important methodological limitations.

Primary or Secondary Mitral Regurgitation in Surgical Candidates

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

The therapy being considered is TMVR using MitraClip.

Comparators

Relevant comparators are open MV repair and open MV replacement.

In symptomatic individuals 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 overall survival, 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.

Systematic Reviews
A systematic review by Takagi et al. (2017) identified 1 RCT and 6 nonrandomized comparative studies evaluating MitraClip and surgery. (60) The RCT (EVEREST II) is described below. The systematic review conducted several pooled analyses. The meta-analysis did not detect a statistically significant difference in early (30-day or in-hospital) mortality between the MitraClip and surgery groups (pooled odds ratio [OR], 0.54; 95% CI, 0.27 to 1.08; p=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 ration [HR], 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/HR, 4.80; 95% CI, 2.58 to 8.93; p<0.001).

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

Trial results are summarized in Table 11. In the intention-to-treat (ITT) analysis, for patients who did not have acute procedural success with MitraClip and subsequently underwent open MV repair, the efficacy endpoint was considered met for MitraClip group subjects if they were free from death, reoperation for MR, and MR grade greater than 2+ at 12 months. The trial had a predetermined efficacy endpoint of noninferiority of the MitraClip strategy, with a margin of 25% for the ITT analysis and 31% for prespecified per-protocol analyses. This implies that the MitraClip strategy would be noninferior to surgery at 12 months if the upper bound of difference in the proportion of patients achieving the primary efficacy endpoint between the 2 groups did not exceed 25 percentage points for the ITT analysis and 31 percentage points for the per-protocol analysis. Results showed that TMVR was less effective at reducing MR than

conventional surgery before hospital discharge. MitraClip group subjects were more likely to require surgery for MV dysfunction, either immediately post-MitraClip implantation or in the 12 months following. Twenty percent (37/181) of the MitraClip group and 2% (2/89) of the surgery group required reoperation for MV dysfunction (p<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 four years (63) and five 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. The FDA concluded that the data did not demonstrate an appropriate benefit-risk profile when compared with standard MV surgery and were inadequate to support device approval for the surgical candidate population.

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

Table 10. Key Randomized Controlled Trial Characteristics

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

AF: atrial fibrillation; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; MR: mitral regurgitation; MV: mitral valve; N: total sample size; n: subset of the sample size; U.S.: United States; TMVR: transcatheter mitral valve repair.

Table 11. Key Randomized Controlled Trial Results

Study; Trial	Freedom From Death, Surgery for MR Dysfunction, and Grade 3+ or 4+ MR	Major AE at 30 Days[a]	Surgery for MV Dysfunction[b]	Death	Grade 3+ or 4+ MR
Feldman et al. (2011) (61) **EVEREST II[c] (1 year)**	270	274	270	270	270
TMVR	100/181 (55%)	27/180 (15%)	37/181 (20%)	11/181 (6%)	38/181 (21%)
Open repair	65/89 (73%)	45/94 (48%)	2/94 (2%)	5/94 (6%)	18/94 (20%)
p	0.007	<0.001	<0.001	1.00	1.00
FDA (2013) (19) EVEREST II (1 year)	Range, 156-208	274	-	-	-
TMVR	97/134 (72%)[d] 37/82 (45%)[e]	27/180 (15%)	NR	NR	NR
Open repair	65/74 (88%)[d] 51/74 (69%)[e]	45/94 (48%)	NR	NR	NR
p	0.001[d, f] 0.169[e, f]	<0.001	NR	NR	NR
Mauri et al. (2013) (63) **EVEREST II (4 years)**	NR	NR	234	234	234
TMVR	NR	NR	40/161 (25%)	28/161 (17%)	35/161 (22%)
Open repair	NR	NR	4/73 (6%)	13/73 (18%)	18/73 (25%)
p	NR	NR	<0.001	0.914	0.745

Feldman et al. (2015) (64) **EVEREST II (5 years)**			197	197	197
TMVR	NR	NR	43/154 (28%)	32/154 (21%)	19/154 (19%)
Open repair	NR	NR	5/56 (9%)	15/56 (27%)	1/56 (2%)
p	NR	NR	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; TMVR: transcatheter mitral valve repair.

[a] The composite primary safety endpoint was major AEs at 30 days, defined as freedom from death, myocardial infarction, nonelective cardiac surgery for AEs, renal failure, transfusion of ≥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 the FDA, noninferiority statistical methods were used to calculate this p value, however, noninferiority was not implied due to the large margin. Therefore, this test shows whether the results show decreased effectiveness by the margin specified of -31%.

Observational Studies

Buzzatti et al. (2019) reported on the results of a retrospective, propensity-weighted analysis that compared 5-year outcomes between low-intermediate risk individuals aged 75 years or older 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 were significantly worse with MitraClip**.**

Table 12. Summary of Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants	Treat-ment	Treat-ment	Follow Up
Buzzatti et al.	Retro-spective Cohort	Italy, Switzerland	2005 - 2017	Individuals aged 75 years and older	MitraClip (N=100)	Surgical repair (N=206)	5 years

(2019) (66)				with degenerative mitral regurgitation and STS-PROM <8%			

N: total sample size; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality

Table 13. Summary of Observational Comparative Study Results

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

CI: confidence interval; HR: hazard ratio; MR: mitral regurgitation; NR: not reported; OR: odds ratio.

Section Summary: MitraClip in Surgical Candidates

The evidence for the use of MitraClip in patients considered candidates for open MV repair surgery includes an RCT (EVEREST II) and a systemic 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 one 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 a MR grade 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 postprocedure, thus limiting the number of patients who had long-term success without surgical intervention. For these reasons, this single trial is not definitive in demonstrating improved clinical outcomes with MitraClip compared to surgery. Further RCTs are needed to corroborate these results. Similarly, in the retrospective study that compared 5-year propensity-weighted outcomes between low-intermediate risk individuals aged ≥75 years with degenerative MR who underwent treatment with MitraClip or surgical mitral repair, although MitraClip was associated with improved 1 year survival and a lower rate of all acute complications, it had lower longer-term survival and greater MR recurrence.

Other Transcatheter Mitral Valve Repair Devices

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

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

Comparators

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

Outcomes

The general outcomes of interest are overall survival, 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.

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

Indirect Annuloplasty Devices

Randomized Controlled Trial

Several indirect annuloplasty devices, including the Carillon Mitral Contour System (Cardiac Dimension) and the Monarc device (Edwards Lifesciences), have been evaluated. The Carillon Mitral Contour System for Reducing Functional Mitral Regurgitation (REDUCE-FMR) study by Witte et al. (2019) was a multicenter, double-blind, sham-controlled randomized trial to report outcomes with the Carillon device in patients with functional SMR. (67) Patients included were taking optimally tolerated doses of guideline-directed medication therapy. Of note, 29.7% of patients included were classified as having mild MR (severity class 1+) based on

echocardiographic evaluation. Patients were randomized to Carillon device (n=87) or sham (n=33). In the treatment group, 73 (84%) of patients had the device implanted. At 1 year, patients with the Carillon device had a statistically significant reduction in MR volume (decrease of 7.1 mL/beat; 95% CI, -11.7 to -2.5) compared to the sham group (decrease of 3.3 mL/beat; 95% CI, -6.0 to 12.6; p=.049). Additionally, the Carillon device significantly reduced LV volumes in symptomatic patients with MR receiving optimal medical therapy (LV end-diastolic volume decrease of 10.4 mL; 95% CI, -18.5 to -2.4; LV end-systolic volume decrease of 6.2 mL; 95% CI, -12.8 to 0.4) compared to sham (LV end-diastolic volume increase of 6.5 mL; 95% CI, -5.1 to 18.2; p=.03; LV end-systolic volume increase of 6.1 mL; 95% CI, -1.42 to 13.6; p=.04). Patient-centered outcomes, including 6-minute walk test and quality of life scores, did not differ between groups. A post-hoc analysis by Khan et al. (2021) assessed patient-centered outcomes only in patients with SMR severity 2+ to 4+. (68) Of the 83 patients included in this analysis, 62 (75%) were randomized to the Carillon device group and 21 (25%) were randomized to sham procedure. A minimally clinically important difference for the outcomes was defined as a ≥30 m increase in 6-minute walk test, a NYHA decrease in ≥1 class, and a ≥3 point increase in KCCQ score at 1 year follow-up. All outcomes at 1 year favored the Carillon group over sham, but the only significant difference was in the 6-minute walk test scores (59% vs. 23%; p=.029; number needed to treat, 2.8). This analysis was not adequately powered to evaluate clinical endpoints. Further studies are needed to determine actual benefit and long-term outcomes beyond 1 year.

Case Series

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

The CINCH post-market registry evaluated the outcomes of percutaneous mitral valve repair using the Carillon Mitral Contour System in patients with functional mitral regurgitation and symptomatic heart failure from 2012 to 2022. (70) The single-arm study enrolled 101 patients at 13 sites in Germany, with a mean age of 75 years and primarily NYHA class III (69%) and MR grade 3 (68%). Over 5 years, all-cause mortality was 40.1%, heart failure hospitalization incidence was 53.9%, and the composite outcome of hospitalization or death was 66.4%. The annualized rate of cumulative heart failure hospitalization through 2 years was 28.8%. Statistically significant reductions in NYHA class and MR grade were reported at each follow-up

interval through 5 years; at the 5-year follow-up, 100% of participants had an improvement or maintained their NYHA class, and none had a mitral regurgitation score of 3+ or greater. There were no device-related serious adverse events reported, and 2 (2%) procedure-related serious adverse events, both of which were minor vascular access complications.

The retrospective TENDER (Tendyne European Experience) registry evaluated the Tendyne TMVR system at 31 high-volume heart valve centers (Germany, Austria, Belgium, France, Italy, Spain, Switzerland, and the United Kingdom). (71) The study included 195 patients eligible for 1-year follow-up, with a median age of 77 years and a median Society of Thoracic Surgeons Predicted Risk of Mortality of 5.6%. Technical success was achieved in 94.9% of patients. Cardiovascular mortality rates were 6.7% at 30 days and 16.9% at 1 year, while all-cause mortality rates were 9.3% at 30 days and 28.6% at 1 year. The rate of heart failure hospitalization significantly decreased from 68.1% in the year prior to the procedure to 25.4% in the 1-year post-procedure period. At 1-year follow-up, a reduction of mitral regurgitation to mild or less (≤1+) was achieved in 97.9% of patients, and 82.5% of patients were in NYHA functional class I or II, compared to 22.6% at baseline. Within the 1-year post-discharge follow-up, major adverse events included disabling stroke (2.4%), myocardial infarction (1.3%), new-onset atrial fibrillation (5.4%), and new conduction disturbances (1.2%). Device-specific events comprised valve thrombosis (3.0%), valve migration (0.6%), and paravalvular leak >1+ inch (5.2%).

Section Summary: Other Transcatheter Mitral Valve Repair Devices

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

Transcatheter Mitral Valve-in-Valve Replacement

Clinical Context and Therapy Purpose

The purpose of transcatheter mitral valve-in-valve replacement (TMViVR) implantation is to provide a treatment option that is an alternative to or an improvement on existing therapies, such as surgical mitral valve repair and medical management, in individuals with a degenerated mitral valve bioprosthesis who are at a high or prohibitive risk for redo surgical mitral valve replacement (rSMVR).

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

Populations

The relevant population of interest is individuals with a previously implanted bioprosthetic mitral valve who experience valve stenosis or mitral regurgitation and are determined to be at high surgical risk.

Interventions

The therapy being considered is TMViVR, a minimally invasive surgical procedure that repairs the mitral valve without removing the old, damaged valve by wedging a replacement valve into the place of the mitral valve.

Comparators
The first comparator of interest is surgical mitral valve repair, performed through sternotomy. The decision to repair a damaged mitral valve depends on the severity of the symptomatic mitral stenosis or regurgitation, the patient's age, and overall health. Medical management, including lipid-lowering therapy, anti-hypertensive drugs, and anti-calcific therapy, is the second comparator of interest in this policy.

Outcomes
The general outcomes of interest are OS, symptoms, morbid events, treatment-related mortality, and treatment-related morbidity. Symptoms may include heart murmur, angina, dizziness or syncope, shortness of breath, fatigue, and heart palpitations. Morbid events may include stroke, coronary obstruction, vascular complications, conduction disturbance, valve malpositioning and sizing, mitral valve injury, annular rupture, myocardial trauma, low cardiac output, cardiogenic shock, and cardiac arrest.

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 longer-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.

Systematic Reviews
Zhou et al. (2023) conducted a meta-analysis of TMViVR (n=1464) versus rSMVR (n=1,574) for patients who have had mitral bioprosthesis failure. (72) Nine retrospective cohort studies were included in the analysis from a literature search through September 2022. TMViVR was associated with a lower reported in-hospital mortality than rSMVR (3.2% vs. 6.8%; OR, 0.44; 95% CI, 0.30 to 0.64; p<.001; I^2 =0%) with no observed heterogeneity. However, 30-day (OR, 0.65; 95% CI, 0.36 to 1.17; p=.15) and 1-year mortality (OR, 0.96; 95 % CI, 0.63 to 1.45; p=.84) did not differ significantly between treatment groups. The TMViVR group had a lower rate of reported stroke (OR, 0.44; 95% CI, 0.29 to 0.67), renal dysfunction (OR, 0.52; 95% CI, 0.37 to 0.75), vascular complications (OR, 0.58; 95% CI, 0.43 to 0.78), pacemaker implantation (OR, 0.23; 95% CI, 0.15 to 0.36), and exploration for bleeding (OR, 0.24; 95% CI, 0.06 to 0.96) than the rSMVR group.

Ismayl et al. (2023) published a meta-analysis comparing TMViVR (n=338) to rSMVR (n=369) for individuals with degenerated bioprosthetic mitral valves. (73) A total of 6 observational studies

with a median follow-up of 2.7 years were included based on a literature search through September 2022; studies with potential overlap from the Nationwide Inpatient Sample and National Readmission Database were excluded from the analysis. Thirty-four patients (9.2%) in the TMViVR group received valve-in-ring rather than TMViVR and could not be separated for outcome assessment. The pooled risk of in-hospital mortality (OR, 0.52; 95% CI, 0.22 to 1.23; p=.14), 30-day mortality (OR 0.65; 95% CI, 0.36 to 1.17; p=.15), 1-year mortality (OR, 0.97, 95% CI, 0.63 to 1.49, p=.89), 2-year mortality (OR, 1.17; 95% CI, 0.65 to 2.13; p=.6) was similar between groups with low heterogeneity (I^2 = 0%). TMViVR had a lower risk of stroke (OR, 0.31; 95% CI, 0.11 to 0.88; p=.03), bleeding (OR, 0.21; 95% CI, 0.12 to 0.39; p<.00001), acute kidney injury (OR, 0.43; 95% CI, 0.22 to 0.84; p=.01), arrhythmias (OR, 0.17; 95% CI, 0.04 to 0.64; p=.009), and permanent pacemaker insertion (OR, 0.18; 95% CI, 0.05 to 0.60; p=.005).

Comparative Studies

Eight retrospective cohort or registry-based studies were identified, which provided indirect comparisons of TMViVR and rSMVR with follow-up periods from 1 to 5 years (Table 14). (68, 74-80) Patients included in the TMViVR groups had higher mean ages (range: 74 to 77) compared to rSMVR (range: 63 to 72) as well as worse Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) (range: 11.9% to 12.7% vs. 8.7% to 10.2%) and EuroScore (range: 15.7% to 39% vs. 15% to 23%). Due to this imbalance of patient characteristics between groups, propensity matching was performed in 4 studies. (68, 74, 76) However, despite efforts to make the treatment groups comparable, 2 of these studies still had baseline imbalances. (74, 80) Five of eight studies reported the device used for valve-in-valve replacement, all of which used either SAPIEN, SAPIEN 3, SAPIEN 3 Ultra or SAPIEN XT; 2 studies included a minority of patients with valve-in-ring procedures and did not report outcomes separately for valve-in-valve (ViV). (74, 75) Several studies were based on registry data and may have recounted participants from other studies with overlapping enrollment periods. (68, 76, 80)

Outcomes for studies comparing TMViVR to rSMVR are reported in Table 15. In-hospital mortality was reported by 4 studies (TMViVR range: 2 to 7.3; rSMVR range: 3.2 to 15.2), with 3 finding equivalent in-hospital mortality and 1 finding that TMViVR was favored over rSMVR. (80) At 30 days post-implantation, 1 of 5 studies (TMViVR range: 2.4% to 14%; rSMVR range: 1.3% to 15.2%) found a significant difference in mortality favoring TMViVR over rSMVR. (75) Mortality at one-year follow-up was reported by 6 studies (TMViVR range: <2.8% to 16.7%; rSMVR range: 4.8% to 18.3%), which found a significantly lower rate in TMViVR when compared to rSMVR in 1. (68) Longer-term follow-up was reported by 3 studies, all of which found numerically higher mortality in the TMViVR group, but statistical tests were provided for only 1 study, which found that rates were comparable with rSMVR. (75, 77, 79) The change in the direction of survival benefit may be due to TMViVR participants having a higher surgical risk and more advanced age, which, despite attempts to control statistically, remained unbalanced in 2 studies or the ability to treat concomitant conditions (e.g., tricuspid regurgitation or atrial fibrillation) during rSMVR which may confer a survival benefit. The length of hospital or intensive care unit (ICU) stay was reported in 6 studies (TMViVR range: 2 to 9.7 days; rSMVR range: 3 to 13 days) 4 of which found fewer in-hospital days amongst valve-in-valve repair patients compared to rSMVR. Complications of acute kidney injury, cardiac arrest, cardiogenic

shock, major bleeding, pacemaker implantation, pneumonia, sepsis, stroke, and vascular complications were greater in the rSMVR group; participants treated with TMViVR were more likely to report a residual defect needing closure or an increased likelihood of paravalvular regurgitation.

Table 14a. Summary of Observational Comparative Study Characteristics

Study	Study Type	Country	Dates	Participants (TMViVR; rSMVR)
Szlapka et al. (2022) (74)	Retro-spective cohort, propensity-matched	Multi-center (10 sites), Germany	2014-2019	Degenerated mitral valve prosthesis or ring who underwent TMViVR or rSMVR without prosthetic endocarditis and failing mechanical prostheses. EuroSCORE II risk: 15.7%; 15.0%; p=.5336 Mean age, years: 74.73; 72.2 years; p=.0030 Incidence of AF: 68%; 21%; p=.0233 Previous aortic valve re- placement: 25%; 12%; p=.042 Moderate or greater regurgitation: 40%; 37% TMViVR approach: Transapical: 92% Transseptal: 8% After PS matching, SS differences remained in several BL characteristics (age, creatinine [mg/dL], GFR [mL/min], previous aortic valve replacement, and AF).
Simard et al. (2022) (75)	Retro-spective cohort	Single center, United States	2014-2020	Degenerated mitral valve prosthesis or ring with mitral regurgitation, mitral stenosis or mixed dysfunction who underwent TMViVR or rSMVR Mean age, years: 74.9; 64.5; p<.0001 Chronic lung disease: 35%; 26%; p=.02 Tricuspid regurgitation ≥moderate: 47%; 60%; p=.07 NYHA class: I: 0%; 3.1%; p=.15 II: 1.2%; 10.1%; p=.01 III: 72.1%; 51.2%; p=.003 IV: 26.7%; 23%; p=.13 TMViVR approach:

				Transapical: 2% Transseptal: 98%
Gill et al. (2022) (76)	Retro-spective cohort, propensity-matched	Multi-center (National Inpatient Sample data)	2016-2018	Degenerated mitral valve prosthesis who underwent TMViVR or rSMVR, excluding those with endocarditis, undergoing other concurrent valvular procedures or CABG, and less than 50 years of age Mean age, years: 76; 67; p<.001 AF: 61%; 71%; p=.05 CHF: 85%; 66%; p<.001 CAD: 69%; 49%; p<.001 After PS matching NS differences in BL characteristics were observed.
Khan et al. (2021) (68)	Retro-spective cohort, propensity-matched	Multi-center (National Inpatient Sample data)	2015-2018	Patients undergoing rSMVR were identified by ICD-10-CM codes. Excluding those with infective endocarditis, undergoing CABG, and less than 50 years of age Mean age, years: 77; 68; p<.01 AF: 62%; 70%; p<.01 CAD: 70%; 42.2%; p<.01 HTN: 82%; 76%; p=.004 PVD: 18%; 11%; p<.01 Median Charlson score: 6; 5; p<.01 After PS matching NS differences in BL characteristics were observed.
Zahid et al. (2021) (80)	Retro-spective cohort, propensity-matched	Multi-center (Nation-wide Re-admission Database)	2015-2019	Patients undergoing redo mitral valve replacement in adults over 18 with ICD-10-CM codes for TMViVR or rSMVR. Excluding those with infective endocarditis, aortic valve disease, pulmonic valve disease, tricuspid valve disease, CABG, SAVR, TAVR, tricuspid valve surgery, pulmonic valve surgery, ASD, or VSD repairs Median age, years: 76; 69; p<.01 CHF: 84%; 73%; p<.01 After PS matching SS differences remained in several BL characteristics (age, CHF, hospital type, and insurance type).

Zubarevich et al. (2021) (79)	Retro-spective cohort	Single center, Italy	2012-2020	Consecutive patients at a single center who underwent either rSMVR or TMViVR, excluding those with infective endocarditis of the mitral valve and those who needed concomitant CABG. Mean age, years: 73.6; 63.7; p=.001 NYHA Class III: 71%; 42% p=.02 NYHA Class IV: 29%; 30%; p=1 Pulmonary HTN: 100%; 67%; p<.001 Diabetes: 34%; 12%; p<.03 Chronic obstructive lung disease: 42%; 15%; p=.02 CAD: 22; 6; p=.1 Prior CABG: 61%; 15%; p<.001 Prior aortic valve replacement: 27%; 9%; p=.05 EuroScore II: 21.2%; 18.2%; p=.024 STS Score: 11.9; 10.2; p=.003 TMViVR approach: Transapical: 100% Transseptal: 0%
Kamioka et al. (2018) (78)	Retro-spective cohort	Multi-center (3 sites), U.S.	2007-2017	Patients with severely degenerated mitral valve prostheses, excluding active cases of endocarditis, those who required concomitant procedures for CAD or aortic disease, or patients who underwent additional valve replacement. Mean age, years: 74.9; 63.7; p<.001 NYHA Class IV: 31%; 32%; p=.85 HTN: 86%; 80%; p=.4 Dyslipidemia: 81%; 64%; p=.05 Diabetes: 24%; 12%; p=.08 Lung disease ≥moderate: 34%; 14%; p=.01 CAD: 53%; 31%; p=.01 History of CABG: 47%; 25%; p=.02 History of aortic valve replacement: 26%; 7%; p=.01 AF: 76%; 27%; p<.001 History of pacing device: 27%; 12%; p=.03 STS PROM: 12.7; 8.7; p<.001

				Time from previous procedure, yrs: 10.3; 8.2; p=.02 TMViVR approach: Transapical: 23% Transseptal: 77%
Murzi et al. (2017) (77)	Retro-spective cohort	Single center, Italy	2005-2015	Patients with failed mitral bio-prostheses treated with TMViVR or rSMVR at a single center; no patients were reported as excluded. Mean age, years: 77; 67; p= .001; NYHA Class III or IV: 86%; 71%; p=.26 Diabetes: 24%; 10%; p=.153 AF: 43%; 10%; p=.006 Chronic kidney failure: 19%; 12.2%; p=.03 Severe pulmonary HTN: 90%; 34%; p=.001 EuroSCORE logistic: 39%; 23%; p=.005 TMViVR approach: Transapical: 100%

AF: atrial fibrillation; ASD: atrial septal defect; BL; baseline; CABG: coronary artery bypass graft; CAD: coronary artery disease; CHF: congestive heart failure; GFR; glomerular filtration rate; HTN: hypertension; NS: non-significant; NYHA: New York Heart Association; PROM: predicted risk of mortality; PS: propensity score; PVD; peripheral vascular disease; rSMVR: redo-surgical mitral valve replacement; SAVR: surgical aortic valve replacement SS: statistically significant; STS: Society of Thoracic Surgeons; TAVR: transcatheter aortic valve replacement; TMViVR: transcathetermitral valve-in-valve replacement; VSD: ventricular septal defect.

Table 14b. Summary of Observational Comparative Study Characteristics

Study	Treatment	Comparator	Follow-Up
Szlapka et al. (2022) (74)	TMViVR (n=79) SAPIEN, SAPIEN 3, or SAPIEN XT *7 pts were valve in ring	rSMVR (n=194) PS Matched (n=79)	1-year
Simard et al. (2022) (75)	TMViVR (n=86) SAPIEN, SAPIEN 3, SAPIEN 3 Ultra, or SAPIEN XT *11 pts were valve in ring	rSMVR (n=129)	5 years
Gill et al. (2022) (76)	TMViVR (n=416) PS Matched (n=310)	rSMVR (n=1474) PS Matched (n=310)	1-year

	Device NR		
Khan et al. (2021) (68)	TMViVR (n=490) PS Matched (n=395) Device NR	rSMVR (n=2250) PS Matched (n=395)	1-year
Zahid et al. (2021) (80)	TMViVR (n=1144) PS Matched (n=403) Device NR	rSMVR (n=6521) PS Matched (n=411)	1 year
Zubarevich et al. (2021) (79)	TMViVR (n=41) SAPIEN 3, SAPIEN XT	rSMVR (n=33)	1 year
Kamioka et al. (2018) (78)	TMViVR (n=62) SAPIEN, SAPIEN 3, SAPIEN XT	rSMVR (n=59)	1 year
Murzi et al. (2017) (77)	TMViVR (n=21) SAPIEN 3, SAPIEN XT	rSMVR (n=40)	2 years

NR: not reported; PS: propensity score; PVD; peripheral vascular disease; rSMVR: redo-surgical mitral valve replacement; TMViVR: transcathetermitral valve-in-valve replacement.

Table 15. Summary of Observational Comparative Study Results

Study	**Mortality**		**Complications**
Szlapka et al. (2024) (74)		**Length of ICU stay, days (IQR)**	
TMViVR (n=79)	30 days: 11 (14.1%) 1 year: 13 (16.7%)	2 (3)	Stroke: 2 (2.5%) Postoperative MI: 1 (1.3%) Life-threatening bleeding: 2 (2.5%) Renal replacement surgery: 10 (12.7%) Atrial fibrillation: 19 (24.1%) Pacemaker implantation: 3 (3.8%) Paravalvular regurgitation: 5 (6.3%) Prosthesis dysfunction: 2 (2.5%)
rSMVR (n=79)	30 days: 10 (12.7%) 1 year: 13 (16.7%)	3 (5)	Stroke: 4 (5.2%) Postoperative MI: 3 (3.8%) Life-threatening bleeding: 12 (15.2%)

			Renal replacement surgery: 16 (20.3%) Atrial fibrillation: 29 (37.7%) Pacemaker implantation: 13 (16.5%) Paravalvular regurgitation: 0 Prosthesis dysfunction: 0
p-value	30 days:.81 1 year: 1	0.2	Stroke:.44 Postoperative MI:.37 Life-threatening bleeding:.01 Renal replacement surgery:.2 Atrial fibrillation:.07 Pacemaker implantation:.02 Paravalvular regurgitation:.03 Prosthesis dysfunction:.25
Simard et al. (2022) (75)		**NYHA I/II class:**	
TMViVR (n=86)	30-days: 2.4% 1 year: 14.7% 2 years: 24.5% 5 years: 49.9%	BL: 1.2% 30 days: 80.3% 1 year: 80.8% 2 years: 72.4% 3 years: 82.4%	
rSMVR (n=129)	30-days: 10.2% 1 year: 17.5% 2 years: 20.7% 5 years: 34%	NR	
OR (95% CI)	30-days: 4.69 (1.25 to 30.5; p=.04)	NA	
Gill et al. (2022) (76)		**Length of hospitalization, days ± SD**	
TMViVR (n=310)	1 year: 3.2%	7.5±0.8	Acute stroke: 5% Acute kidney injury: 18% Cardiac arrest: 0% Cardiogenic shock: 6.5% Peri-operative hemorrhage: 11% Sepsis: 5%
rSMVR (n=310)	1 year: 4.8%	13±0.5	Acute stroke: 8% Acute kidney injury: 27% Cardiac arrest: 16% Cardiogenic shock: 16% Peri-operative hemorrhage: 22% Sepsis: 13%

OR (95% CI)	1 year: 1.53 (0.67 to 3.45; p=.31)	p-value: <.001	Acute stroke: 1.73 (0.89 to 3.34; p=.11) Acute kidney injury: 1.75 (1.19 to 2.57; p = 0.004) Cardiac arrest:16% vs. 0%; p <0.001 Cardiogenic shock: 2.79 (1.62 to 4.81; p <0.001) Peri-operative hemorrhage: 3.12 (1.75 to 8.53; p =0.02) Sepsis: 3.1 (1.11 to 8.64; p=.03)
Khan et al. (2021) (68)		**Length of hospital stay, days (IQR):**	
TMViVR (n=395)	1 year: <2.8%	3 (1-8)	Acute kidney injury: 13.9% Pneumonia: <2.8% Residual atrial defect needing closure: 8.9%
rSMVR (n=395)	1 year: 7.6%	10 (7-16)	Acute kidney injury: 36.7% Pneumonia: 10.1% Residual atrial defect needing closure: 0%
OR (95% CI)	1 year: 2.2 (1.3 to 3.6; p<.01)	p-value:<.01	p-value:<.001 for each complication
Zahid et al. (2021) (80)		**Readmission:**	
TMViVR (n=403)	In-hospital: 2.6% 30-day: <1.4% 6 months: <1.4%	30-day: 15.1% 6 months: 25.2%	Stroke: 1.6% Vascular complications: 9.2% Blood transfusion: 12.1% Cardiac arrest with CPR: <1.4% Pneumonia: 7.4% Pericardial effusion: 1.6% Permanent pacemaker: 2.9%
rSMVR (n=411)	In-hospital: 7.3% 30-day: <1.3% 6 months: <1.4%	30-day: 14.2% 6 months: 29.8%	Stroke: 4.3% Vascular complications: 15% Blood transfusion: 29.1% Cardiac arrest with CPR: 2.4% Pneumonia: 12.2% Pericaridal effusion: 3.1% Permanent pacemaker: 11.1%
p-value	In-hospital: <.01 30-day:.36 6 months:.11	30-day:.57 6 months:.13	p<.05 for all comparisons

Zubarevich et al. (2021) (79)		**Time in hospital, days**	
TMViVR (n=41)	In-hospital: 7.3% 30-day: 9.8% 1 year: 25.4% 3 years: 37.4%	9.7	Postoperative MR > trace: 17.1% New onset AF: 12.2%
rSMVR (n=411)	In-hospital: 15.2% 30-day: 15.2% 1 year: 18.3% 3 years: 27.1%	11	Postoperative MR > trace: 0% New onset AF: 27.3%
p-value	In-hospital:.45 30-day:.50 1 year:.19 3 years: NR	.06	Postoperative MR > trace:.15 New onset AF:.13
Kamioka et al. (2018) (78)		**Length of stay, days ± SD**	
TMViVR (n=62)	In-hospital: 3.2% 30-day: 3.2% 1 year: 11.3%	6.3 (4.8)	Major vascular complications: 1.6% Major bleeding: 8.1% Stroke: 0% New complete heart block: 0% New onset AF: 1.6% LVOT obstruction: 3.2%
rSMVR (n=59)	In-hospital: 3.4% 30-day: 3.4% 1 year: 11.9%	10.6 (6.6)	Major vascular complications: 5.1% Major bleeding: 33.9% Stroke: 3.4% New complete heart block: 5.1% New onset AF: 30.5% LVOT obstruction: 0%
p-value	In-hospital: 1 30-day: 1 1 year:.92	<.001	Major vascular complications:.36 Major bleeding: p<.001 Stroke:.24 New complete heart block:.07 New onset AF: <.001 LVOT obstruction:.16
Murzi et al. (2017) (77)		**Length of stay, days ± SD**	
TMViVR (n=20)	In-hospital: 4.7% 1 year: ~10% 2 years: 14% 3 years: ~36%	5±4	Stroke: 1 (4.7%) Low cardiac output syndrome: 1 (4.7%) Renal dysfunction: 1 (4.7%) Pulmonary complications: 2 (9.4%) Reoperation for bleeding: 1 (4.7%)

rSMVR (n=40)	In-hospital: 7.5% 1 year: ~9% 2 years: 13% 3 years: ~17%	14±7	Stroke: 5 (12.8%) Low cardiac output syndrome: 2 (4.9%) Renal dysfunction: 4 (10%) Pulmonary complications: 8 (20%) Reoperation for bleeding: 6 (14.6%)
p-value	NS difference at all points	.03	NS difference at all complications

AF: atrial fibrillation; CI: confidence interval; HR: hazard ratio; LVOT: Left ventricular outflow tract; MR: Mitral Regurgitation; NR: Not Reported; NS: non-significant difference; OR: Odds Ratio; rSMVR: redo-surgical mitral valve repair; SD: standard deviation; TMViVR: transcatheter mitral valve-in-valve repair.

Observational Studies

Nine retrospective cohort studies reported outcomes of patients undergoing TMViVR from 30 days to 7 years post-implantation (Table 16). (20, 81-88) Participants ranged in age from a mean of 72.6 years to 77.5 years. Mean STS scores over 8, which indicates a high risk for surgery, were reported for 7 studies (range: 5.9 to 11.1); EuroScore was reported in 4 studies (range 8.9 to 11.5). All studies reported that SAPIEN, SAPIEN 3, SAPIEN 3 Ultra, or SAPIEN XT were used for ViV procedures, but 2 studies included a minority of patients who were treated with non-US FDA-approved valves (Lotus, Direct Flow, and Melody devices). (86, 87)

Observational study outcomes for TMViVR are reported in Table 17. Technical success during TMViVR was reported by 5 studies and ranged from 73.6%to 96.8%, with device success ranging from 28.6% to 88.2% in 3 studies; however, different definitions of technical and device success were applied, which makes comparisons across studies challenging. (81, 85-88) Four studies reported an improvement in NYHA functional class from baseline levels. (83-85, 89) Three studies found improvements from baseline on the Kansas City Cardiomyopathy Questionnaire (KCCQ), with the longest follow-up being 5 years. (84-85, 89) Mortality at 30 days post-implantation ranged from 2.5% to 6.8% in 4 studies; (81-82, 86, 88) at 1 year, this range increased to 3% to16% in 8 studies. (81-88) Mortality at 2 years follow-up was only reported by 2 studies and had a wide range from 6.7% to 29.4%, (84, 88) and at 5 years follow-up, mortality increased to a range of 21.4% to 58.1% in 3 studies. (83-85) A single observational study reported that at 7 years after TMViVR the mortality rate was 64.3%. (82) Complications reported by more than one author included conversion to open surgery, left ventricular outflow tract obstruction, major vascular complications, new pacemaker implantation, stroke, and transcatheter heart valve thrombosis.

Table 16. Summary of Observational Study Characteristics

Study	Study Type	Country	Dates	Participants	Treatment	Follow-Up
Akodad et al. (2023) (81)	Retro-spective cohort	Single center, Canada	2008-2021	Patients with a degenerated mitral bioprosthetic valve treated with TMViVR.	SAPIEN 3 or SAPIEN 3 Ultra (N=119)	Mean 3.4years

				Mean age, years: 76.8 Euroscore: 11.1% STS PROM: 10.7% NYHA Class ≥ 3: 90.8% TMViVR approach: Transapical: 64% Transseptal: 36%		
Wilbring et al. (2023) (82)	Retro-spective-cohort	Single center, Switzerland	2011-2021	Consecutive patients treated with a failed mitral bioprosthetic valve treated with TMViVR. Mean age, years: 77.4 Euroscore: 11.5% STS PROM: 5.9% NYHA Class ≥ 3: 76% Moderate or severe MR: 88% Moderate or severe MS: 64% TMViVR approach: Transapical: 88% Transseptal: 12%	SAPIEN or SAPIEN XT (N=25)	Mean 4.8years
Pravda et al. (2022) (83)	Retro-spective cohort	Single center, Israel	2010-2019	Patients with mitral bioprosthetic valve treated with TMViVR. Mean age, years: 77.4 Euroscore: 8.9% STS PROM: 7.7% NYHA Class ≥ 3: 75% TMViVR approach: Transapical: 35% Transseptal: 65%	SAPIEN or SAPIEN XT (N=49)	5 years
Gurrero et al. (2021 & 2022) & Eleid et al. (2022) (91, 84, 90)	Prospective registry (MITRAL trial)	Multicenter (13 sites), U.S.	2016-2017	Patients with symptomatic moderate to severe or severe MR or MS due to failed mitral bioprosthetic valve treated with TMViVR Mean age, years: 77.5	SAPIEN 3 (N=30)	5 years

				STS PROM: 9.4% NYHA Class ≥3: 80% TMViVR approach: Transseptal: 100%		
Whisenant et al. (2020) (85)	Prospective registry (Mitral Valve-in-Valve Registry)	Multicenter (295 sites), U.S.	2015-2019	Consecutive patients treated with a failed mitral bioprosthetic valve treated with TMViVR at centers participating in the registry. Mean age, years: 73.3 STS PROM: 11.1% NYHA Class ≥ 3: 87.1% MR:24.8% MS: 55.4% Combined MR and MS: 19.8% TMViVR approach: Transseptal: 87% Transapical: 13%	SAPIEN 3 (N=1529)	1 year
Simonato et al. (2020) (86)	Retro-spective registry (Valve-in-Valve International Database)	Multicenter (90 sites worldwide)	2006-2020	Patients with a failed mitral bioprosthetic valve treated with TMViVR at centers participating in the registry. Mean age, years: 74.1 STS PROM: 9% NYHA Class ≥ 3: 89% MR:10% MS: 31% Combined MR and MS: 59% Severe MR: 42% TMViVR approach: Transseptal: 65% Transapical: 35%	SAPIEN, SAPIENXT, SAPIEN 3, Lotus, Direct flow, and Melody devices (N=857)	4 years
Yoon et al. (2019) (87)	Retro-spective registry (TMVR Registry)	Multicenter (40 sites), U.S. and Europe	2009-2018	Patients with a failed mitral bioprosthetic valve treated with TMViVR at centers	SAPIEN, SAPIEN XT, SAPIEN 3, Lotus, Direct flow,	1 year

				participating in the registry. Mean age, years: 72.6 STS PROM: 9.2% NYHA Class ≥ 3: 87.6% MR:37% MS: 41% Combined MR and MS: 23% TMViVR approach: Transseptal: 60% Transapical: 40%	and Melody devices (N=322); 90% Sapien valves	
Urena et al. (2018) (88)	Retro-spective cohort	Single center, U.S.	2010-2017	Patients with a failed mitral bioprosthetic valve treated with TMViVR at a single-center. Mean age, years: 73 EuroSCORE-II: 10.9% NYHA Class ≥ 3: 91.2% Moderate or severe MR: 47% TMViVR approach: Transseptal: 92% Transapical: 8%	SAPIEN or SAPIEN XT (N=34)	2 years
U.S. Food and Drug Admin-istration (2017) (20)	Retro-spective registry (TVT Registry)	Multicenter (112 sites), U.S. and Europe	2014-2016	Mean age, years: 73.4 STS PROM: 13% NYHA Class ≥ 3: 89.3% Moderate or severe MR: 62.5% Inoperable or extreme risk: 34.5% TMViVR approach: Transseptal: 27% Transapical: 65.3%	SAPIEN 3 or SAPIEN XT (N=290)	1 year

MR: mitral regurgitation; MS: mitral stenosis; NR: not reported; NS: non-significant; NYHA: New York Heart Association; STS-PROM: Society of Thoracic Surgeons Predicted Risk of Mortality; TMVR: transcatheter mitral valve replacement; TMViVR: transcatheter mitral valve-in-valve replacement.

Table 17. Summary of Observational Study Results

Study	Mortality	Treatment success or symptom improvement	Complications, n (%)

Akodad et al. (2023) (81)	30 days: 2.5% 1 year: 10.1% 3.4 years (median f/u): 46.2%	Technical success (successful access, delivery, deployment, and positioning of a single device in the absence of procedural death, surgical conversion, or emergency reintervention): 97.5% Device success (Significant mitral stenosis ≥ 5 mm Hg): 28.6% Device success (Significant mitral stenosis ≥ 10 mm Hg): 88.2%	Rehospitalization for heart failure: 13 (10.9%) THV thrombosis: 7 (5.9%) Major bleeding: 6 (5%) Mitral valve reintervention: 3 (2.5%) Moderate or greater MR: 1 (1%) Reintervention for THV dysfunction: 2 (1.6%)
Wilbring et al. (2023) (82)	Median survival: 4.4 years 30 days: 4% 1 year: ~10% 4.4 years: 50% 5 years: 58.1% 7 years: 64.3%	BL Moderate + Severe MR: ~97% Post- Implant Moderate + Severe MR: 10% 1-year Moderate + Severe MR: 12%	Sepsis: 2 (8%) Stroke: 2 (8%)
Pravda et al. (2022) (83)	1 year: 16% 5 years: 35% *In a sub-group analysis, there were no differences in mortality between patients who underwent the procedure via transapical or transfemoral/ transseptal access*	NYHA Functional Class I/II: Baseline: 25% 1 year: 98% 5 years: 91%	
Gurrero et al. (2021 & 2022) & Eleid et al. (2022); (91, 84, 90**)**	All-cause mortality: 1 year: 3% 2 years: 6.7% 5 years: 21.4%	MR Severity none/1+: Baseline: 51% 1 year: 100% 5 years:96% NYHA Functional Class I/II: BL: 19% 1 year: 86% 2 years: 77% 3 years: 75%	Rehospitalization for HF: 5 (16.7%) Septostomy closure: 2 (6.7%) Intracranial hemorrhage: 1 (3.3%)

		4 years: 78% 5 years: 75% *P<.001 for all time points vs BL; includes valve-in-ring patients* Median KCCQ Score: BL: ~33 1 year: ~55 2 years: ~54 3 years: ~57 4 years: ~58 5 years: ~50 *P<.001 for all time points vs BL; includes valve-in-ring patients*	
Whisenant et al. (2020) (85)	1 year: 15.8%	Technical success: 96.8% 1-year KCCQ Improvement, mean (SD): 39.4 (27.1) NYHA Functional Class III/IV: Baseline: 87% 30 days: 14% 1 year: 10%	Device embolization: 3 (0.2%) Cardiac perforation: 14 (1.1%) Conversion to open surgery: 9 (0.7%) ASD closure: 101 (7.6%) Cardiovascular death: 24 (1.8%) Stroke: 9 (0.7%) Mitral valve reintervention: 4 (0.3%) LVOF obstruction: 10 (0.8%) New pacemaker: 15 (1.1%) Periprocudural MI: 4 (0.3%) Device thrombosis: 2 (0.2%) Major vascular complications: 16 (1.2%)
Simonato et al. (2020) (86)	30 days: 6.5% 1 year: 13.8% 4 years: 37.5%	Technical success (MVARC Criteria: exit from the hybrid suite, patient is alive with	Major vascular complications: 8.8% Malposition: 21 (2.4%)

	Sub-group analyses showed no difference in transseptal access vs. other approaches	successful access, delivery, and retrieval of the device delivery system, successful deployment and correct position of the first intended device, and freedom from emergency surgery): 93.5% Device success (Reduction of MR to optimal levels): 41.3% Device success (Reduction of MR to acceptable levels): 84%	Required second transcatheter valve implantation: 24 (2.8%) LVOT obstruction: 15 (1.8%) MR ≥ moderate: 3.1% Rate of repeat MVR at 4 years: 16 (1.9%)
Yoon et al. (2019) (87)	1 year: 14%	Technical success (MVARC Criteria: exit from the hybrid suite, patient is alive with successful access, delivery, and retrieval of the device delivery system, successful deployment and correct position of the first intended device, and freedom from emergency surgery): 73.6% Device success (Reduction of MR to acceptable levels): 84.8%	Conversion to open surgery: 3 (0.9%) Valve embolization: 3 (0.9%) Cardiac perforation: 4 (1.2%) Need for second valve implantation: 8 (2.5%) LVOT obstruction: 7 (2.2%) Re-intervention: 73 (14%) Stroke: 7 (2.3%) Bleeding (major or extensive): 14 (4.6%) Bleeding (life-threatening or fatal): 7 (2.3) Major vascular complication: 5 (1.6%) Acute kidney injury: 14 (4.6%)
Urena et al. (2018) (88)	30 day: 5.9% 1 year: 13.2% 2 years: 29.4%	Technical success: 94.1%	Stroke: 2 (5.9%) Life-threatening or fatal bleeding: 2 (5.9%) Major vascular complications: 2 (5.9%) LVOT obstruction: 2 (5.9%)

			THV thrombosis: 3 (8.8%)
U.S. Food and Drug Administration (2017) (89)	All-cause mortality: 30 day: 6.8% Cardiac death: 30 day: 4.3%	NYHA Class Change at 30 days f/u: Improved, %: 85.6% Same: 13.4% Worsened: 1% Mitral Regurgitation Severity (Moderate-severe to severe, %): Baseline: 48.2% 30 days: 0.6% Mean change in 6-minute walk test (BL to 30 days): 474.7±442.9 Mean change in KCCQ summary score (BL to 30 days): 36.6	Stroke: 2 (0.7%) Readmission for heart failure: 4 (1.6%) Readmission cardiac: 2 (0.8%) Readmission non-cardiac: 12 (4.6%) Mitral valve intervention: 1 (0.4%) Bleeding at access site: 7 (2.3%) Other bleeding: 17 (5.8%) Atrial septal defect closure: 15 (4.9%) Cardiac arrest: 12 (4%) Unplanned vascular surgery or intervention: 8 (2.6%) Major vascular complication: 2 (0.6%) Device embolization: 1 (0.4%) Device migration: 2 (0.7%)

ASD: atrial septal defect; BL: baseline; CI: confidence interval; HF: heart failure; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVOT: Left ventricular outflow tract; MR: Mitral Regurgitation; MVARC: Mitral Valve Academic Research Consortium; NR: Not Reported; NYHA: New York Heart Association; OR: Odds Ratio; THV: transcatheter heart valve.

Section Summary: Transeptal Mitral Valve-in-Valve Replacement

The evidence for the use of TMViVR in patients who are at a high risk for open surgery includes 8 retrospective cohort or registry studies that compared TMViVR to rSMVR as well as 9 observational studies and 2 meta-analyses. The meta-analyses had mixed early-term findings, with one observing a benefit for in-hospital mortality favoring TMViVR, but at 30 days, 1 year, and 2-year follow-up, no difference between groups was observed in either review. Both analyses found that complications of stroke, renal dysfunction, vascular complications, pacemaker implantation, and bleeding were more common in the rSMVR group. The comparative studies generally found that mortality was equivalent or favored TMViVR through 1-year follow-up; however, several studies observed that at longer durations of follow-up, the trend in mortality was reversed with numerically higher mortality in the TMViVR group. TMViVR was associated with a shorter length of hospital or ICU stay than rSMVR. Several adverse events

(acute kidney injury, cardiac arrest, cardiogenic shock, major bleeding, pacemaker implantation, pneumonia, sepsis, stroke, and vascular complications) were more commonly reported in the rSMVR group compared to TMViVR. These results were supported by observational studies which provided data on mortality, functional outcomes and complications through up to 7 years post-implantation. A high level of technical success for TMViVR was also observed in these studies, although the rate of device success, which had multiple definitions across studies, varied. Benefits to NYHA functional class and improvements in Kansas City Cardiomyopathy Questionnaire outcomes were observed in 3 studies with maximum follow-up of 5 years. Despite the potential early benefits in mortality, duration of hospital stay, functional outcomes, and complications, there is uncertainty due to the lack of direct comparisons, imbalanced patient groups, different valve-in-valve approaches used, and concerns that at longer-term follow-up mortality may favor rSMVR. Given that no RCTs are available, selection bias cannot be ruled out. However, randomizing patients who are at high or prohibitive risk for open surgery to rSMVR is ethically prohibitive so retrospective comparisons will likely continue to represent the best available evidence for this intervention. The evidence is sufficient to determine that the technology results in 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 (TMVR) using MitraClip or PASCAL, the evidence includes a noninferiority randomized controlled trial (RCT) and single-arm prospective cohort with historical cohort and registry studies. Relevant outcomes are overall survival (OS), 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 studies 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%), postimplantation 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 SF-36 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 (HF) 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 RCT comparing TMVR with medical management is not feasible or ethical. The postmarketing data from the U.S. is supportive that MitraClip surgery is being performed with short-term effectiveness and safety in select patient population. 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. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have HF and symptomatic secondary mitral regurgitation (SMR) despite the use of maximally tolerated guideline-directed medical therapy who receive TMVR 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 discrepant results potentially related to differences in primary outcomes. The larger trial, with 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 TMVR. 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 TMVR using MitraClip, the evidence includes a systematic review, 1 RCT, and a retrospective comparative observational study in individuals aged 75 years or more. 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 1 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 or more 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 TMVR using devices other than MitraClip or PASCAL, the evidence includes a randomized study, 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. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have valve dysfunction and mitral stenosis or regurgitation after prior bioprosthetic mitral valve replacement, who are at a high or prohibitive risk for redo surgical mitral valve replacement (rSMVR), and who receive a transcatheter mitral valve-in-valve replacement (TMViVR) using an FDA-approved device, the evidence includes 2 meta-analyses, 8 comparative retrospective cohort studies, and 9 observational studies. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. The meta-analyses had mixed early-term findings, with one observing a benefit for in-hospital mortality favoring

TMViVR over rSMVR, but at 30 days, 1-year, and 2-year follow-up, no difference between groups in OS was observed in either review. Both analyses found that complications of stroke, renal dysfunction, vascular complications, pacemaker implantation, and bleeding were more common in the rSMVR group. The comparative studies generally found that mortality was equivalent or favored TMViVR through1-year follow-up; however, several studies that reported longer-term outcomes observed that the trend in mortality was reversed with numerically higher rates in the TMViVR group. TMViVR was associated with a shorter hospital or ICU stay than rSMVR. Several adverse events (acute kidney injury, cardiac arrest, cardiogenic shock, major bleeding, pacemaker implantation, pneumonia, sepsis, stroke, and vascular complications) were more commonly reported in the rSMVR group compared to TMViVR. These results were supported by observational data, which provided data on mortality, functional outcomes, and complications through up to 7 years post-implantation. The evidence base is limited primarily by the lack of experimental studies, but assigning patients who are at high or prohibitive risk for open surgery to rSMVR is ethically prohibitive so retrospective comparisons will likely continue to represent the best available evidence for this intervention. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

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

Also in 2020, the American College of Cardiology and American Heart Association released updated guidelines on the management of valvular heart disease. (5) The guidelines state that TMVR is of benefit to patients with severely symptomatic primary MR who are at high or prohibitive risk for surgery, and to a subset of patients with secondary MR who remain severely symptomatic despite guideline-directed management and therapy for heart failure. Individuals who have prosthetic valve stenosis are recommended to be offered revision surgery, but for severely symptomatic patients who are at high risk for surgery, a transcatheter aortic valve-in-valve procedure may be reasonable (B level of evidence, moderate class of recommendation); no recommendation is given regarding mitral valve-in-valve procedures. Relevant recommendations on interventions for primary and secondary MR and prosthetic valve stenosis are shown in Table 18.

Table 18. Recommendations on Interventions for Primary and Secondary MR

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% with an expected mortality rate of <1% when it can be performed at a Primary or Comprehensive Valve Center	2a (Moderate)	B-NR[1]
In asymptomatic patients with severe primary MR and normal LV systolic function (LVEF >60% and LVESD <40 mm) (Stage C1) but with a progressive increase in LV size or decrease in EF on ≥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]
Intervention for Prosthetic Valve Stenosis		
In patients with symptomatic severe stenosis of a bioprosthetic or mechanical prosthetic valve, repeat surgical intervention is indicated unless the surgical risk is high or prohibitive	1 (Strong)	B-NR[1]
For severely symptomatic patients with bioprosthetic aortic valve stenosis and high or prohibitive surgical risk, a transcatheter ViV procedure is reasonable when performed at a comprehensive valve center	2a (Moderate)	B-NR[1]
For patients with significant bioprosthetic valve stenosis attributable to suspected or documented valve thrombosis, oral anticoagulation with a VKA is reasonable	2a (Moderate)	B-NR[1]

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, valve-in-valve; VKA, vitamin K antagonist.

<u>American College of Cardiology, American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons</u>

The American College of Cardiology, American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons (2014) issued a position statement on transcatheter therapies for MR. (93) 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.

The European Society of Cardiology and the European Association for Cardio-Thoracic Surgery

The European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) issued guidelines on the management of valvular heart disease in 2022. (98) A new position on the management of prosthetic valve dysfunction was issued, stating, "Transcatheter valve-in-valve implantation in the mitral and tricuspid position may be considered in selected patients at high risk for surgical intervention." This recommendation was given a class IIb recommendation, indicating that there is conflicting evidence about the usefulness or efficacy of this treatment, with the opinion being supported by less well-established evidence.

National Institute for Health and Care Excellence

The NICE guideline on heart valve disease management (2021) makes the following recommendations related to TMVR: (94)

- "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."

Another NICE guideline was issued in 2021 on the use of transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis: (95)

- "1.1 - Evidence on the safety of transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis is adequate and shows some serious but well-recognised complications. Evidence on its efficacy is limited in quality. So, this procedure should only be used with special arrangements for clinical governance, consent, and audit or research."
- "1.4 - Patient selection should be done by a multidisciplinary team which must include interventional cardiologists experienced in the procedure, cardiac surgeons, an expert in cardiac imaging, and where appropriate, a cardiac anaesthetist and a specialist in medicine for older people. The multidisciplinary team should determine the risk level for each patient and the device most suitable for them."
- "1.6 - The procedure is technically challenging and should only be done in specialised centres, and only by clinical teams with special training and experience in complex endovascular cardiac interventions, including regular experience in transcatheter valve implantation procedures. Centres doing these procedures should have cardiac surgical support for emergency treatment of complications and subsequent patient care."
- "1.7 - NICE encourages further research into transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis. Studies should include details on patient selection, type and size of valve used, functional outcomes (New York Heart Association functional class, mitral valve regurgitation), quality of life,

patient-reported outcome measures, survival and complications. Studies should report long-term follow up of clinical outcomes and valve durability. NICE may update this guidance on publication of further evidence."

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 19.

Table 19. Summary of Key Trials

NCT Number	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 (Unknown Status)
NCT01626079[a]	Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (The COAPT Trial)	614 in COAPT and 162 in COAPT CAS	Jul 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	Mar 2025
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

NCT03271762	Multicentre and Randomized Study of MITRACLIP® Transcatheter Mitral Valve Repair in Patients With Severe Primary Mitral Regurgitation Eligible for High-risk Surgery	330	May 2027
NCT04402931	Randomized Trial of Transcatheter Valve-in-Valve Intervention vs Redo Surgery for the Treatment of Structural Mitral Bioprosthetic Dysfunction	150	Dec 2031
NCT03193801	PARTNER 3 Trial - SAPIEN 3 Transcatheter Heart Valve Implantation in Patients With a Failing Mitral Bioprosthetic Valve	53	Aug 2031

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.
[b] Primary results have been published, long-term follow-up ongoing.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	33418, 33419, 0345T, 0483T, 0484T, 0544T
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
02/01/2025	Document updated with literature review. The following changes were made to Coverage: 1) Removed “Transcatheter mitral valve implantation/ replacement is considered experimental, investigational and/or unproven for all indications.” 2) Added Transcatheter Mitral Valve-in-Valve Replacement criteria. References 16, 20-25, 32, 47, 54, 59, 65, 70-91, 95, 97-98 added.
01/01/2024	Reviewed. No changes.
09/15/2022	Document updated with literature review. Coverage unchanged. The following references were added: 15, 55-60, 65, and 67.
01/01/2022	Document updated with literature review. Coverage unchanged. The following references were added: 5, 32, 40, 43, 45, and 54.
10/15/2020	Reviewed. No changes.
12/15/2019	Document updated with literature review. The following changes were made to Coverage: 1) Added statement considering transcatheter mitral valve repair with an FDA-approved device as medically necessary for patients with heart failure and secondary mitral regurgitation despite the use of maximally tolerated guideline-directed medical therapy; 2) Added NOTEs 2 and 3. Added the following references: 6, 8-11, 21, 23, 25, 27, 30-31, 40-46, 53-55.
01/15/2019	Reviewed. No changes.
01/01/2018	Document updated with literature review. The following change(s) were made to Coverage: 1) Added experimental, investigational and/or unproven statement for transcatheter mitral valve implantation/replacement (TMVI) for all indications; and 2) Added NOTE 2 to refer to medical policy SUR707.028 for Transcatheter Aortic Valve Implantation for Aortic Stenosis. Document title changed from “Transcatheter Mitral Valve Repair”.
10/15/2017	Reviewed. No changes.
02/15/2016	Document updated with literature review. Coverage changed to: 1) Transcatheter mitral valve repair with a device cleared by the U.S. Food and Drug Administration (FDA) for use in mitral valve repair may be considered medically necessary for patients with symptomatic, degenerative mitral regurgitation who are considered at prohibitive risk (see NOTE 1 below) for open surgery. 2) Transcatheter mitral valve repair is considered experimental, investigational and/or unproven in all other situations.3) added NOTE 1: Prohibitive risk for open surgery may be determined based on the presence of a Society for Thoracic Surgeons predicted mortality risk of 12% or greater; and/or the presence of a logistic EuroSCORE of 20% or greater. 4) Transcatheter mitral valve repair using percutaneous annuloplasty is considered experimental, investigational, and/or unproven for the treatment of mitral valve regurgitation (insufficiency).
09/15/2014	Document updated with literature review. Coverage unchanged. Document title changed from “Percutaneous Endovascular Mitral Valve Repair” to “Transcatheter Mitral Valve Repair.”
04/01/2013	Document updated with literature review. Coverage unchanged.

05/15/2011	Document updated with literature review. Coverage unchanged.
11/01/2009	Updated document with literature search. References added. No change to Coverage statement.
07/01/2007	Revised/Updated Entire Document.
01/01/2005	New Medical Document. Percutaneous endovascular mitral valve repair using leaflet clips and/or annuloplasty is considered experimental, investigational and unproven for treatment of mitral valve regurgitation (insufficiency).