



FEP Medical Policy Manual

FEP 2.02.30 Transcatheter Mitral Valve Repair

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Related Policies:

7.01.132 - Transcatheter Aortic-Valve Implantation for Aortic Stenosis

Transcatheter Mitral Valve Repair

Description

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

Mitral regurgitation (MR) is the second most common valvular heart disease, occurring in 7% of people older than age 75 years and accounting for 24% of all patients with valvular heart disease.^{1,2} MR with accompanying valvular incompetence leads to left ventricular (LV) volume overload with secondary ventricular remodeling, myocardial dysfunction, and left heart failure. Clinical signs and symptoms of dyspnea and orthopnea may also be present in patients with valvular dysfunction.³ MR severity is classified as mild, moderate, or severe disease on the basis of echocardiographic and/or angiographic findings (1+, 2+, and 3+ to 4+ angiographic grade, respectively).

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

OBJECTIVE

The objective of this evidence review is to determine whether transcatheter mitral valve repair improves the net health outcome in patients with primary (degenerative) or secondary (functional) mitral regurgitation.

POLICY STATEMENT

Transcatheter mitral valve repair (TMVR) with a device approved by the U.S. Food and Drug Administration (FDA) for use in mitral valve repair may be considered **medically necessary** for individuals with symptomatic, primary mitral regurgitation (MR) who are considered at prohibitive risk for open surgery (see Policy Guidelines section).

TMVR with a device approved by the U.S. FDA may be considered **medically necessary** for individuals with heart failure and moderate-to-severe or severe symptomatic secondary MR despite the use of maximally tolerated guideline-directed medical therapy (see Policy Guidelines section).

TMVR is considered **investigational** in all other situations.

POLICY GUIDELINES

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

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

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

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

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

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

Surgical Management

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

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

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

Transcatheter Mitral Valve Repair

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

Direct Leaflet Approximation

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

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

Other Mitral Valve Repair Devices

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

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

Transcatheter Mitral Valve Replacement

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

Medical Management

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

Regulatory Status

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

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

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

FDA product code for MitraClip and PASCAL: NKM.

RATIONALE

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 study, and the CLASP IID/IIF study. Studies evaluating MitraClip have demonstrated that MitraClip implantation is feasible with a procedural success rate greater than 90%, 30-day mortality ranging from 2.3% to 6.4% (less than predicted Society of Thoracic Surgeons [STS] mortality risk score for MR repair or replacement; range, 9.5% to 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 ySF-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, an 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 a 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. 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 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.

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

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

American College of Cardiology and American Heart Association

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

Also in 2020, the American College of Cardiology and American Heart Association released updated guidelines on the management of valvular heart disease.⁵ The guidelines state that TMVR is of benefit to patients with severely symptomatic primary MR who are at high or prohibitive risk for surgery, and to a subset of patients with secondary MR who remain severely symptomatic despite guideline-directed management and therapy for heart failure. Relevant recommendations on interventions for primary and secondary MR are shown in Table 1.

Table 1. Recommendations on Interventions for Primary and Secondary Mitral Regurgitation

Recommendation	COR	LOE
Primary MR		
In symptomatic patients with severe primary MR (Stage D), mitral valve intervention is recommended irrespective of LV systolic function	1 (Strong)	B-NR ¹
In asymptomatic patients with severe primary MR and LV systolic dysfunction (LVEF <60%, LVESD >40 mm) (Stage C2), mitral valve surgery is recommended	1 (Strong)	B-NR ¹
In patients with severe primary MR for whom surgery is indicated, mitral valve repair is recommended in preference to mitral valve replacement when the anatomic cause of MR is a degenerative disease, if a successful and durable repair is possible	1 (Strong)	B-NR ¹
In asymptomatic patients with severe primary MR and normal LV systolic function (LVEF >60% and LVESD >40 mm) (Stage C1), mitral valve repair is reasonable when the likelihood of a successful and durable repair without residual MR is >95% 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

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

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

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

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

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

National Institute for Health and Care Excellence

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

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

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

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

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

- "1. The procedure is furnished with a [TMVR] system that has received FDA [Food and Drug Administration] premarket approval (PMDA).
2. The patient (preoperatively and postoperatively) is under the care of a heart team...
3. Each patient's suitability for surgical mitral valve repair, [TMVR], or palliative therapy must be evaluated, documented...
4. An interventional cardiologist or cardiac surgeon from the heart team must perform the mitral valve [TMVR]...
5. Mitral valve [TMVR] must be furnished in a hospital with appropriate infrastructure and experience...
6. The heart team and hospital are participating in a prospective, national, audited registry...
7. The registry shall collect all data necessary and have a written executable analysis plan..."

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2015	New policy	Transcatheter mitral valve repair considered medically necessary for degenerative mitral regurgitation in patients at prohibitive surgical risk.
September 2016	Replace policy	Policy updated with literature review through March 30, 2016; references 25, 29, 31, 37, and 41 added. Policy statements unchanged.
September 2018	Replace policy	Policy updated with literature review through March 5, 2018; references 27-29, 34-36, and 53 added. "Cleared, changed to "approved, in the medically necessary policy statement. In the policy degenerative mitral regurgitation was replaced with primary mitral regurgitation and functional mitral regurgitation was replaced with secondary mitral regurgitation including the policy statement to be in consistent with language used in the guidelines. Data from FDA documents were added.
September 2019	Replace policy	Policy updated with literature review through March 6, 2019, references 50-51 added. Regulatory status section updated with new indication. Policy statement added; transcatheter mitral valve repair with an FDA-approved device considered medically necessary for patients with heart failure and secondary mitral regurgitation despite the use of maximally tolerated guideline-directed medical therapy. Information regarding optimal medical therapy added to the Policy Guidelines section.
September 2020	Replace policy	Policy updated with literature review through March 23, 2020; references added. Policy statements unchanged.
September 2021	Replace policy	Policy updated with literature review through March 30, 2021; references added; guidelines section updated. Policy statements unchanged.
September 2022	Replace policy	Policy updated with literature review through March 16, 2022; references added to review of evidence for 'Other Transcatheter Mitral Valve Repair Devices'; guidelines section updated. Minor editorial refinements to policy statements; intent unchanged.
September 2023	Replace policy	Policy updated with literature review through March 13, 2023; references added. Relevant PICOs updated to reflect FDA regulatory actions. Policy statements unchanged.

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