

# Protocol

## Transcatheter Mitral Valve Repair

(20230)

<b>Medical Benefit</b>		<b>Effective Date:</b> 04/01/20	<b>Next Review Date:</b> 01/21
<b>Preauthorization</b>	No	<b>Review Dates:</b> 01/16, 01/17, 01/18, 01/19, 01/20	

### **Preauthorization is not required.**

*The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.*

Populations	Interventions	Comparators	Outcomes
Individuals: • With symptomatic primary or secondary mitral regurgitation and are at prohibitive risk for open surgery	Interventions of interest are: • Transcatheter mitral valve repair using MitraClip	Comparators of interest are: • Medical management	Relevant outcomes include: • Overall survival • Morbid events • Functional outcomes • Treatment-related morbidity
Individuals: • With heart failure and moderate-to-severe or severe symptomatic secondary mitral regurgitation despite the use of maximally tolerated guideline-directed medical therapy	Interventions of interest are: • Transcatheter mitral valve repair using MitraClip	Comparators of interest are: • Medical management	Relevant outcomes include: • Overall survival • Morbid events • Functional outcomes • Treatment-related morbidity
Individuals: • With symptomatic primary or secondary mitral regurgitation and are surgical candidates	Interventions of interest are: • Transcatheter mitral valve repair using MitraClip	Comparators of interest are: • Open mitral valve repair • Open mitral valve replacement	Relevant outcomes include: • Overall survival • Morbid events • Functional outcomes • Treatment-related morbidity
Individuals: • With symptomatic primary or secondary mitral regurgitation	Interventions of interest are: • Transcatheter mitral valve repair using devices other than MitraClip	Comparators of interest are: • Open mitral valve repair • Open mitral valve replacement	Relevant outcomes include: • Overall survival • Morbid events • Functional outcomes • Treatment-related morbidity

### **DESCRIPTION**

Transcatheter mitral valve repair (TMVR) is an alternative to surgical therapy for mitral regurgitation (MR). MR is a common valvular heart disease that can result from a primary structural abnormality of the mitral valve (MV) complex or a secondary dilatation of an anatomically normal MV due to a dilated left ventricle caused by ischemic or dilated cardiomyopathy. Surgical therapy may be underutilized, particularly in patients with multiple comorbidities, suggesting that there is an unmet need for less invasive procedures for MV repair. One device,

MitraClip, has approval from the U.S. Food and Drug Administration for the treatment of severe symptomatic MR due to a primary abnormality of the MV (primary MR) in patients considered at prohibitive risk for surgery and for patients with heart failure and moderate-to-severe or severe symptomatic secondary MR despite the use of maximally tolerated guideline-directed medical therapy.

## SUMMARY OF EVIDENCE

For individuals who have symptomatic primary MR and at prohibitive risk for open surgery who receive TMVR using MitraClip, the evidence includes a 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 and Transcatheter Valve Therapy Registry studies. These studies have demonstrated that MitraClip implantation is feasible with a procedural success rate greater than 90%, 30-day mortality ranging from 2.3% to 6.4% (less than predicted Society of Thoracic Surgeons 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 36-Item Short-Form Health Survey scores). At one year, freedom from death and MR more than 2+ was achieved in 61% of patients but the one year mortality or heart failure hospitalization rates remain considerably high (38%). Conclusions related to the treatment effect on mortality based on historical controls cannot be made because the control groups did not provide unbiased or precise estimates of the natural history of patients eligible to receive MitraClip. Given that primary MR is a mechanical problem and there is no effective medical therapy, a randomized controlled trial (RCT) comparing MitraClip with medical management is not feasible or ethical. The 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 evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have heart failure and symptomatic secondary MR despite the use of maximally tolerated guideline-directed medical therapy who receive TMVR using MitraClip, the evidence includes two RCTs as well as 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 a longer duration and patients selected for nonresponse to maximally tolerated therapy, found a significant benefit for MitraClip after two years compared to medical therapy alone. The evidence is sufficient to determine that the technology results in a meaningful 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 and an RCT. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. The RCT found that MitraClip did not reduce MR as often or as completely as the surgical control, although it could be safely implanted and was associated with fewer adverse events at one year. Long-term follow-up from the RCT showed that significantly more MitraClip patients required surgery for MV dysfunction than conventional surgery patients. For these reasons, this single trial is not definitive in demonstrating improved clinical outcomes with MitraClip compared with surgery. Additional RCTs are needed to corroborate these results. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals who have symptomatic primary or secondary MR who receive TMVR using devices other than MitraClip, the evidence includes primarily noncomparative feasibility studies. Relevant outcomes are OS, morbid events, functional outcomes, and treatment-related morbidity. The body of evidence consists only of very small case series and case reports. Controlled studies, preferably RCTs, are needed to draw conclusions about the net health benefit. The evidence is insufficient to determine the effects of the technology on health outcomes.

Clinical input obtained in 2015 supported the use of TMVR in patients with primary MR considered at a prohibitive risk for open surgery, which is a U.S. Food and Drug Administration-approved indication for the MitraClip device. Given the lack of other treatment options for this population, the suggestive clinical evidence, and supportive clinical input, TMVR with the MitraClip may be considered medically necessary for this patient population.

## POLICY

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

Transcatheter mitral valve repair with a device approved by the U.S. Food and Drug Administration may be considered **medically necessary** for patients with heart failure and moderate-to-severe or severe symptomatic secondary mitral regurgitation despite the use of maximally tolerated guideline-directed medical therapy (see Policy Guidelines section).

Transcatheter mitral valve repair 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 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).

## MEDICARE ADVANTAGE

For Medicare Advantage TMVR for MR is considered **medically necessary** under Coverage with Evidence Development (CED), with the following conditions (not an inclusive list):

Treatment of significant symptomatic degenerative MR when furnished according to an FDA-approved indication and when all of the following conditions are met:

1. The procedure is furnished with a complete TMVR system that has received FDA premarket approval (PMA) for that system’s FDA-approved indication.

2. Both a cardiothoracic surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease have independently examined the patient face-to-face and evaluated the patient's suitability for mitral valve surgery and determination of prohibitive risk; and both surgeons have documented the rationale for their clinical judgment and the rationale is available to the heart team.
3. The patient (pre-operatively and post-operatively) is under the care of a heart team: a cohesive, multidisciplinary, team of medical professionals. The heart team concept embodies collaboration and dedication across medical specialties to offer optimal patient-centered care.

TMVR is considered **not medically necessary** for the treatment of MR when not furnished under CED according to the above-noted criteria.

TMVR used for the treatment of any non-MR indications are considered **not medically necessary**.

TMVR may be eligible for uses that are not expressly listed as an FDA-approved indication when performed within an eligible clinical trial.

## BACKGROUND

### MITRAL REGURGITATION

#### Epidemiology and Classification

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.<sup>1,2</sup> 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.<sup>3</sup> MR severity is classified as mild, moderate, or severe disease on the basis of echocardiographic and/or angiographic findings (1+, 2+, and 3-4+ angiographic grade, respectively).

Patients with MR generally fall into two categories  $\frac{3}{4}$  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).<sup>4</sup> 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.<sup>3</sup> 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

##### *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), b-blocker and mineralocorticoid receptor antagonist, and diuretic therapy as needed to treat volume overload.<sup>4,3</sup> Resynchronization therapy may provide symptomatic relief, improve LV function, and in some patients, lessen the severity of MR.

##### *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, which are outlined in Table 1.<sup>4</sup>

Table 1. Guidelines on Mitral Value Surgery

Recommendation	COR	LOE
MV surgery is recommended for the symptomatic patient with acute severe MR.	I	B
MV surgery is beneficial for patients with chronic severe MR and NYHA functional class II, III, or IV symptoms in the absence of severe LV dysfunction (severe LV dysfunction is defined as ejection fraction less than 0.30) and/or end-systolic dimension greater than 55 mm.	I	B
MV surgery is beneficial for asymptomatic patients with chronic severe MR and mild-to-moderate LV dysfunction, ejection fraction 0.30 to 0.60, and/or end systolic dimension greater than or equal to 40 mm.	I	B
MV repair is recommended over MV replacement in the majority of patients with severe chronic MR who require surgery, and patients should be referred to surgical centers experienced in MV repair.	I	C
MV repair is also reasonable for asymptomatic patients with chronic severe MR with preserved LV function ... in whom the high likelihood of successful MV repair without residual MR is greater than 90%.	Ila	B
MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and new onset of atrial fibrillation.	Ila	C
MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and pulmonary hypertension.	Ila	C
MV surgery is reasonable for patients with chronic severe MR due to a primary abnormality of the mitral apparatus and NYHA functional class III-IV symptoms and severe LV dysfunction ... in whom MV repair is highly likely	Ila	C

COR: class of recommendation; LOE: level of evidence; LV: left ventricular; MR: mitral regurgitation; MV: mitral valve; NYHA: New York Heart Association.

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 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.<sup>5</sup>

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<sup>6,7</sup> 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.<sup>8-11</sup>

#### 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.<sup>1,12</sup> Approaches to MV repair include direct leaflet repair,<sup>13</sup> repair of the mitral annulus via direct annuloplasty, or indirect repair based on the annulus's proximity to the coronary sinus. There are also devices in development to counteract ventricular remodeling, and systems designed for complete MV replacement via catheter.

#### *Direct Leaflet Approximation*

One device that undertakes direct leaflet repair, the MitraClip Clip Delivery System (Abbott Vascular), has been approved through the premarket approval process by the U.S. Food and Drug Administration (FDA) for use in certain patients with symptomatic primary MR (see Regulatory Status section). Of the transcatheter MV repair devices under investigation, MitraClip has the largest body of evidence evaluating its use; it has been in use in Europe since 2008.<sup>13</sup> 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 transeptal puncture used to access the left side of the heart and the MV. Placement of MitraClip leads to coapting of the mitral leaflets, thus creating a double-orifice valve.

#### *Other MV Repair Devices*

Devices for transcatheter MV repair that use different approaches are in development. Techniques to repair the mitral annulus include those that target the annulus itself (direct annuloplasty) and those that tighten the mitral annulus via manipulation of the adjacent coronary sinus (indirect annuloplasty). Indirect annuloplasty devices include the Carillon® Mitral Contour System (Cardiac Dimension) and the Monarc™ device (Edwards Lifesciences). The CE-marked Carillon Mitral Contour System is comprised of self-expanding proximal and distal anchors connected with a nitinol bridge, with the proximal end coronary sinus ostium and the distal anchor in the great cardiac vein. The size of the connection is controlled by manual pullback on the catheter (CE-marked). 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.<sup>14</sup> The Monarc system also involves two 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 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.<sup>15</sup>

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 enCorSQ™ Mitral Valve Repair System, and the Cardioband™ Annuloplasty System (Valtech Cardio), an implantable annuloplasty band with a transfemoral venous delivery system.

#### *Transcatheter MV Replacement*

PermaValve™ (MicroInterventional 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 MV replacement device. These replacement valves are outside the scope of this evidence review.

## **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 ≥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.”<sup>16</sup> FDA product code: NKM.

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.”

## RELATED PROTOCOLS

Transcatheter Aortic Valve Implantation for Aortic Stenosis

Transcatheter Pulmonary Valve Implantation

---

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

## REFERENCES

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Chiam PT, Ruiz CE. Percutaneous transcatheter mitral valve repair: a classification of the technology. *JACC Cardiovasc Interv.* Jan 2011;4(1):1-13. PMID 21251623.
2. Fedak PW, McCarthy PM, Bonow RO. Evolving concepts and technologies in mitral valve repair. *Circulation.* Feb 19 2008;117(7):963-974. PMID 18285577.
3. Carabello BA. The current therapy for mitral regurgitation. *J Am Coll Cardiol.* Jul 29 2008;52(5):319-326. PMID 18652937.
4. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* Sep 23 2008;52(13):e1-142. PMID 18848134.
5. Goel SS, Bajaj N, Aggarwal B, et al. Prevalence and outcomes of unoperated patients with severe symptomatic mitral regurgitation and heart failure: comprehensive analysis to determine the potential role of MitraClip for this unmet need. *J Am Coll Cardiol.* Jan 21 2014;63(2):185-186. PMID 24036029.
6. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol.* Jul 11 2017; 70(2):252-289. PMID 28315732.
7. Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology, European Association for Cardio-Thoracic Surgery, Vahanian A, et al. Guidelines on the management of valvular heart disease (version 2012). *Eur Heart J.* Oct 2012;33(19):2451-2496. PMID 22922415.
8. Diodato MD, Moon MR, Pasque MK, et al. Repair of ischemic mitral regurgitation does not increase mortality or improve long-term survival in patients undergoing coronary artery revascularization: a propensity analysis. *Ann Thorac Surg.* Sep 2004;78(3):794-799; discussion 794-799. PMID 15336993.
9. Wong DR, Agnihotri AK, Hung JW, et al. Long-term survival after surgical revascularization for moderate ischemic mitral regurgitation. *Ann Thorac Surg.* Aug 2005;80(2):570-577. PMID 16039207.

10. Mihaljevic T, Lam BK, Rajeswaran J, et al. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. *J Am Coll Cardiol*. Jun 5 2007;49(22):2191-2201. PMID 17543639.
11. Smith PK, Puskas JD, Ascheim DD, et al. Surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med*. Dec 4 2014;371(23):2178-2188. PMID 25405390.
12. Young A, Feldman T. Percutaneous mitral valve repair. *Curr Cardiol Rep*. Jan 2014;16(1):443. PMID 24281977.
13. Minha S, Torguson R, Waksman R. Overview of the 2013 Food and Drug Administration Circulatory System Devices Panel meeting on the MitraClip Delivery System. *Circulation*. Aug 20 2013;128(8):864-868. PMID 23960257.
14. Siminiak T, Wu JC, Haude M, et al. Treatment of functional mitral regurgitation by percutaneous annuloplasty: results of the TITAN Trial. *Eur J Heart Fail*. Aug 2012;14(8):931-938. PMID 22613584.
15. Harnek J, Webb JG, Kuck KH, et al. Transcatheter implantation of the MONARC coronary sinus device for mitral regurgitation: 1-year results from the EVOLUTION phase I study (Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for the Treatment of Mitral Regurgitation). *JACC Cardiovasc Interv*. Jan 2011;4(1):115-122. PMID 21251638.
16. Food and Drug Administration. Summary of Safety and Effectiveness Data (SSED): Mitral Valve Repair Device. 2013; [https://www.accessdata.fda.gov/cdrh\\_docs/pdf10/P100009b.pdf](https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100009b.pdf). Accessed April 19, 2018.
17. Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). Percutaneous mitral valve repair. TEC Assessments 2014;Volume 29:Tab 4. PMID.
18. Reichenspurner H, Schillinger W, Baldus S, et al. Clinical outcomes through 12 months in patients with degenerative mitral regurgitation treated with the MitraClip(R) device in the ACCESS-Europe Phase I trial. *Eur J Cardiothorac Surg*. Oct 2013;44(4):e280-288. PMID 23864216.
19. Lim S, Kar S, Fail P, et al. The EVEREST II high surgical risk cohort: effectiveness of transcatheter reduction of significant mitral regurgitation in high surgical risk patients. *J Am Coll Cardiol*. 2013;61(10 Suppl):E1958. PMID.
20. Lim DS, Reynolds MR, Feldman T, et al. Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation after transcatheter mitral valve repair. *J Am Coll Cardiol*. Jul 15 2014;64(2):182-192. PMID 24184254.
21. Ware J, Kosinski M, Bjorner JB, et al. User's Manual for the SF-36v2 Health Survey (2nd Ed). Lincoln, RI: QualityMetric; 2007.
22. Sorajja P, Mack M, Vemulapalli S, et al. Initial experience with commercial transcatheter mitral valve repair in the United States. *J Am Coll Cardiol*. Mar 15 2016;67(10):1129-1140. PMID 26965532.
23. Sorajja P, Vemulapalli S, Feldman T, et al. Outcomes With transcatheter mitral valve repair in the United States: An STS/ACC TVT Registry Report. *J Am Coll Cardiol*. Nov 7 2017;70(19):2315-2327. PMID 29096801.
24. Glower DD, Kar S, Trento A, et al. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. *J Am Coll Cardiol*. Jul 15 2014;64(2):172-181. PMID 25011722.
25. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. *J Am Coll Cardiol*. Aug 18 2009;54(8):686-694. PMID 19679246.
26. Chan PH, She HL, Alegria-Barrero E, et al. Real-world experience of MitraClip for treatment of severe mitral regurgitation. *Circ J*. Jul 2012;76(10):2488-2493. PMID 22785461.
27. Whitlow PL, Feldman T, Pedersen WR, et al. Acute and 12-month results with catheter-based mitral valve leaflet repair: the EVEREST II (Endovascular Valve Edge-to-Edge Repair) High Risk Study. *J Am Coll Cardiol*. Jan 10 2012;59(2):130-139. PMID 2222076.
28. Wan B, Rahnnavardi M, Tian DH, et al. A meta-analysis of MitraClip system versus surgery for treatment of severe mitral regurgitation. *Ann Cardiothorac Surg*. Nov 2013;2(6):683-692. PMID 24349969.
29. Bail DH, Doebler K. The MitraClip System: a systematic review of indications, procedural requirements, and guidelines. *Thorac Cardiovasc Surg*. Feb 2014;62(1):18-25. PMID 24297637.



30. Estvez-Loureiro R, Franzen O, Winter R, et al. Echocardiographic and clinical outcomes of central versus noncentral percutaneous edge-to-edge repair of degenerative mitral regurgitation. *J Am Coll Cardiol*. Dec 24 2013;62(25):2370-2377. PMID 24013059.
31. Grasso C, Ohno Y, Attizzani GF, et al. Percutaneous mitral valve repair with the MitraClip system for severe mitral regurgitation in patients with surgical mitral valve repair failure. *J Am Coll Cardiol*. Mar 4 2014;63(8):836-838. PMID 24161329.
32. Munkholm-Larsen S, Wan B, Tian DH, et al. A systematic review on the safety and efficacy of percutaneous edge-to-edge mitral valve repair with the MitraClip system for high surgical risk candidates. *Heart*. Mar 2014;100(6):473-478. PMID 23813844.
33. Swaans MJ, Bakker AL, Alipour A, et al. Survival of transcatheter mitral valve repair compared with surgical and conservative treatment in high-surgical-risk patients. *JACC Cardiovasc Interv*. Aug 2014;7(8):875-881. PMID 25147032.
34. Philip F, Athappan G, Tuzcu EM, et al. MitraClip for severe symptomatic mitral regurgitation in patients at high surgical risk: a comprehensive systematic review. *Catheter Cardiovasc Interv*. Oct 1 2014;84(4):581-590. PMID 24905665.
35. Vakil K, Roukoz H, Sarraf M, et al. Safety and efficacy of the MitraClip(R) system for severe mitral regurgitation: a systematic review. *Catheter Cardiovasc Interv*. Jul 1 2014;84(1):129-136. PMID 24323764.
36. Bail DH. (Meta)-analysis of safety and efficacy following edge-to-edge mitral valve repair using the MitraClip system. *J Interv Cardiol*. Feb 2015;28(1):69-75. PMID 25689550.
37. Velazquez EJ, Samad Z, Al-Khalidi HR, et al. The MitraClip and survival in patients with mitral regurgitation at high risk for surgery: A propensity-matched comparison. *Am Heart J*. Nov 2015;170(5):1050-1059 e1053. PMID 26542516.
38. Hayashida K, Yasuda S, Matsumoto T, et al. AVJ-514 Trial-baseline characteristics and 30-day outcomes following MitraClip((R)) Treatment in a Japanese cohort. *Circ J*. Jul 25 2017;81(8):1116-1122. PMID 28321004.
39. Obadia, JJ, Messika-Zeitoun, DD, Leurent, GG, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. *N. Engl. J. Med.*, 2018 Aug 28;379(24). PMID 30145927.
40. Atianzar, KK, Zhang, MM, Newhart, ZZ, Gafoor, SS. Why Did COAPT Win While MITRA-FR Failed? Defining the Appropriate Patient Population for MitraClip. *Interv Cardiol*, 2019 Mar 13;14(1). PMID 30858892.
41. Nishimura, RR, Bonow, RR. Percutaneous Repair of Secondary Mitral Regurgitation - A Tale of Two Trials. *N. Engl. J. Med.*, 2018 Dec 24;379(24). PMID 30575469.
42. Yancy, CC, Jessup, MM, Bozkurt, BB, Butler, JJ, Casey, DD, Colvin, MM, Drazner, MM, Filippatos, GG, Fonarow, GG, Givertz, MM, Hollenberg, SS, Lindenfeld, JJ, Masoudi, FF, McBride, PP, Peterson, PP, Stevenson, LL, Westlake, CC. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J. Card. Fail.*, 2017 May 4;23(8). PMID 28461259.
43. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J*. Sep 21 2017;38(36):2739-2791. PMID 28886619.
44. Takagi H, Ando T, Umemoto T. A review of comparative studies of MitraClip versus surgical repair for mitral regurgitation. *Int J Cardiol*. Feb 01 2017;228:289-294. PMID 27865200.
45. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med*. Apr 14 2011;364(15):1395-1406. PMID 21463154.
46. Mauri L, Garg P, Massaro JM, et al. The EVEREST II Trial: design and rationale for a randomized study of the evalve mitraclip system compared with mitral valve surgery for mitral regurgitation. *Am Heart J*. Jul 2010; 160(1):23-29. PMID 20598968.
47. Mauri L, Foster E, Glower DD, et al. 4-year results of a randomized controlled trial of percutaneous repair versus surgery for mitral regurgitation. *J Am Coll Cardiol*. Jul 23 2013;62(4):317-328. PMID 23665364.

48. Feldman T, Kar S, Elmariah S, et al. Randomized comparison of percutaneous repair and surgery for mitral regurgitation: 5-year results of EVEREST II. *J Am Coll Cardiol*. Dec 29 2015;66(25):2844-2854. PMID 26718672.
49. Schofer J, Siminiak T, Haude M, et al. Percutaneous mitral annuloplasty for functional mitral regurgitation: results of the CARILLON Mitral Annuloplasty Device European Union Study. *Circulation*. Jul 28 2009;120(4):326-333. PMID 19597051.
50. O’Gara PT, Calhoon JH, Moon MR, et al. Transcatheter therapies for mitral regurgitation: a professional society overview from the American College of Cardiology, The American Association for Thoracic Surgery, Society for Cardiovascular Angiography and Interventions Foundation, and The Society of Thoracic Surgeons. *J Thorac Cardiovasc Surg*. Mar 2014;147(3):837-849. PMID 24529172.
51. Centers for Medicare & Medicaid Services. National Coverage Determination (NCD) for Transcatheter MITRAL Valve Repair (TMVR) (20.33). 2015; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=363&ncdver=1&CoverageSelection=National&KeyWord=mitral&KeyWordLookUp=Title&KeyWordSearchType=And&bc=gAAAABAAAAAAAAAA%3d%3d&>. Accessed March 25, 2019.