Mitral Valve Interventions Literature Summary

Appendix to Boston Scientific comment to CMS on July 30, 2020 (prepared Dec. 2019)

Boston Scientific advocates for a future coverage policy that focuses on transcatheter options for mitral regurgitation, singularly accommodating a variety of technologies to address mitral valve function. We support a single coverage policy that accommodates a range of technologies to address mitral valve function, regardless of which valvular structure (annulus, chordae, leaflet) is treated. This approach will provide CMS with flexibility in extending coverage to new therapies, when safety and effectiveness have been established, and facilitate appropriate access to treatment for patients with mitral regurgitation.

This literature review provides the background and rationale for supporting our recommendation for future expansion of the scope of this NCD and supports the expansion of coverage within the policy to include functional mitral regurgitation (FMR), in addition to currently covered, degenerative mitral regurgitation (DMR).

Background on Mitral Regurgitation

Mitral valve disease is the most common of the valvular heart disorders and shows increasing frequency and prevalence in an aging population. In the US, moderate or severe mitral regurgitation affects approximately 1.7% of the US population, with the prevalence increasing from 0.5% in 18- to 44-year-olds to 9.3% in those ≥75 years old.[1] Severe symptomatic MR can develop gradually over time and has an annual mortality rate in excess of 5%.[2]

Mitral regurgitation (MR) has a strong impact on patients' morbidity and mortality, yet very few receive adequate therapy. In fact, it is estimated that only 2% of the affected patients receive surgery.[3] If left untreated, MR produces chronic left ventricular (LV) volume overload and leads to LV remodeling, dilatation and dysfunction.[3] Patients often experience pulmonary hypertension, heart failure, and have a high mortality and morbidity burden.[3-5] A Cleveland Clinic study of 5,737 patients with severe MR who did not undergo surgery showed overall 1-year and 5-year mortality rates of 20% and 50%, respectively.[6] In these unoperated patients, the proportion of surviving patients hospitalized for heart failure reached 90% by 5 years.[6] Hence, both disease prevalence and treatment patterns showcase the high unmet clinical need for mitral regurgitation.

Mitral regurgitation is a complex disease that mirrors the complexity of the underlying valve. It can manifest as acute or chronic; range from mild to severe; and present as asymptomatic or symptomatic. However, most MR is broadly classified into two main types:[5,7]

1. Primary (organic), an underlying structural or degenerative abnormality of the mitral valve apparatus. Includes mitral valve prolapse or leaflet flail. May be rheumatic in origin. **DMR (degenerative mitral regurgitation)**

2. Secondary (functional), caused by remodeling of the left ventricle, and/or severe dilation of the left atrium. Includes dilated LV with tethering of one or both leaflets. May be ischemic in origin. **FMR (functional mitral regurgitation)**

Primary or degenerative MR (DMR)

Most primary MR patients remain asymptomatic for years due to progressive underlying ventricular dilation that compensates for mitral dysfunction. Symptoms arise due to decompensation as a result of hemodynamic overload in the left ventricle.[4,5] Because early interventions may result in excellent long-term outcomes in primary MR, it is critical to recognize, diagnose, and provide appropriate intervention at the right time in patients suspected of having MR.[4,5]

Treatment options for DMR include surgical repair of the valve components or replacement of the entire valve. There is no effective medical therapy and although heart failure medications may palliate symptoms, they are not a substitute for or a reason to delay surgery.[8] Mitral valve surgery is seen as the standard of care for severe DMR patients.[9]

In a single center retrospective observational study to determine the incidence and treatment patterns for patients with severe MR, less than 50% of patients with DMR received surgical intervention.[10] The most common reason for lack of intervention was that MR was not addressed by the treating physician, despite 59% of patients having at least one indication for surgical intervention.[10] In addition, nearly 30% of patients did not meet criteria for surgery, were considered high surgical risk, or refused surgery. Thus, for DMR patients there is a need for additional types of mitral valve (MV) intervention.

Mitral valve repair is usually the treatment of choice over valve replacement due to inherent complications associated with artificial prosthetic valves and increased risk of operative mortality.[5,10] A significant advantage of mitral valve repair is the potential for early intervention that can provide a major impact on the natural progression of the disease.

Moreover, surgical mitral valve repair is highly effective and associated with relatively low rates of early and long-term complications.[11] In the STS risk model for valvular surgery, patients with valve replacements were over three times more likely to die within 30 days of surgery (5.7% to 1.6%), and more than twice as likely to experience at least one major morbidity or morality event (26.7% to 12.7%) compared to mitral valve repair procedures.[12] Moreover, patients selected for valve repair have better survival rates than patients receiving replacement valves.[13,14]

Recently, a large multicenter registry of patients with degenerative MR, was analyzed for long-term outcomes after MV repair or replacement.[14] The authors identified 1922 patients with degenerative flail leaflet who had undergone MV repair or replacement in order to compare treatment outcomes. In both the entire population and the propensity-score matched cohorts, operative mortality was lower and 20-year survival was better for MV repair than MV

replacement. The authors also reported that MV repair was associated with reduced incidence of valve-related complications and reoperations. The authors note that while the 35-year timeframe of the registry enabled analysis of long-term outcomes, surgical techniques and MR severity criteria have changed over the years.[14]

The guidelines for management of patients with valvular disease by AHA/ACC American Heart Association/American College of Cardiology Clinical Practice Taskforce have consistently recommended surgical correction for patients with primary MR.[9,15] Below is a table of the Class I recommendations for DMR patients:

TABLE 1: Class I interventional recommendations for chronic primary MR

based on AHA/ACC Clinical Practice Taskforce Guidelines[9]

Intervention	Patients & Conditions	Yr Recommended
Mitral Valve Surgery	Symptomatic with chronic severe primary MR (stage D) and LVEF> 30%	2014; 2017
Mitral Valve Surgery	Asymptomatic with chronic severe primary MR and LV dysfunction	2014; 2017
Mitral Valve Repair	Over replacement when surgical treatment is indicated for chronic severe primary MR limited to posterior leaflet	2014; 2017
Mitral Valve Repair	Over replacement when surgical treatment is indicated for chronic severe primary MR involving anterior leaflet or both leaflets and successful durable repair can be accomplished	2014; 2017
Mitral Valve Repair or Replacement	Concomitant with cardiac surgery for other indications in patients with chronic severe primary MR	2014; 2017

Thus, surgical valve repair is the standard of care for managing DMR patients. However, not all patients receive surgery[10], nor are all patients candidates for surgery due to advanced age or comorbidities. Moreover, with no medical therapy options indicated for the treatment of DMR[5], patients who are not surgical candidates have no available options for averting disease progression.

Less invasive catheter-based approaches, such as MitraClip, have been developed with the aim to fulfill this unmet need. Currently, MitraClip (Abbott) is an edge-to-edge device for percutaneous repair of the mitral valve. In this procedure, the anterior and posterior mitral leaflets are clipped together to create a double orifice valve that reduces regurgitation.[16] In the guidelines for management of patients with valvular disease by AHA/ACC Clinical Practice Taskforce, transcatheter mitral valve repair is a class IIb recommendation[9]: "may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe primary MR (stage D) …with prohibitive surgical risk because of comorbidities and remain severely symptomatic despite optimal guideline directed medical therapy for heart failure."

While MitraClip provides an alternative to surgery for certain DMR patients, the technology has limitations- showing limited efficacy and a singular approach to addressing complex anatomy of the mitral valve. The concept for MitraClip is based on an edge-to-edge leaflet repair, a simple

surgical technique that reduces MR by essentially reducing the orifice size of the valve and fixating the prolapsed valve segment to an opposing non-prolapsing segment.[16] This anatomy-disrupting surgical technique, pioneered by Alfieri, was typically performed in combination with mitral annuloplasty, although a select group of DMR patients showed durable outcomes with only edge-to-edge leaflet repair.[16] MitraClip provides an important first step in advancing transcatheter options, however additional technologies are needed to more effectively address the clinical needs of DMR patients.

Secondary or functional MR (FMR)

Secondary MR is essentially a disease of the ventricle and represents approximately 31% of the MR population[17] yet may account for 60% of the moderate and severe MR patients.[10] FMR occurs when mitral leaflets fail to achieve adequate coaptation due to underlying LV dysfunction and/or mitral annular dilatation.[7]

FMR can be further categorized as due to either ischemic heart disease or nonischemic cardiomyopathies. A recent meta-analysis of 53 studies involving over 45,000 patients analyzed the outcomes of FMR patients with ischemic or idiopathic cardiomyopathies and found that patients with FMR have significantly higher rates of all-cause mortality, heart failure hospitalizations, and cardiac mortality compared to patients without FMR.[7] These correlations held true independent of how MR was detected or graded. Even patients with mild FMR had worse outcomes, yet higher grades of FMR severity were associated with worse left ventricle function.[7] In heart failure patients, secondary MR is associated with increased hospitalization rates, and unfavorable long-term clinical outcomes, poor quality of life and shortened survival.[7,18] FMR is an independent predictor of long-term mortality.[18] In particular, ischemic MR is associated with excess mortality after MI, independent of baseline characteristics and degree of ventricular dysfunction.[19]

Most functional MR patients are treated with guideline directed medical therapy for left ventricle dysfunction.[5] This includes ACE inhibitors, beta blockers, angiotensin receptor antagonists, and aldosterone antagonists. However, an institutional database review of 1095 severe MR patients with HF highlight the poor outcomes in medically managed patients: 20% mortality at 1 year; 50% mortality at 5 years; and up to 90% heart failure hospitalization rates at 5 years.[6]

Surgical interventions to repair or replace the mitral valve are typically only considered for FMR patients when symptoms are unresponsive to optimum medical therapy, and/or the patient is undergoing concurrent cardiac surgery, such as aortic valve (AV) replacement or coronary artery bypass graft (CABG).[9,10] Yet, for FMR patients, surgical outcomes are not highly favorable; surgery is used because it is one of the few options available to treat MR, not because it is highly effective for FMR.

FMR patients are not typically indicated for surgery, as reflected in real world data:

- In a single center study of electronic medical records of 43,690 patients, out of 331 patients with moderate or severe MR, 38% received surgery and 62% received medical therapy. Of those not receiving surgery, 70% had FMR.[20]
- In a single center retrospective observational study of patients with severe MR, the authors classified treatment patterns among those receiving transthoracic echocardiography. A total of 17% of patients with FMR received surgical intervention, usually in cases of severe symptoms despite maximal medical therapy or those with concurrent cardiac surgery.[10]
- An analysis of the Society for Thoracic Surgeons (STS) adult cardiac surgery database yielded very few surgical patients with FMR (4.3%).[21]

In addition, controlled studies on surgical repair or replacement of the mitral valve have not shown to lower mortality rates or hospitalization in secondary MR.[22,23] MV surgery has not been appropriately studied against medical therapy in a randomized study and there are no Class I recommendations for patients with FMR.[9] The AHA/ACC Clinical Practice Taskforce guidelines recommend MV surgery as reasonable in only certain instances[9,15] (Table 2). The taskforce authors comment that the high mortality rates in both mitral valve repair and replacement at 2 years[23] highlight the poor prognosis for secondary FMR patients generally.[9] Therefore, additional therapeutic options are needed to address FMR patients.

TABLE 2: Interventional recommendations for secondary MR

based on AHA/ACC Clinical Practice Taskforce Guidelines[9]

Intervention	Patient and Condition	Recommendation
Mitral valve surgery	Patients with chronic severe secondary MR who are undergoing CABG or AVR	IIa
Chordal sparing Mitral valve replacement over MV repair	NYHA Class III-IV patients with chronic severe secondary MR who have persistent severe symptoms despite optimal GDMT for HF	IIa
Mitral valve repair or replacement	NYHA Class III-IV patients with chronic severe secondary MR who have persistent severe symptoms despite optimal GDMT for HF	IIb

When surgery is used for FMR patients, published literature is contradictory in assessing MV repair vs replacement as the preferred mode. Several non-randomized studies have indicated that MV repair has lower operative mortality, improved LV function and higher rates of long-term survival.[14,24-27] One meta-analysis pointed to a 35% higher risk of death with MV replacement vs repair.[27] While meta-analyses consistently point to better short term results

with repair, there is a higher recurrence of MR in patients receiving MV repair compared to MV replacement.[27-30]

A randomized control trial of MV repair vs replacement was conducted in 251 severe ischemic MR patients.[22] In this study, mortality at 1 year was 14% with MV repair and 18% with MV replacement. In both groups at one year, 30% of patients reached the composite endpoint of death, stroke, subsequent MV surgery, heart failure hospitalization, or NYHA increase of at least one class. At 1 and 2 years there was no significant difference in left ventricular remodeling, survival, or serious adverse events (heart failure, arrhythmias, major infection, respiratory failure) between the two groups.[22,23] Quality of life measures over the duration of the follow up were similar in both groups; with most improvement occurring in the first 6 months. [22,23] However, at 1 and 2 years the proportion of surviving patients with recurrence of severe MR was higher in the repair (4%; 14%) than the replacement (0%; 0%) group. This difference was reinforced in a meta-analysis of MV repair or replacement for severe ischemic MR patients; however, there was no significant difference in reoperation rates between MV repair or replacement.[28] Recurrence of MR could also contribute to the difference in cardiovascular readmissions at two years. In the RCT, patients undergoing MV replacement had lower rates of CV readmissions (32.2%) than those undergoing MV repair (48.3%).[23] Of note, concomitant procedures were performed in 86% of the patients in this RCT[22] so this study may be a better clinical assessment of MV repair vs replacement in patients undergoing concomitant procedures such as CABG (74% of randomized patients)[22] than of the FMR patient group as a whole. Among survivors in this study, those with most improved ventricular dimensions were repair patients who had low recurrence of MR.[31] Further analysis suggest that a predictive score may help identify patients for whom repair will be successful, offering durable outcomes with less MR.[31]

More treatment options are needed for FMR patients since surgery does not appear to be as clearly beneficial for FMR patients as it is in DMR patients, and medical management is usually insufficient. Novel therapeutic alternatives based on transcatheter mitral valve manipulation offer less invasive alternatives to surgery in patients with severe MR who are deemed inoperable or are at a severely increased surgical risk.

The safety and efficacy of MitraClip to treat patients with secondary mitral regurgitation has been investigated in several clinical studies.[32-35] MitraClip recently received FDA approval to treat heart failure patients with moderate/severe or severe secondary MR based on data from the randomized pivotal COAPT trial (Cardiovascular Out-comes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation).[33] In heart failure patients with secondary MR who remained symptomatic even on maximal guideline directed medical therapy (GDMT), MitraClip plus medical therapy (test group) demonstrated significantly lower rate of mortality (29.1%) and heart failure-related hospitalization (35.8% per patient-year) compared to GDMT alone (control group; mortality 46.1%; hospitalization 67.9% per patient-year) within 2 years of follow-up. [33] Additionally, the

primary safety endpoint of freedom from device-related complications at 1-year was 96.6% in the test group, significantly better than the performance goal of 88.0% (P<0.0001). [33]

Conversely, the European MITRA-FR randomized controlled trial (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) also assessed the efficacy of MitraClip + GDMT vs GDMT for FMR patients and found no significant difference in all-cause mortality or heart failure hospitalization at one year.[32] COAPT and MITRA-FR differed in several key areas that may help explain the contradictory results: management of medical therapy; heart failure characteristics and NYHA class; degree/severity of MR; left ventricular dimensions; and anatomic MV criteria. A predominant interpretation is that MitraClip works well in a particular set of patients; that COAPT and MITRA-FR provide complementary guidance for patient selection, demonstrating which patients with HF and secondary MR are likely and unlikely to benefit from solely reducing MR.[36,37] Furthermore, it is possible that patients with FMR represent a heterogenous group, which can be subdivided based on relationship between effective regurgitant orifice area (EROA) and left ventricular end-diastolic volume (LVEDV).[38] The MITRA-FR trial enrolled patients who had MR that was proportionate to the degree of LV dilatation, and during long-term follow-up, the LVEDV and clinical outcomes of these patients did not differ from medically-treated control subjects. In comparison, the patients enrolled in the COAPT trial had an EROA nearly 30% higher but LV volumes that were about 30% smaller, indicative of disproportionate MR.[38]

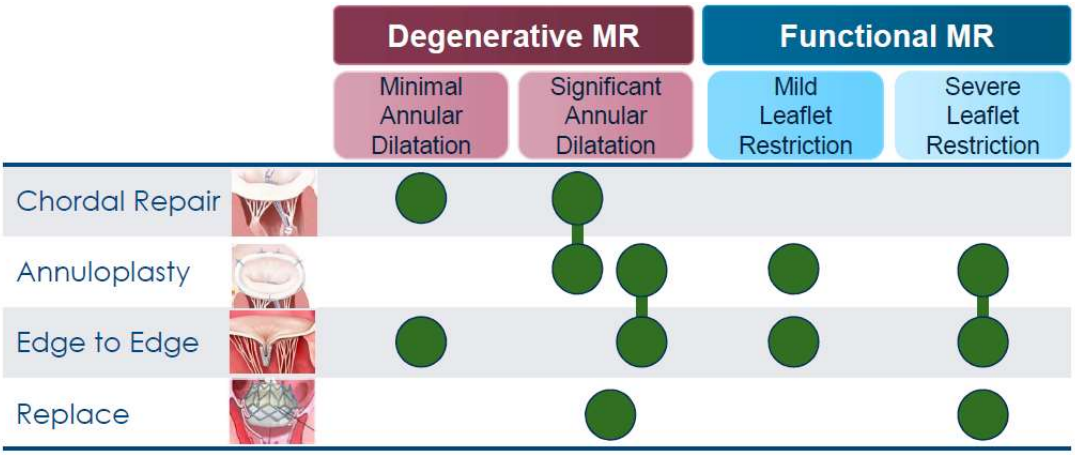
While MitraClip introduces an interesting addition to the MR treatment arsenal, it is insufficient to fulfill the unmet need of the MR population. Using COAPT eligibility criteria, approximately 240K patients would benefit from MitraClip.[39] Yet that leaves a substantial portion (87%) of heart failure patients experiencing severe MR without a treatment option beyond medical therapy.[39] In addition, real world outcomes suggest that MitraClip may be a limited option even for FMR patients. In the STS/ACC registry, patients receiving MitraClip had occurrence of either death or heart failure hospitalization at one year of 38%; and for FMR patients it was 49%.[40] And at three years, COAPT MitraClip patients had 43% mortality and annual heart failure hospitalization rate of 35%.[41] More treatment options are needed for FMR patients beyond medical management, surgery, and MitraClip.

Transcatheter Options for Mitral Valve

Surgical Precedence

Development of transcatheter (TC) options for mitral valve repair that adapt and replicate the various MV surgical techniques is a growing trend. For the mitral valve, transcatheter approaches are likely to involve a "toolkit" approach in order to provide the most relevant repair based on the etiology of MR and deficiency of the valve (Figure 1). This is predicated on the idea that MV surgery uses multiple repair approaches to accommodate physiological and structural deficiencies of the mitral valve. [21]

FIGURE 1: A toolkit approach: Mitral valve repair technologies by MV etiology



In an STS database analysis, Gammie et al analyzed trends of MV surgery, focusing on isolated MV operations, without concomitant CABG or AV procedures.[21] The overall isolated MV repair rate was 65.6% and MV replacement was 34.4%. Annuloplasty was the most commonly used surgical technique for mitral repairs and mitral surgeries overall.[21] (Table 3, repair interventions are not mutually exclusive). Mitral ring annuloplasty corrects the valve insufficiency by increasing leaflet coaptation and restoring the native physiology of the mitral valve.[42] Interestingly, edge-to-edge treatment is not well represented in the surgical world,[21] and the transcatheter MitraClip may represent an early and basic approach in the evolution of TC mitral technologies. Surgeons may prefer annuloplasty because it is more physiologically appropriate in allowing valve and leaflets to function normally. In addition, annuloplasty may allow for a higher probability of a successful procedure because there is less of a trade-off between eliminating MR and creating stenosis. Annuloplasty also leaves options available for future intervention.

TABLE 3: Mitral Valve Surgical Techniques Summary

based on STS database report[21] with possible future TC device option in blue:

Surgical Intervention	% MV surgical repairs	% All mitral surgeries	TC device type
Replacement Valve		**34%**	Valve replacement
Annuloplasty	**94.3**	**65%**	Annuloplasty
Annuloplasty ring	*68.9*		
Annuloplasty band	*19.4*		
Other Annuloplasty	*6.0*		
Leaflet Repair	**75**	**50%**	
Leaflet Resection	*46.5*		
Artificial ePTFE cords	*22.7*		Chordal replacement
Edge to Edge	*5.8*	**4%**	MitraClip

Future of Transcatheter MV options

There is a need for novel devices enabling interventional cardiologists and cardiothoracic surgeons to perform mitral interventions in a non-invasive fashion and without cardiopulmonary bypass, to repair the mitral valve. Transcatheter-based options are being pursued to address clinical need and to accommodate complex MV anatomy. Surgical history has pointed to anatomically appropriate mechanisms of transcatheter repair, such as annuloplasty and leaflet repair. Transcatheter mitral valve manipulation by either annuloplasty or leaflet repair could fulfill the unmet need for FMR patients and deliver safer and less invasive choices for DMR patients.

The possibility of treating MR patients with appropriately researched and proven transcatheter options is eminent. A European study recently evaluated MitraClip edge-to-edge device with Cardioband annuloplasty ring in a matched cohort analysis of patients with FMR at high surgical risk.[43] Both achieved significant reduction in MR grade, and the annuloplasty ring showed statistically significant improvements in outcomes including NHYA class, all cause readmission, and mortality rates at 1 year compared to MitraClip, the only currently approved TC mitral valve repair option on the US market.

Clinical trials are being conducted in the US and globally to evaluate a number of transcatheter mitral devices, with more technologies in development. Tables 4 & 5 summarize transcatheter mitral valve repair and replacement technologies currently in clinical trials. Boston Scientific's Millipede Transcatheter Annuloplasty Ring System has been implanted in more than twenty patients to date, as part of feasibility studies. The Millipede System is based on a similar working principle as an annuloplasty ring: to reduce the mitral valve's annular diameter and bring the mitral leaflets closer for optimal coaptation and reduced regurgitation. The Millipede System is also designed to be adjustable to control the diameter of the mitral annulus, so it can be customized for each patient.

As discussed above, more therapeutic options are needed for FMR patients since surgery does not provide a clear benefit (unlike for DMR patients), and medical management is usually insufficient. Novel alternatives based on transcatheter mitral valve interventions are less invasive and offer alternatives to surgery for patients with severe MR who are deemed high or extreme surgical risk.

Based on the diverse needs of this patient population, and the large number of devices likely to come to market, it is important that CMS consider establishing a mitral valve coverage policy that is comprehensive, streamlined, and ensures uninterrupted patient access to innovative therapies for mitral regurgitation. As CMS revises the existing TMVR NCD, we encourage consideration of a broad policy in the future that provides a pathway to uninterrupted coverage for future TMV therapies when furnished according to an FDA-approved indication. This "coverage to label" policy could include continued data collection through CED and would align with goals to reduce burden and encourage innovation. A singular NCD for all MR patients with all FDA approved transcatheter mitral valve interventions is the best approach to achieve that goal as the field continues to evolve.

TABLE 4: Landscape of Key Transcatheter Mitral Valve Repair Technologies in Development

Device Name (Company)	Device Type	Clinical Trial (N): Patient Population
Cardioband (Edwards)	Repair-annuloplasty band	Feasibility[a] (N=51): FMR Tricuspid Early Feasibility[b] (N=35): FTR
Carillon (Cardiac Dimensions)	Repair-indirect annuloplasty	TITAN[c] (N=53): FMR; TITAN II[d] (N=36): FMR REDUCE FMR[e] (N=163): FMR; Carillon[f] (N=352): FMR
Neochord DS1000 (Neochord)	Repair-suture as replacement neochordae	TACT[g] (N=30): MR ReChord[h] (N=585): DMR
Harpoon (Edwards)	Repair-chordal repair	Early Feasibility Study[i] (N=13): MR TRACER[j] (N=26): DMR
PASCAL (Edwards)	Repair-leaflet capture	CLASP[k] (N=245): MR CLASP IID/IIF[l] (N=1275): MR

TABLE 5: Landscape of Key Transcatheter Mitral Valve Replacement Technologies in Development

Device Name (Company)	Device Type	Clinical Trial (N): Patient Population
SAPIEN M3 (Edwards)	Replacement valve	Early Feasibility Study[m] (N=35 to date): MR US Pivotal Trial[n]
Evoque (Edwards)	Replacement valve	Early Feasibility Study[o] (N=58): MR
Tendyne (Abbott)	Replacement valve	MAC[p] (N=11): MR and mitral annular calcification; Feasibility[q] (N=110): MR; SUMMIT[r] (N=958): MR
Intrepid (Medtronic)	Replacement valve	APOLLO[s] (N=1380): MR

a) NCT01841554
b) NCT03382457
c) Siminiak, T. et al. Treatment of functional mitral regurgitation by percutaneous annuloplasty; results of the TITAN Trial; Eur J Heart Failure. 2012; 14, 931-938
d) Lipiecki, J. et al. Coronary sinus-based percutaneous annuloplasty as treatment for functional mitral regurgitation: the TITAN II trial; Open Heart. 2016; 3, 1-8.
e) NCT02325830
f) NCT03142152
g) NCT01777815
h) NCT02803957
i) NCT02771275
j) NCT02768870
k) NCT03170349
l) NCT03706833
m) Whisenant, Brian. *Updated 30-Day Outcomes for the U.S. Early Feasibility Study of the SAPIEN M3 Transcatheter Mitral Valve Replacement System*. Sep. 2019, PowerPoint Presentation.
n) http://ir.edwards.com/static-files/76ed84fa-adc1-4c22-aa30-cd405801e1b9
o) NCT02718001
p) NCT03539458
q) NCT02321514
r) NCT03433274
s) NCT03242642

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