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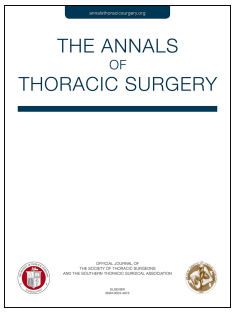

The Choice of Treatment in Ischemic Mitral Regurgitation with Reduced Left Ventricular Function

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The Choice of Treatment in Ischemic Mitral Regurgitation with Reduced Left Ventricular Function

Running Head: Choice for Ischemic Mitral Regurgitation

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Abstract

Background. Ischemic mitral regurgitation is a condition characterized by mitral insufficiency secondary to an ischemic left ventricular.Primarily, the pathology is the result of perturbation of normal regional left ventricular geometry combined with adverse remodeling.We present a comprehensive review of contemporary surgical, medical, and percutaneous treatment options for ischemic mitral regurgitation, rigorously examined by current guidelines and literature.

Methods. We conducted a literature search of the PubMed database, EMBASE and the Cochrane Library (through November 2018) for studies reporting perioperative or late mortality and echocardiographic outcomes following surgical and non-surgical intervention for ischemic mitral regurgitation.

Results. Treatment of this condition is both challenging and often requires a multimodality approach.These patients usually have multiple comorbidities that may preclude surgery as a viable option.A multidisciplinary team discussion is crucial in optimizing outcomes.There are several options for treatment and management of ischemic mitral regurgitation with differing benefits and risks.Guideline-directed medical therapy for heart failure is the treatment choice for moderate and severe ischemic mitral regurgitation, with consideration of coronary revascularization, mitral valve surgery, and/or cardiac resynchronization therapy in appropriate candidates.The use of transcatheter mitral valve therapy is considered appropriate in high risk patients with severe ischemic mitral regurgitation, heart failure and reduced left ventricular ejection fraction especially in those with hemodynamic instability.

Conclusions. The role of mitral valve surgery and transcatheter mitral valve therapy continues to evolve.

Abstract word count: 223

Keywords: mitral valve, ischemic mitral regurgitation, transcatheter mitral valve therapy.

Abbreviations:

CABG= coronary artery bypass grafting

IMR=ischemic mitral regurgitation

LV=left ventricle

LVEF=left ventricular ejection fraction

MR=mitral regurgitation

MV=mitral valve

TEE=transoesophageal echocardiogram

TTE= transthoracic echocardiogram

Optimal medical therapy has proven beneficial in patients with severe ischemic mitral regurgitation (IMR) presenting with heart failure and reduced left ventricular ejection fraction (LVEF).The mechanism of benefit appears to be by modulation of profibrotic changes of the tethered mitral valve, neurohormonal regulation and left ventricular mass reduction[1-3].However, pharmacotherapy has limitations in IMR with reduced LVEF complicated by adverse reverse remodeling, especially in the presence of persistently reduced coronary perfusion[4-6].

The medical treatment options in IMR with reduced LVEF include diuretics, beta-blockade, and inhibition of the renin-angiotensin-aldosterone axis resulting in symptomatic improvement without the expectation of a substantial mortality benefit[4,7-9].Surgical mitral valve (MV) replacement or repair combined with coronary artery bypass grafting (CABG) is considered the treatment of choice for low and intermediate-risk patients with severe IMR[10-12].Outcomes of surgical mitral valve repair plus CABG in patients with reduced LVEF and left ventricular (LV) remodeling are mixed and deserve careful evaluation[13,14].In this high-risk cohort, determining the potential risk-benefit ratio for IMR therapy is difficult as the evidence is limited to registries and subgroup analyses of randomized clinical trials. An evolving catheter-based option for severe IMR with reduced LVEF is transcatheter mitral valve therapy[15-18].The use of transcatheter mitral valve therapy is considered appropriate in high risk patients with severe IMR and reduced LVEF especially in patients with hemodynamic instability. It provides a less invasive approach which may be better tolerated in high-risk heart failure patients with IMR and LV dysfunction. Recently published clinical trial data have confirmed the benefit of transcatheter mitral valve therapy despite the discordance in the results of the two trials[19,20].Enrolled patients primarily included those with severe secondary MR, reasonable life expectancy, and prohibitive surgical risk due to comorbidities**.**

Material and Methods

Methodology of literature search and synthesis is enclosed in the ***Supplemental Material.***

Pathophysiology

Ischemic mitral regurgitation is caused by the geometric disturbance of valve and subvalvular apparatus of mitral valve. The imbalance between the tethering and closing forces is a consequence of adverse left ventricular remodeling after myocardial injury with enlargement of the left ventricle and mitral annulus, posterior and lateral displacement of the papillary muscles (PMs), leaflet tethering, and reduced closing forces.Leaflet coaptation is compromised resulting in varying degrees of mitral regurgitation[21]-(*Figure 1; Panel I, II*).These pathologic perturbations most commonly occur following ischemic events involving the left circumflex coronary artery, but may occur with lesions in the right coronary and left anterior descending coronary arteries depending on the coronary distribution to the posteromedial papillary muscle. MR resulting from such acute mitral valve distortion often resolves upon myocardial revascularization and restoration of myocardial kinesis[22,23].Despite revascularization, some myocardial segments may not recover sufficiently to reduce IMR which persists in with the onset of myocardial scarring.IMR, particularly in patients with reduced LVEF, commonly results in LV dilatation, a known independent risk factor for mortality[12,22].

Echocardiography-based studies have identified two types of restricted systolic leaflet motion according to the tethering shape: the asymmetrical pattern with predominant posterior tethering of both leaflets which is often observed with an inferior/posterior myocardial infarction, and the symmetrical pattern with predominant apical tethering most commonly seen with anterior myocardial infarctions[22,24].Three tethering vectors (posterior, apical, and lateral) were observed in IMR and the displacement of one of the PMs exerts a traction and

tethering effect on both MV leaflets.In the asymmetric type, the posterior leaflet is moved more posteriorly than apically due to its parallel position in respect to the posterior LV wall resulting in asymmetric tethering and an eccentric mitral regurgitant jet[24]-*(Figure 1; Panel III).*Conversely, in the symmetrical type there is a combination of apical and posterolateral vectorial tethering, with a more displaced coaptation point.The regurgitant jet is usually located centrally, and its direction reflects the equal involvement of the systolic motion in both leaflets[24].*(Figure 1; Panel IV)*

New experimental contributions are discussed in the ***supplemental material.***

Results

Evaluation and Treatment

International Guidelines

The latest American College of Cardiology/American Heart association-(ACC/AH) and European Society of Cardiologists-(ESC) Guidelines-(2017) for the management of IMR support optimal medical therapy, surgical revascularization, and cardiac resynchronization as therapies that result in an improvement of MR severity.These therapeutic interventions improve regional wall motion, promote reverse LV remodeling and improve LV synchrony[1,2].***Figure 2-5*** show the disease stages in patients with IMR and a proposed algorithm for management.

Medical therapy of IMR with reduced LVEF is discussed in the ***supplemental material.***

Cardiac resynchronization

Cardiac resynchronization Therapy-(CRT) is a firmly established treatment choice in selected patients with severe IMR and reduced LVEF who have LV dyssynchrony.The use of CRT is recommended by current guidelines and position papers of professional societies-(Class I) in patients presenting in sinus rhythm with New York Heart Association-(NYHA)

functional class II to IV symptoms on guide direct medical therapy with LVEF ≤35%, left bundle branch block, and QRS duration ≥150ms. Moreover, clinical benefit after CRT implantation was noted in patients with sinus rhythm and non- left bundle branch block pattern with QRS duration ≥150ms, and in those with left bundle branch block and QRS duration 120 to 149 ms-(Class IIa recommendation)[25]. Randomized controlled trials have shown improvement in rehospitalization rates for heart failure and survival for CRT recipients (with and without defibrillator function)[26],together with reduction in LV end-diastolic and end-systolic dimensions and improved LVEF.Although most reports show reduced overall MR severity with restoration of synchronous ventricular contraction and LV remodeling, the effect of CRT implantation in secondary MR is inconsistent.One sham-controlled trial-(MIRACLE/Multicenter InSync Randomized Clinical Evaluation)[27] included 450 patients in NYHA functional class III/IV and heart failure with LVEF ≤35% and QRS duration ≥130ms, reported a significant improvement in LV end-diastolic, LV end-systolic volumes and LVEF with preserved reduction in MR.Another study reported a significant reduction of secondary mitral regurgitation by restoring papillary muscle geometry and altering the balance between the closing and tethering forces on the mitral valve[28].The clinical benefit associated with the use of CRT was evident in no more than half of the patients, although this improvement identifies CRT recipients who have an improved prognosis[29]. Nonetheless, patients with severe IMR and heart failure with an EROA ≥0.20cm^2 have a poor response to CRT alongside increased mortality and heart failure re-hospitalization rates.

Surgery for ischemic secondary mitral regurgitation: when and how to treat?

Combined revascularization and mitral surgery should be offered to patients with moderate-to-severe IMR with high-grade proximal coronary lesions.The indications for mitral valve surgery are limited due to the lack of a survival benefit.Therefore, surgical treatment for

IMR is only recommended in patients who remain symptomatic despite optimal medical and device therapies[1,2,13].The American Association of Thoracic Surgeon/ Society of Thoracic Surgeons-(AATS/STS)[30] and ACC/AHA 2017 guidelines recommend that mitral valve surgery is reasonable for patients with chronic severe ischemic MR-(stages C and D) undergoing CABG or aortic valve replacement-(Class IIa,LOE:C)[1,10].The usefulness of surgical mitral repair is uncertain in patients with chronic moderate IMR-(stage-B) undergoing CABG-(Class IIb,LOE:B-R)[1,11]

Mitral valve repair for IMR utilizing an undersized restrictive mitral annuloplasty ring, may be performed at the time of myocardial revascularization in patients with moderate IMR, although the overall benefit is certain [31-34].This is of particular concern for patients who are undergoing CABG with an LVEF≤ 30%[35].Restrictive mitral annuloplasty is burdened by high rate of MR recurrence ranging from 30% to 40% at 6 to 12 months and about 60% at 5 years[10,12,22].Several causal factors of MR are identifiable on preoperative echocardiography: symmetric leaflet tethering,posterior leaflet tethering angle of >45°,tenting height >11 mm, presence of a basal aneurysm/dyskinesis,greater degree of LV dilation, and LV sphericity index[22].MR recurrence is more frequent with use of partial annuloplasty bands or flexible complete rings[36,37].High rates are also noted with complete rigid ring insertions[10,12,38]

Observational, non-randomized, and single-center experiences are heterogenous in nature and contain many confounders that limit the quality of evidence.They lack robustness in study design, including non-rigorous definitions of the degree of MR especially in patients with moderate and severe degrees[34,39,40].Michler et al published a randomized controlled trial (CTSN trial)[11] of 301 patients with moderate ischemic MR undergoing CABG, revealing a mortality rate of 10.0% in the group undergoing CABG plus mitral valve repair versus 10.6% after CABG alone at 2 year follow-up (HR in the combined-procedure group = 0.90; 95% CI: 0.45 to 1.83; p=0.78).There was a higher rate of moderate or severe residual MR in the

CABG-alone group (32.3% versus 11.2%;p<0.001), despite similar LV reverse remodeling.Although hospital readmission and serious adverse event rates were similar, neurological events and heart rhythm disorders were more frequent in patients undergoing CABG plus mitral valve repair suggesting that current evidence to support concomint mitral valve repair for moderate IMR at the time of CABG is weak[11].

Two other randomized controlled trials-(RCTs) are of particular interest: the Randomized Ischemic Mitral Evaluation-(RIME) trial[31] and the POINT trial[33].In these RCTs the authors demonstrated that the addition of restrictive mitral annuloplasty to CABG in patients with severe IMR resulted in improvements in LV reverse remodeling LVEF, New York Heart Association functional class-(NYHA), and MR grade, but not in survival.In the POINT trial 102 patients were randomly assigned to undergo CABG alone or CABG plus restrictive mitral annuloplasty.The CABG plus valve repair arm had significantly reduced LV end-systolic dimension-(LVESd).In the RIME trial, 73 patients were randomly assigned to undergo CABG alone or CABG plus valve repair.Their CABG plus restrictive mitral annuloplasty cohort demonstrated a 28% reduction in LV-end-systolic-volume index-(LVESVI) compared to baseline.

The three randomized trials highlight that improvements in global and regional wall motion, as well as reverse LV remodeling after CABG with and without mitral valve repair, are indicative of viable myocardium.Penicka and colleagues noted that patients with moderate IMR who underwent CABG alone and experienced resolution of MR after surgery had more viable LV segments and less dyssynchrony at baseline[41].Michler et al., similarly noticed that patients with resolution of IMR showed greater reverse remodeling and better wall motion scores than those who did not regardless of the treatment group[11].Given the importance of myocardial viability in ensuring good outcomes, the three RCTs deserve a more detailed analysis.

Firstly, the number of patients enrolled in the studies differ widely, especially in the Cardiothoracic Surgical Trials Network-(CTSN) which enrolled three times the number of patients included in the other RCTs (CTSN =301, RIME =73 and POINT=102). Secondly, the clinical endpoints adjudicated in the studies were different. CTSN utilized the Left Ventricular End Systolic Volume Index as the primary measure of outcome but POINT utilized the left ventricular end-systolic diameter-(LVESD), left ventricular end-diastolic diameter-(LVEDD), and left ventricular ejection fraction-(LVEF) as measures to elucidate reversal of LV remodelling.RIME's primary endpoint was derived from cardiopulmonary exercise testing. POINT also assessed the tolerability to exercise in patients with residual MR of grade 2+ or less alongside variability of the MR grade during exercise and its effect on dyspnea and systolic pulmonary artery pressure whereas CTSN focused on echocardiographic measures using a wall motion score and using questionnaires/patient reported outcomes to evaluate quality of life. Thirdly,different analytical statistical approaches were employed in the CTSN study, which included deceased patients as treatment failures in the primary endpoint analysis, while the other studies utilised simple survival analyses. Fourthly, in the CTSN trial, recipients of surgical treatment had a significantly lower prevalence of prior myocardial infarction, potentially resulting in less LV scar tissue burden. Fifthly, and perhaps most importantly, patients in the CTSN trial had a baseline LV size that was less dilated and remodeled as compared with the POINT and RIME trials, respectively.

All these variables favor CABG plus restrictive mitral annuloplasty, especially in the presence of extensive myocardial scar tissue-***(figure-5)***. In fact, in these patients CABG alone would less likely result in an improvement in the LV wall motion and reverse remodeling, which favor a reduction in the burden of IMR[42].As highlighted in the RIME trial, CABG plus papillary muscle approximation reduced the LV size by 28% from baseline, whereas in the CTSN trial CABG plus subvalvular repair was associated with only a 9% reduction.Patients

in the CTSN trial had smaller ventricles at baseline and, as the evidence suggests, more viable myocardium—precisely the clinical substrate that is likely to benefit most from CABG alone. Other factors such as the predicted probability of significant functional improvement should lead to the provision of a mitral valve reparative procedure.This category includes patients with documented scar tissue or basal aneurysm or dyskinesia in the inferoposterior lateral LV, large ventricles-(LVESVI>60 mL/m2 with left-ventricular-end-diastolic-diameter>50 mm), and poor coronary targets in the left circumflex and right coronary distributions,all of which reduce the likelihood that revascularization will provide significant enhancement of LV contractility and LV reverse remodeling[12,22,42].

In patients presenting with severe ischemic MR, mitral valve surgery (replacement or repair) combined with CABG is suitable-***(figure-4,5).*** 2017 AHA/ACC Focused Update on VHD consider severe secondary MR an effective regurgitant orifice area-(EROA) > 0,4 cm^2, a regurgitant volume-(Rvol) ≥ 60 ml and a regurgitant fraction-(RF) ≥ 50% while 2017 ESC Guidelines consider severe secondary MR an EROA ≥ 0,2 cm^2 or a Rvol ≥ 30 ml

A CTSN randomized trial of surgical mitral valve repair versus surgical mitral valve replacement in 251 patients with severe IMR showed a mortality rate of 19.0% in the repair group and 23.2% in the replacement group-(p=0.39) at 2 years, with similar degrees of LV reverse remodelling[10].The rate of recurrence of MR over 2 years was higher in the repair group (58.8% vs 3.8%,p<0.001), leading to a higher incidence of heart failure and repeat hospitalizations.Several valvular measures (e.g.,tenting area, anteroposterior annular diameter, coaptation length) and ventricular measures (e.g., LVESVI, LV-sphericity index, and interpapillary-muscle-distance) have been identified as possible predictors of recurrent mitral regurgitation in patients who undergo restrictive mitral annuloplasty alone using rings with a predefined geometry, which overcorrects for the increased tethering of the P2 and P3 segments of the posterior mitral leaflet[10,38,43].The high mortality rate at 2 years in both

groups[10] emphasizes the poor prognosis of IMR, which clearly differs from primary MR – the former being due to myocardial and coronary disease, and latter a purely valvular condition. In patients with advanced NYHA class III-IV symptoms, isolated mitral surgery (replacement or repair) may be considered for patients who have persistent symptom despite optimal guideline-directed medical and cardiac resynchronization therapy in appropriate candidates-(Class IIb;LOE-B)[1,10].The experience of the surgeon, alongside consultation with the heart valve team, are critical in the decision-making for surgical mitral valve repair versus surgical mitral valve replacement [10,12,22,36,39-42]; however, it is reasonable to perform a chordal-sparing MV replacement or MV repair in combination with a subvalvular procedure-(Class IIb;LOE:B-R)[1,10,12,22,44,45]-***(figure-4,5).*** Surgical decision making for patients with IMR therefore could be enhanced by preoperative identification of those who would most likely have an improvement in regional wall motion and global LV function with combined CABG.Despite this, preoperative assessment of myocardial viability is often scarce in randomized controlled trials[46].Viability assessment can predict the effectiveness of revascularization in specific patient populations, particularly within the present context[37].

The optimal valvular prosthesis for mitral valve replacement is unclear.Patients with IMR who undergo MV replacement with conventional stented prostheses may have worse hemodynamic performance and reduced functional capacity, when compared with patients who had a mechanical prosthesis implanted.However, these data require prospective validation with long-term follow-up[47].Prospective trials on subvalvular repair techniques are currently insufficient to derive definitive conclusions[12,22,43].However, in patients with dilated ventricles (especially in those with scar tissue, dyskinesia, or a basal aneurysm) in whom surgical mitral valve repair is feasible, a subvalvular procedure such as papillary muscle approximation should be considered.Our previous analysis of patients who underwent CABG plus restrictive mitral annuloplasty with papillary muscle approximation identified

echocardiographic preoperative symmetric tethering, the presence of a LV lateral wall dysfunction, persistent LV dyskinesis, and predominant apical tethering of both leaflets as independent predictors of recurrent mitral regurgitation[48].Additionally, IMR recurrence after restrictive mitral annuloplasty with and without papillary muscle approximation is determined by persistent tethering of the posterior leaflet[12,22,49-52].Aggressive annuloplasty ring under-sizing causes a mismatch of the LV dimension and ring size increasing the risk recurrent IMR. Meticulous ring-sizing may prevent IMR recurrence after MV repair and correctly identify patients in whom combined restrictive mitral annuloplasty and sub-valvular intervention or chordal-sparing mitral valve replacement may be preferable.A recent post-hoc analysis by the CTSN authors noted that an LV end-systolic diameter/ring size ratio $\geq$ 2 was associated with increased risk of persistent or recurrent IMR.Therefore, avoidance of smaller annuloplasty rings and incorporation of the LV size into surgical planning is prudent to improve repair durability and avoid iatrogenic mitral stenosis[53].

Our current decision algorithms for managing IMR focuses on 5 preoperative factors that help determine the surgical plan.In conjunction with echocardiography and cardiac catheterization, cardiac magnetic resonance imaging is useful for evaluating the following:

1) severity of IMR
2) severity of LV dysfunction
3) severity of LV remodeling-(LVESVI)
4) presence and extent of LV scar tissue
5) Quality and distribution of the left circumflex and right coronary artery circulation

(figure 4-5)

Two extremes to the decision algorithms must be noted.Firstly, when medical treatment of IMR does not improve symptoms or quality of life, or progressive LV remodeling with increased LV dysfunction occurs, then heart transplantation or destination LV assist device

therapy is a more effective treatment strategy as opposed to mitral valve surgery[10,12,43].Secondly, in patients who have isolated inferobasal myocardial infarction and develop severe IMR due to posterior leaflet tethering despite normal LV size and function, the MR is the cause of heart failure and mitral valve surgery may be indicated for symptomatic relief[10-12,38,42,43,54].The grey area consists of patients in between the described extremes.Particular attention is directed at patients with moderate-to-severe IMR with evolving symptomatology for which CABG is not indicated, representing a potential benchmark for transcatheter mitral valve therapy [19,20]***(figure-2,5).***

Non-surgical Intervention for secondary ischemic mitral regurgitation

The aim of transcatheter mitral valve therapy is to develop a lower-risk procedure that effectively reduces the severity of MR and improve clinical outcomes.The increasing prevalence of MR in the elderly population with significant comorbidities has driven the attractiveness for transcatheter interventions.The transcatheter procedure is based on the surgical edge-to-edge mitral valve repair using a clip to approximate scallops of the anterior and posterior leaflets-***(Figure-6).***

Results from TMVT-edge-to-edge repair from Randomized Controlled Trials

To date, there are 3 RCTs comparing percutaneous TMV repair to optimal medical therapy or standard mitral valve surgery[16,19,20]-***(Supplemental Table-1,2)***. COAPT-(Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) and MITRA-FR-(Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) enrolled eligible patients with ischemic or non-ischemic cardiomyopathy who had a depressed LV ejection fraction,

moderate-to-severe or severe secondary MR despite the administration of stable maximal doses of guideline-directed medical therapy and cardiac resynchronization therapy.Baseline characteristics and results from these RCTs are reported in Supplemental ***table-1,2.***

The primary effectiveness endpoints of the COAPT study was all hospitalizations for heart failure within 24 months of follow-up, including recurrent events in patients with more than one event. In MITR-FR the primary effectiveness endpoints was composite of death from any cause or unplanned hospitalization for heart failure at 12 months after randomization.

Baseline LV end-diastolic volume was higher in COAPT-(Mitraclip procedure versus medical therapy: 194.4±69.2 vs 191.0±72.9 ml) than the MITRA-FR study (136.2±37.4 vs.134.5±33.1 ml).There was a marked difference in the rate of data available at 1 year of follow-up-(COAPT > 94%; MITRA-FR < 55%)[19,20]. At 2-year follow-up in the COAPT study, Mitraclip procedure reduced the incidence of all-cause mortality by 38% ([HR] 0.62; 95% CI 0.46-0.92; p<0.001) and all-cause hospitalizations by 24% ([HR] 0.76; 95% CI 0.6-0.96;p=0.02), and was associated with significant LV reverse remodelling[19]

The extraordinary results from COAPT were beyond the expectations of the authors themselves, because the rate of freedom from device-related complications with Mitraclip procedure exceeded their prespecified objective performance goal.Moreover, in the subgroup analysis, the benefits of transcatheter mitral valve therapy were consistent both in ischemic and non-ischemic cardiomyopathy, and in patients who were considered high risk for surgery alongside low risk patients.This benefit was independent of the MR grade and LV volume and function at baseline[19].Conversely, Obadia and colleagues reported that patients with severe secondary MR who received transcatheter mitral valve therapy in the MITRA-FR study did not experience a clinical benefit when compared with patients randomized to medical treatment alone.This result was consistent across all the subgroups tested.The missing data reported by Obadia et al., remains a cause for concern and results from the two trials should

be interpreted within their respective contexts[20].A complete description of the two trails is shown in ***supplemental table 2***.

The COAPT trial sheds light that an effective and sustainable percutaneous treatment can improve the prognosis and the risk of death of patients with secondary MR[19].However, the main lesson of the Mitra-FR trial not all patients presenting with secondary MR will be improved by Mitraclip procedure[20].The differences of these results can be explained by the different inclusion criteria of both studies that led to include two different populations of patients with secondary MR[19,20].

Patients included in the COAPT study[19] presented with more severe MR-(EROA 0.41 cm2 vs. 0.31 cm2 in the Mitra-FR study) and were treated more efficiently by transcatheter mitral valve therapy than in the Mitra-FR study (early recurrence of severe MR (grade 3/4): 5% vs. 9%; one-year severe recurrence MR of severe MR (grade 3/4): 5% vs. 17%) respectively.Furthermore, in the COAPT trial, maximally optimized medical treatment was assessed before inclusion and randomization by a central adjudication committee including an heart failure specialist.The rigorous follow-up may have played a role in COAPT, an industry funded trial, accounting for its improved outcomes compared to the institutional RCT, MITRA-FR.

The MITRA-FR study[20] included some patients with less severe MR, more advanced LV disease with more dilated LVEDD-(135 mL/m^2 vs 101 mL/m^2) increased incidences of pulmonary hypertension.It is possible to surmise that transcatheter mitral valve therapy was performed too late in the course of the heart failure disease in these patients.Finally, Grayburn et al[55] recently reported that COAPT patients presented with a disproportionate number of secondary MR (severe MR and few dilated LV) while Mitra-FR patients presented with proportioned MR.In patients with disproportionate MR, the mitral disease is in the foreground, explaining that an effective and sustainable treatment may improve the

prognosis.In patients with proportionate MR, the secondary MR is linked to the severity of LV disease and prognosis may not be linked to MR treatment[55]

In the EVEREST-(Endovascular Edge-to-Edge Repair) II study[16], transcatheter mitral valve therapy was compared to conventional mitral valve surgery although only 27% of patients have FMR.Results showed that the 5-year freedom from death, mitral valve surgery or reoperation, and moderate to severe MR was lower in the mitraclip group versus surgery group (44.2% vs. 64.3%; p=0.01).This was driven by lower rates of MV surgery or reoperation (95% vs. 72.1%; p=0.003) and moderate to severe MR (98.2% vs. 87.7%;p=0.02), as opposed to survival (79.2% vs. 73.2%; p=0.36).Interestingly, a subgroup analysis showed the potential benefits of transcatheter mitral valve therapy having been derived in patients ≥ 70 years of age, with surgery performing better than percutaneous repair in younger patients (interaction p=0.005)[16].

Results from TMVT-edge-to-edge repair from observational and registry studies are reported in the ***supplemental material.***

Areas of Uncertainty and Future Direction

Areas of uncertainty remain with regards to the optimal treatment in both populations with severe IMR because rigorous randomized trials of medical treatment versus surgery are lacking in patients not suitable for CABG with reduced LVEF and moderate-severe MR.Therefore, medical therapy, cardiac resynchronization therapy and revascularization when indicated, should be considered the preferred treatment choice.

Currently transcatheter mitral valve therapy of IMR is limited to edge-to-edge mitral valve repair, although new techniques could be extended to the annulus or chordae, either exclusively or in combination.

Small studies using novel interventional therapies have demonstrated feasibility and efficiency in reducing MR and improving heart failure symptoms.The Carillion, Cardioband, and Mitralign devices were designed to reduce annular dilatation, a frequent and important perpetuator of secondary MR-***(Figure-3***).Several transcatheter mitral valve replacement systems (Tendyne,CardiAQ-Edwards, Neovasc, Tiara, Intrepid, Caisson, High Life, MValve System, and NCSI NaviGate Mitral) are emerging as transcatheter valve replacement may offer more durability compared to transcatheter valve repair[56]

Conclusion

There are several options for treatment and management of IMR with differing prognostic benefits; however, patients who manifest IMR with heart failure and LV dysfunction have a worse prognosis.Guideline-directed medical therapy is the first treatment choice for moderate and severe secondary MR, with cardiac resynchronization therapy and coronary revascularization performed in appropriate candidates.The role of mechanical intervention, conventional surgery, or transcatheter mitral valve therapy are less clear and still evolving. Long-term follow-up of patients with secondary MR and ischemic cardiomyopathy receiving surgical or percutaneous intervention should be guided by consistent evaluations of valve durability, functional outcomes, and survival.Finally, better communication between members of the multidisciplinary heart team will also assist in determining the appropriate intervention.

Figures Legends

Figure 1. *Panel I*: Carpentier type IIIb represents restricted leaflet motion in systole. *Panel II* Multi-modality echocardiographic imaging for IMR.TTE: para-sternal long axis view***(****A)* and TEE-LVOT view*(B)* show eccentric jet of MR due to asymmetrical tethering. *(C):*3D TEE-« en face view from LA» showed marked indentations between P2-P3 and P2-P1 (white arrow) due to LV remodeling *(D):*3D TEE-«en face view from LV» shows an apical and posterior secondary displacement of posterior papillary muscle (white arrow). *(E-F)*: reconstruction and modelization of mitral valve shows the malcoaptation of mitral leaflets due to a tethering of the posterior valve. *Panel III:* Asymmetric pattern of mitral valve tethering on two- and three-dimensional echocardiography in the inferior/posterior direction (yellow arrow) results in posteriorly-directed eccentric ischemic mitral regurgitation (IMR) *(A-D). Panel IV:* Symmetric pattern of mitral valve tethering on two- and three-dimensional echocardiography. Note central ischemic mitral regurgitant jet (*Figures A-D*).

Figure 2. Overview of decision making for patients presenting with mitral regurgitation secondary to ischemic cardiomyopathy. Data were derived from Nappi F et al Ann Thorac Surg[48] and Nappi F et al J Thorac Cardiovasc Surg[22].

Abbreviation. RHC = right heart catheterization; LV gram= left ventriculogram; MRI=cardiovascular magnetic resonance

Figure 3. Decision-making of feasibility for high-risk patients suitable of percutaneous repair with transcatheter mitral valve therapy edge to edge.

Figure 4**.** TTE evaluation for decision tree in assessing severity of chronic ischemic mitral regurgitation.

Figure 5**.** Decisional algorithm for surgery of moderate to severe IMR.

Abbreviation. EROA=effective regurgitant orifice area;RF=regurgitant fraction;RVol= regurgitant volume

Figure 6. Percutaneous edge-to-edge mitral valve repair of a patient with IMR.3D-TEE *(A)* and 3D-TEE color *(B)* en-face view showing central secondary IMR**.***(C)***:** 3D-TEE en-face view after a successful procedure with implantation of 2 central MitraClips.*(D)*: TTE 3-chamber view showing persistent good results at 1 year with residual mild MR and a gradient at 4 mmHg.

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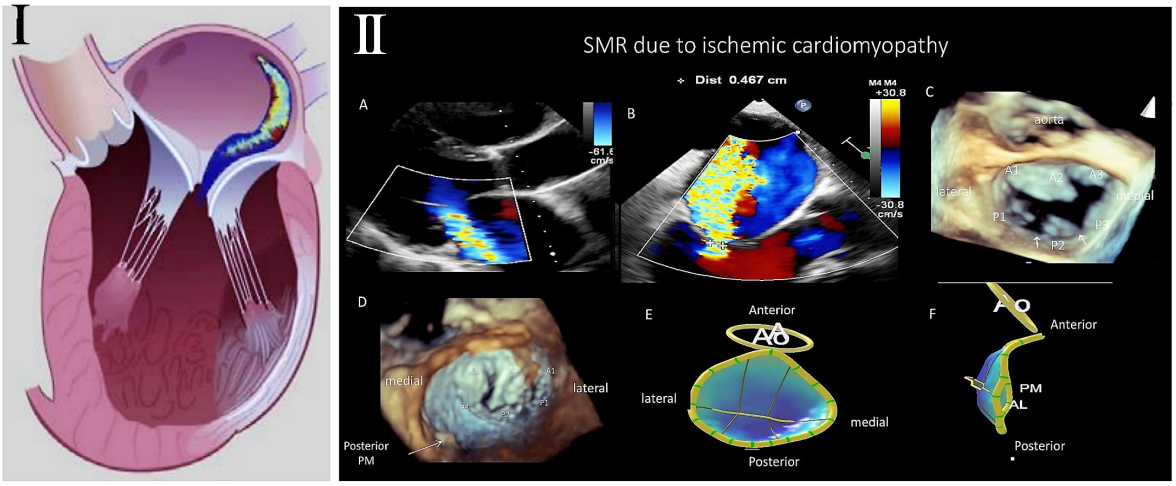
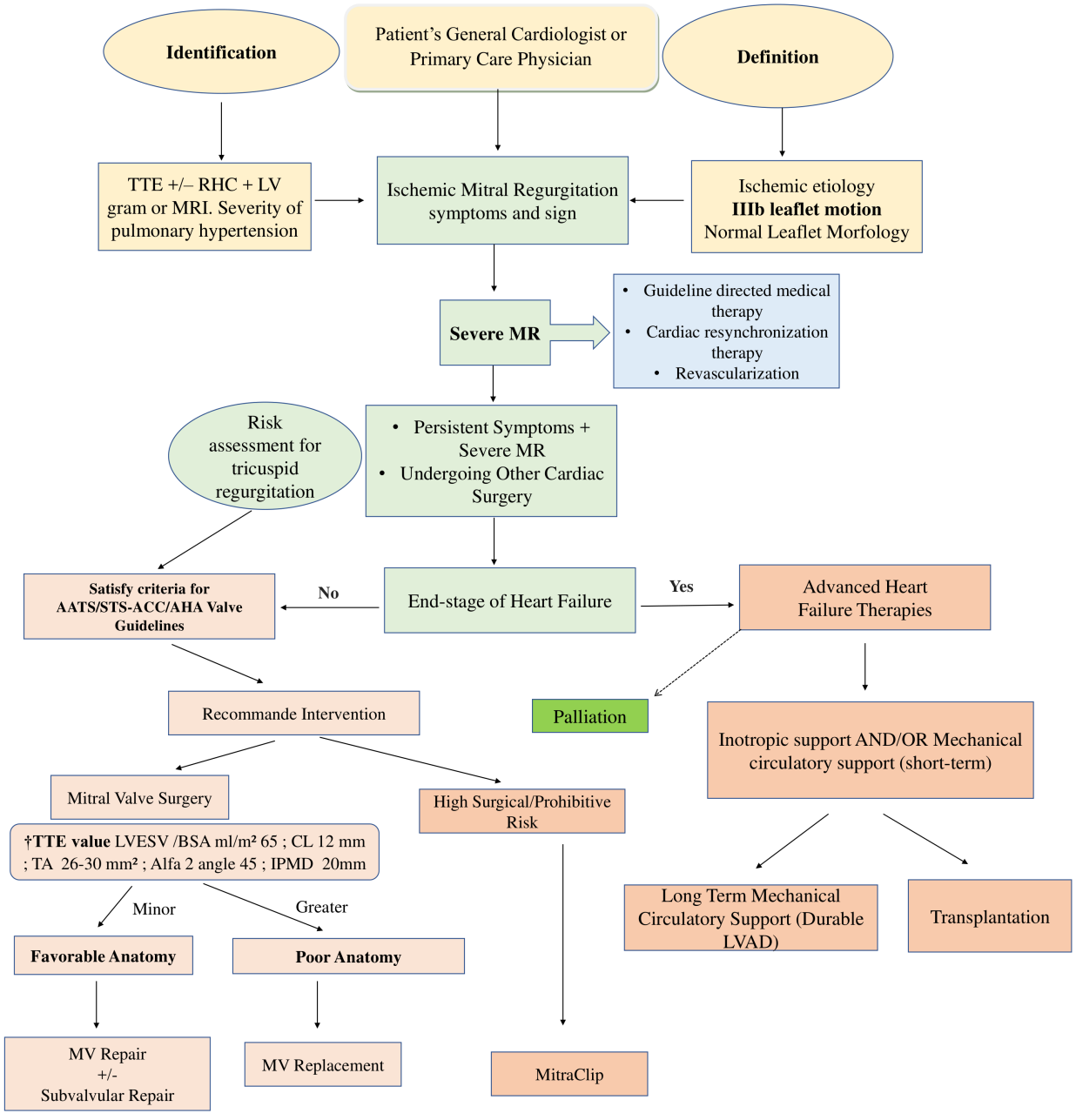
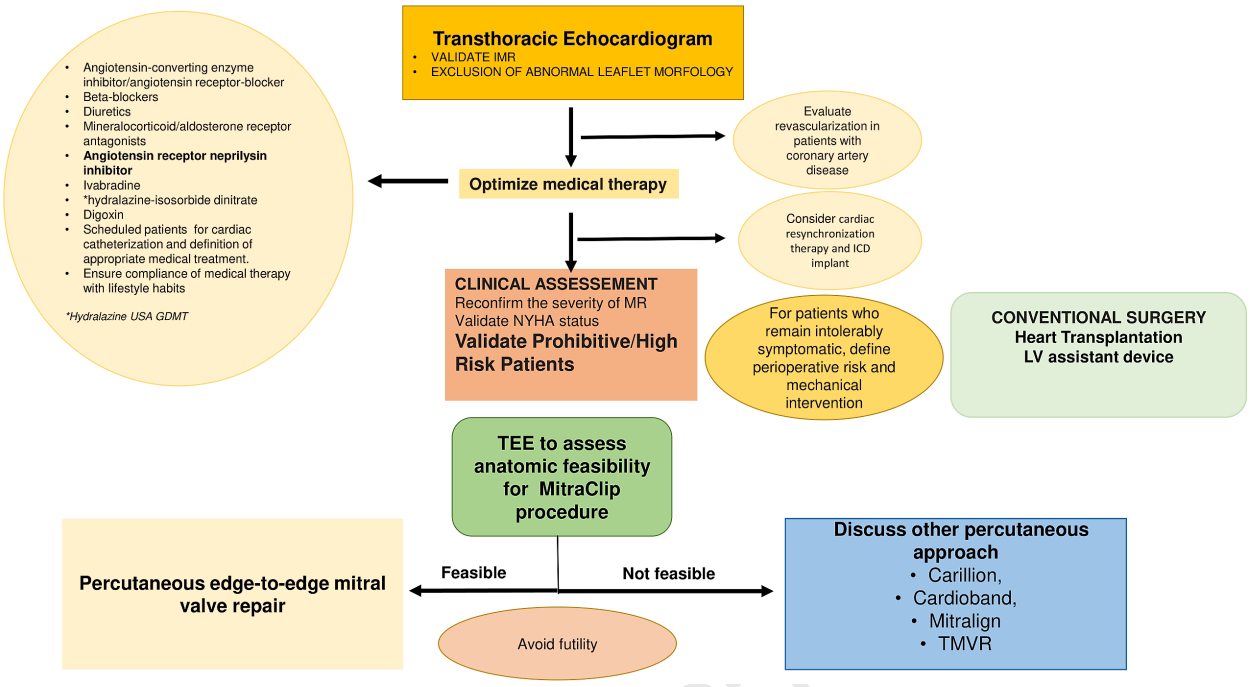
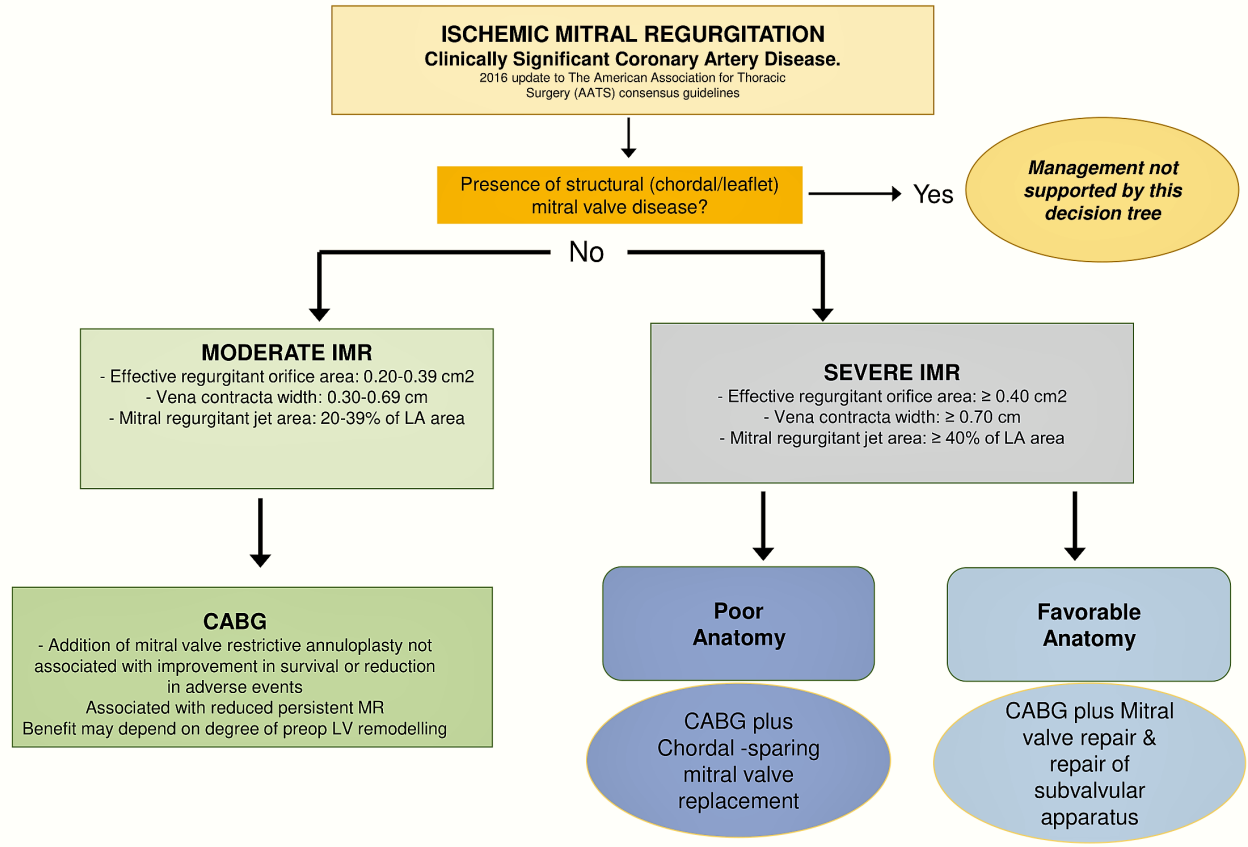
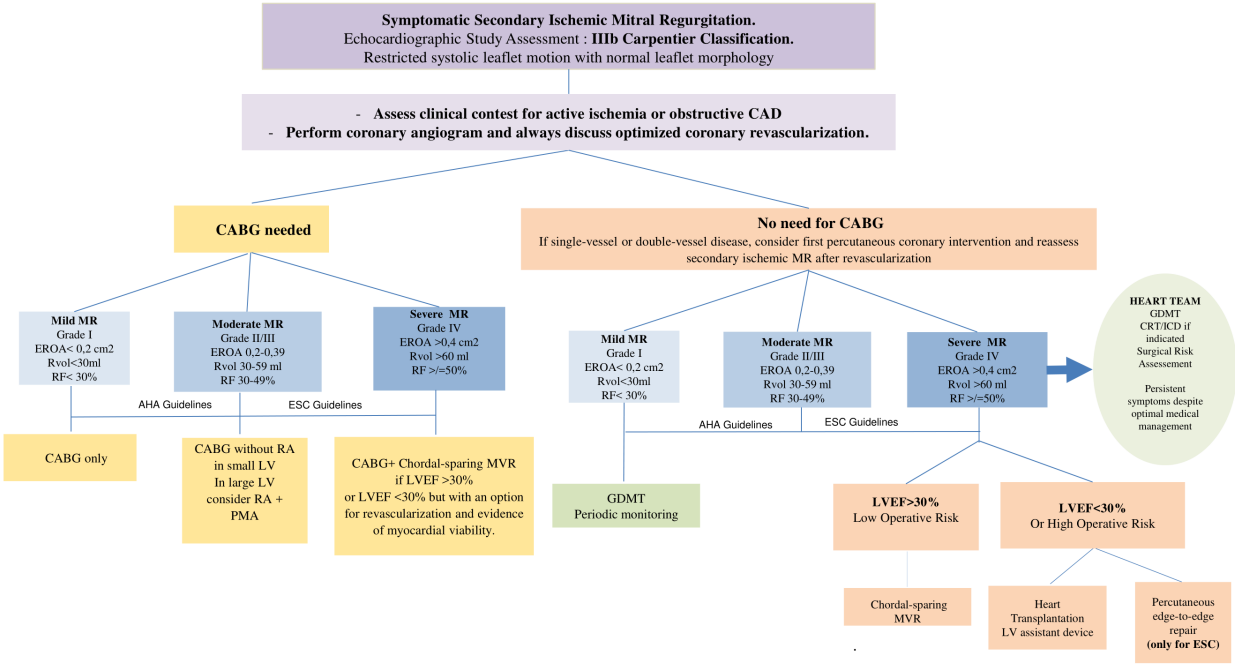
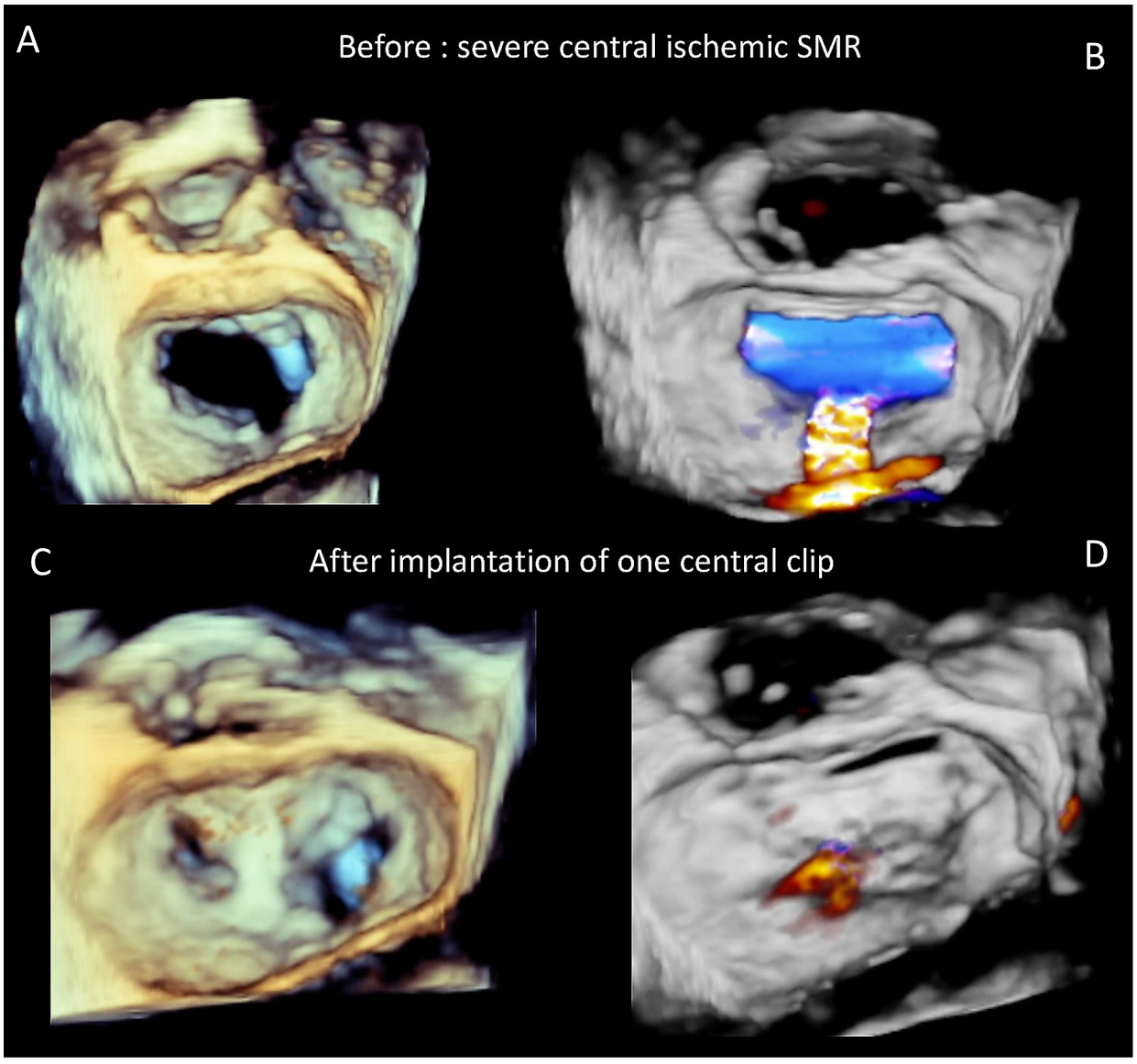

I
II
SMR due to ischemic cardiomyopathy
Dist 0.467 cm
A
B
C
D
E
F
aorta
lateral
medial
Anterior
Posterior
PM
AL
Ao
III
IV
LV
LA
Inferior/Posterior Tethering
Eccentric IMR
Apical Tethering
Central IMR
Aorta
AML
PML


Identification
Patient's General Cardiologist or Primary Care Physician
Definition
TTE +/– RHC + LV gram or MRI. Severity of pulmonary hypertension
Ischemic Mitral Regurgitation symptoms and sign
Ischemic etiology
IIIb leaflet motion
Normal Leaflet Morfology
Severe MR
• Guideline directed medical therapy
• Cardiac resynchronization therapy
• Revascularization
Risk assessment for tricuspid regurgitation
• Persistent Symptoms + Severe MR
• Undergoing Other Cardiac Surgery
Satisfy criteria for AATS/STS-ACC/AHA Valve Guidelines
No
End-stage of Heart Failure
Yes
Advanced Heart Failure Therapies
Recommande Intervention
Palliation
Inotropic support AND/OR Mechanical circulatory support (short-term)
Mitral Valve Surgery
High Surgical/Prohibitive Risk
†TTE value LVESV /BSA ml/m² 65 ; CL 12 mm ; TA 26-30 mm² ; Alfa 2 angle 45 ; IPMD 20mm
Minor
Greater
Favorable Anatomy
Poor Anatomy
Long Term Mechanical Circulatory Support (Durable LVAD)
Transplantation
MV Repair +/- Subvalvular Repair
MV Replacement
MitraClip




ISCHEMIC MITRAL REGURGITATION
Clinically Significant Coronary Artery Disease.
2016 update to The American Association for Thoracic Surgery (AATS) consensus guidelines
Presence of structural (chordal/leaflet) mitral valve disease?
Yes
Management not supported by this decision tree
No
MODERATE IMR
- Effective regurgitant orifice area: 0.20-0.39 cm2
- Vena contracta width: 0.30-0.69 cm
- Mitral regurgitant jet area: 20-39% of LA area
SEVERE IMR
- Effective regurgitant orifice area: ≥ 0.40 cm2
- Vena contracta width: ≥ 0.70 cm
- Mitral regurgitant jet area: ≥ 40% of LA area
CABG
- Addition of mitral valve restrictive annuloplasty not associated with improvement in survival or reduction in adverse events
Associated with reduced persistent MR
Benefit may depend on degree of preop LV remodelling
Poor Anatomy
Favorable Anatomy
CABG plus Chordal -sparing mitral valve replacement
CABG plus Mitral valve repair & repair of subvalvular apparatus


Symptomatic Secondary Ischemic Mitral Regurgitation.
Echocardiographic Study Assessment : IIIb Carpentier Classification.
Restricted systolic leaflet motion with normal leaflet morphology
- Assess clinical contest for active ischemia or obstructive CAD
- Perform coronary angiogram and always discuss optimized coronary revascularization.
CABG needed
No need for CABG
If single-vessel or double-vessel disease, consider first percutaneous coronary intervention and reassess secondary ischemic MR after revascularization
Mild MR
Grade I
EROA< 0,2 cm2
Rvol<30ml
RF< 30%
Moderate MR
Grade II/III
EROA 0,2-0,39
Rvol 30-59 ml
RF 30-49%
Severe MR
Grade IV
EROA >0,4 cm2
Rvol >60 ml
RF >/=50%
AHA Guidelines
ESC Guidelines
CABG only
CABG without RA
in small LV
In large LV
consider RA +
PMA
CABG+ Chordal-sparing MVR
if LVEF >30%
or LVEF <30% but with an option
for revascularization and evidence
of myocardial viability.
Mild MR
Grade I
EROA< 0,2 cm2
Rvol<30ml
RF< 30%
Moderate MR
Grade II/III
EROA 0,2-0,39
Rvol 30-59 ml
RF 30-49%
Severe MR
Grade IV
EROA >0,4 cm2
Rvol >60 ml
RF >/=50%
HEART TEAM
GDMT
CRT/ICD if
indicated
Surgical Risk
Assessement
Persistent
symptoms despite
optimal medical
management
AHA Guidelines
ESC Guidelines
GDMT
Periodic monitoring
LVEF>30%
Low Operative Risk
LVEF<30%
Or High Operative Risk
Chordal-sparing
MVR
Heart
Transplantation
LV assistant device
Percutaneous
edge-to-edge
repair
(only for ESC)


A
Before : severe central ischemic SMR
B
C
After implantation of one central clip
D