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Treatment options for ischemic mitral regurgitation: a meta-analysis

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28 **Central Message**

29 Ischemic mitral regurgitation can be treated in a variety of ways, with some conferring greater
30 survival benefits compared to others.

31

32 **Perspective Statement**

33 Ischemic mitral regurgitation is a complex condition with multiple treatment options available
34 depending on clinical factors and valve-related factors. Additional Randomized Clinical Trials
35 between the choice of mechanical intervention and optimal medical therapy are needed to
36 better define the optimal treatment strategies tailored to individual patients with ischemic
37 mitral regurgitation.

38

39

Abstract

Background. Treatment of ischemic mitral regurgitation (IMR) is in evolution as percutaneous procedures and complex surgical repair have been recently investigated in randomized clinical trials and matched studies. This study aims to review and compare the current treatment options for IMR.

Methods. A comprehensive literature search was conducted using electronic databases. The primary outcome was all-cause long-term mortality. The secondary outcomes were perioperative mortality, unplanned rehospitalization, reoperation, and composite endpoints as defined in the original articles.

Results. A total of 12 articles met the inclusion criteria and were included in the final meta-analysis. The MitraClip procedure did not confer a significant benefit in mortality and repeated hospitalization compared to medical therapy alone. In patients with moderate IMR, the adjunct of mitral procedure over CABG is not associated with clinical improvements. When evaluating mitral valve (MV) replacement vs repair, hospital mortality was higher among patients undergoing replacement (OR 1.91, $P=0.009$), but both reoperation and readmission rates were lower (OR 0.60, $P=0.05$ and OR 0.45, $P<0.02$, respectively). Comparing restrictive annuloplasty alone with adjunctive subvalvular repair, subvalvular procedures resulted in fewer readmissions (OR 0.50, $P=0.06$) and adverse composite endpoints($P=0.009$).

Conclusions. MitraClip procedure is not associated with improved outcomes compared with medical therapy. MV replacement is associated with increased early mortality but reduced reoperation rate and readmission rate compared to MV repair using annuloplasty in moderate-to-severe IMR. Despite no significant benefit in isolated outcomes comparing annular and adjunct subvalvular procedures, the adjunct of subvalvular procedures reduces the risk of major postoperative adverse events.

65

66 **Keyword:** Mitral Valve, Mitral Valve Repair, Mitral Valve Replacement, Ischemic Mitral
67 Regurgitation

68

69

70 **Abbreviations list**

71 ARB: angiotensin receptor blocker

72 CABG: coronary artery bypass graft

73 CI: confidence interval

74 EROA: effective regurgitant orifice area

75 GDMT: guideline directed medical therapy

76 HF: heart failure

77 IMR: ischemic mitral regurgitation

78 LVEDD: left ventricular end diastolic diameter

79 LVEDV: left ventricular end diastolic volume

80 LVEF: left ventricular ejection fraction

81 MACE: major adverse cardiovascular events

82 MI: myocardial infarction

83 MV: mitral valve

84 MVRpl: mitral valve replacement

85 PMA: papillary muscle approximation

86 RCT: randomized controlled trial

87 RMA: restrictive mitral annuloplasty

88

Introduction

The optimal choice of treatment for moderate-to-severe ischemic mitral regurgitation (IMR) remains a challenge within the cardiology and cardiac surgery community despite the recommendations of current guidelines. This is particularly true for patients with significant left ventricular dysfunction. The majority of patients with moderate-to-severe IMR in North America and Europe are mainly directed to the treatment of their underlying cardiomyopathy using guideline directed medical therapy (GDMT) and resynchronization (CRT)[1-3]. Resistance by the heart team to directly recommend a surgical procedure can be explained, at least in part, because a significant clinical benefit of mitral valve surgery has not been confirmed by rigorous randomized controlled trials (RCTs). No survival benefit is noted for patients undergoing surgery compared to those who receive GDMT, with a recognized improvement in symptoms for recipients of MV surgery[3-7]. The role of MV surgery as the first approach to improve clinical outcomes remains in evolution[8]. In addition, patients with severe IMR and left ventricular systolic dysfunction with suitable coronary targets affected by high-grade proximal stenosis should receive CABG and a mitral valve procedure. In these cases, revascularization with coronary artery bypass graft (CABG) should be considered because it improves long-term prognosis and all-cause mortality[9].

In patients with moderate IMR, advocating repair of the mitral valve in addition to CABG remains debatable as reported in a recent RCT[4]. Although the benefits in terms of outcomes without an increase in perioperative complications are uncertain, the benefits seen in patients with remodeled ventricles and scar favor combined MV repair and CABG[10]. The use of percutaneous therapy in patients with IMR who do not need coronary revascularization has shown benefit in the COAPT RCT and in contrast, no benefit in the MITRA-FR RCT [11, 12].

To address the differences in RCT results, we performed a meta-analysis of the clinically different groups of patients who were treated for moderate-to-severe IMR in an attempt to overcome the limitations of individual trials and propensity-matched observational series in detecting differences in clinical outcomes.

Methods

Protocol and registration

The design of the analysis was first published in the International Prospective Register of Systematic Reviews (ID#146937). This meta-analysis follows the guidelines of the Cochrane Handbook and Meta-analysis of Observational Studies in Epidemiology guidelines[13] and was written according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. Further details on the methodology is available in the online supplement (**Supplementary file: “Detailed methodology of meta-analysis”**).

In brief, patients with ischemic mitral regurgitation included in randomized trials and propensity-score observational studies were included in this study. Evaluated interventions were guideline-directed medical therapy (GDMT), mitral valve repair (percutaneous and surgical), mitral valve replacement associated with myocardial revascularization. **Surgical mitral valve repair refers to restrictive annuloplasty with rings that can be associated with subvalvular procedures (papillary muscle approximation or relocation), while percutaneous MV repair refers to Mitraclip procedure.** Comparisons were performed between GDMT alone and combined with either a MitraClip procedure, mitral valve replacement (MVRpl) and mitral valve repair (MVR), restrictive mitral annuloplasty (RMA) and restrictive mitral annuloplasty plus papillary muscle approximation (RMA+PMA), CABG alone and combined to RMA. A literature search was performed through PubMed, Embase, EBSCO, Cochrane

database of systematic reviews, and Web of Science from its inception up to April 2, 2019 using the following search keywords (and their MeSH terms when available) in various combinations: “mitral valve”, “repair”, “replacement”, “ischemic mitral regurgitation”, “MitraClip”, “ischemic mitral disease”, “subvalvular”, “annular”, “coronary artery bypass graft”. Only English language studies with full publications were considered for this study.

Data Extraction and Quality Assessment (Risk of bias)

Data extraction was performed independently by 2 investigators (F.N. and A.N) (Supplementary Figure 1, Supplementary Table 1, Supplementary Table 2, Supplementary Table 3). The following variables were included: study details (sample size, number of centers, institutions involved, publication year, study period, design and country, length of follow-up), patient demographics (age, sex, diabetes mellitus, and ejection fraction) and procedural (GDMT, Mitraclip, Surgery) and postoperative data. The methodological quality of the selected studies was assessed with the Cochrane risk-of-bias tool for RCTs, and with the Newcastle-Ottawa scale scoring for non-randomized studies. Only RCTs and observational studies of high quality (Newcastle–Ottawa Scale score>6) were included in the final analysis (Supplementary Figure 2).

Outcomes

The primary outcome was all-cause long-term mortality. The secondary outcomes were perioperative mortality (30-day or in-hospital mortality), unplanned rehospitalization (readmission during follow-up), reoperation, and composite endpoint as defined in the original articles. Study-level analyses were conducted for primary and secondary outcomes.

Data synthesis & statistical analysis

Measures of treatment effect and summary measures

Analysis of outcome variables was carried out using the odds ratio (OR) with 95% confidence interval (CI) as the summary statistic. Summary estimates were calculated using the random-effect model considering the clinical heterogeneity among the studies in terms of inclusion criteria, baseline characteristics and time frame of endpoints.

Assessment of heterogeneity

Inter-study heterogeneity was examined with the Cochran's Q (χ^2) test, and we further quantified inconsistency by calculating I², interpreted using the following guide: 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; and 75% to 100% may represent considerable heterogeneity.

Statistical software

Statistical analysis was performed with Review Manager (RevMan) version 5.3 from The Cochrane Collaboration.

Results

Study selection and characteristics

From 1,846 titles of manuscripts, 26 pertinent studies were identified and included in a full-text review. After review, 14 articles were excluded because they reported unmatched observational series and did not meet the inclusion criteria while 12 articles met the inclusion criteria and were included in the final meta-analysis (**Supplementary Figure 1**). Five studies

were international and multicenter, 2 studies were from Canada, 2 from Italy and 1 each from the United Kingdom, USA and France (**Supplementary Table 1**).

Results of individual studies

A total of 2848 patients were included (GDMT plus MitraClip vs GDMT, 918 patients in 2 studies; CABG plus RMA vs CABG, 615 patients in 5 studies; MVRpl vs RMA, 1109 patients in 3 studies and RMA plus PMA vs RMA 206 patients in 2 studies) from 8 RCTs (n=1772) and 4 observational studies(n=1076). Demographic data are shown in **Table 1 and Supplementary Table 1**.

Risk of bias assessment

Risk of bias assessment is summarized in **Supplementary Figure 2**.

Synthesis of results (Table 2)

MitraClip vs optimal medical therapy

Two studies were included[11, 12] with a pooled sample size of 464 patients treated with GDMT alone and 454 patients treated with MitraClip. No differences were found in terms of hospital mortality(P=0.36), death at follow-up(P=0.44), hospital readmission(P=0.34) and MACEs(P=0.21). Reoperation was more common in patients discharged on GDMT alone (for MitraClip; OR 0.40; 95%CI 0.22-0.72; P=0.003) (**Figure 1 & Table 2**).

CABG alone vs CABG associated with mitral valve procedure

Five studies were included[5, 6, 14-16] with a pooled sample size of 314 patients treated with CABG alone and 301 patients treated with CABG and mitral valve procedure. No differences were found in terms of hospital mortality(P=0.73), death at follow-up(P=0.71), hospital

readmission(P=0.58), reoperation (P=0.16) and MACEs(P=0.40). However, reoperation was evaluated only in two studies (Chan et al[14]., Michler et al.[5] and this might have influenced the results (Figure 2 & Table 2).

Mitral valve replacement vs mitral valve repair

Three studies were included[4, 17, 18] with a pooled sample size of 556 undergoing MV repair and 553 patients undergoing MV replacement. No differences were found in terms of long-term mortality (P=0.43). However, hospital mortality was higher among patients undergoing MV replacement (OR 1.91; 95%CI 1.18-3.12, P=0.009; OR refers to the MV replacement compared to MV repair group), but both reoperation and readmission rates were lower (OR 0.60; 95%CI 0.36-1.00; P=0.05 and OR 0.45; 95%CI 0.23-0.87; P=0.02, respectively). No differences were found in terms of composite adverse events (Figure 3 & Table 2).

Restrictive annuloplasty vs restrictive annuloplasty with subvalvular repair

Two studies were included[3, 7] with a pooled sample size of 103 patients in each group. No differences were found in terms of long-term mortality (P=0.55), hospital mortality (P=0.55), and reoperation rates (P=0.19). However, RMA with subvalvular procedures resulted in a trend towards fewer readmissions (OR 0.50; 95%CI 0.24-1.02; P=0.06 where OR refers to the associated subvalvular repair group compared to RMA only group) and adverse composite endpoints (OR 0.30; 95%CI 0.12-0.74; P=0.009) (Figure 4 & Table 2).

Discussion

This is the first meta-analysis specifically addressing the differences in clinical outcomes according to the type of mechanical intervention in patients with ischemic mitral regurgitation, treated with either MitraClip procedure or “conventional” surgery, i.e. with restrictive annuloplasty **only. Due** to the lack of a consistent correlation between the choice of mechanical intervention and clinical events, a deeper understanding of the clinical impact of the type of the treatment used for moderate-to-severe IMR seems of major relevance[19, 20]. In this study-level meta-analysis of RCTs and adjusted or matched observational studies we compared the different strategy for the treatment of moderate-to-severe ischemic mitral regurgitation (**Figure 5, Figure 6**).

The percutaneous approach

Patient selection is essential for MitraClip procedure in patients with ischemic mitral regurgitation. The use of MitraClip procedure was associated with a significantly lower risk of reoperation compared to the use of GDMT alone at a mean follow-up of 15.8 months. The clinical benefit associated with the use of MitraClip procedure is by pathoanatomical and pharmacological means as it was more evident in correcting geometric changes of mitral valve than medical treatment alone including renin-angiotensin system inhibitors[21-28] and beta-adrenergic blockade[29-35] on reducing mitral regurgitation. These medications work by attenuating LV remodeling in chronic severe MR[36, 37] often in association with temporary use of diuretics[38].

The MitraClip procedure did not offer significant benefits in terms of mortality and repeated hospitalizations compared to medical therapy alone in ischemic mitral regurgitation. These results may due to the MITRA-FR[12] and COAPT[11] study enrolling two distinctly different patient cohorts (**Table 3**). The patients in the MITRA-Fr RCT had a mean LVEDV of 252 ml and an EROA of 0.31cm². Of these more than 50% had an EROA<0.3 cm², and

only 16% had an EROA $\geq$ 0.4cm². Conversely patients in the COAPT trial had a mean LVEDV of 192 ml, with a mean EROA of 0.41 cm². A small percentage (14%) of patients had an EROA<0.3 cm² with 41% had an EROA $\geq$ 0.4cm². When comparing the two RCTs we noted that in the patients of COAPT study EROA was ~30% greater but their LV volumes were ~30% lower compared with those of MITRA-FR study. As a result, the patients in COAPT had severe and disproportionate MR compared to MITRA-FR who had severe and proportionate MR or non-severe MR.

The difference between proportionate and disproportionate MR is reflected by the results following GDMT. Neurohormonal antagonist administration reduces morbidity and mortality in patients with IMR and chronic heart failure leading to a decreased of LVEDV[21, 24, 29, 30, 36, 37]. These patients showed a reduction of mitral regurgitation if the degree of MR is proportionate to the LVEDV[12]. Therefore, the effect of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) decrease the magnitude of MR primarily in mild-to-moderate MR[12]. A double blinded randomized trial reported that the addition of a neprilysin inhibitor to ARB (Sacubitril/Valsartan) improved MR in patients who have LVEDV>200 ml and mild-to-moderate MR[25]. Patients with marked LVEDD>6.8cm, however, had little to no improvement from medical therapy[25]. Losartan was noted to have anti-apoptotic and anti-fibrotic effects by transforming growth factor (TGF- β) inhibition. This opposes mitral valve fibrosis post-MI which is associated with excessive endothelial-to-mesenchymal transition, driven by TGF- β overexpression. Its reduction in leaflet thickness and favorable results of therapy are noted by modulation of profibrotic changes of tethered MV leaflets post-MI without eliminating adaptive growth[27]. A recent study showed maximally tolerated doses of neurohormonal antagonists sufficiently decreased regurgitant flow in ~40% of patients with severe MR at up to 4-years follow-up and severe MR was only noted in a third of patients[28].

A double-blind placebo-controlled trial showed metoprolol was effective in ameliorating functional MR in more than 40% of treated patients (vs <20% of the control group) in patients with reduced EF, and LVEDV ~200 ml (28). Another RCT showed metoprolol therapy reduced LV end-diastolic dimensions from 73 to 64 mm and decreased the MR grade[30]. Carvedilol causes reverse remodeling with a reduction of MR ratio ameliorating functional MR in patients with ischemic or non-ischemic cardiomyopathy primarily in mild-to moderate MR and reduced LVEF[31-34]. In another report, carvedilol reduced LVEDV and the severity of MR with a significant reduction in EROA in 30% of patients. The action of betablocker was most pronounced in LV end-diastolic dimension>37 mm/m² that corresponds to a LVEDV of ~250 ml[32]. 80% of patients with chronic HF due to idiopathic cardiomyopathy had improvements in MR 1 year post carvedilol therapy (LVEDV of 230.5±80.7 ml, and MR estimated at 2.15±1.09)[34]. B-blocker administration reduced EROA dimension by 80% in a study of patients with chronic heart failure (17 dilated/ischemic vs 28 non-ischemic cardiomyopathy) with severe mitral regurgitation with low ejection fraction (24±7%) at 6 months follow-up[35]. The target action of drug therapy was not found to be a significant effect modifier to limit the geometric disturbance and detrimental effect of tethering forces, avoiding the need for intervention when the degree of MR is disproportionate to LVEDV[6].

The role of conventional (“annular”) surgery

The use of conventional surgery (with restrictive annuloplasty) to treat severe IMR is recommended by current guidelines and the position papers of professional societies, predominantly on the basis of randomized clinical trials that have reported a benefit with regards to outcomes after mitral valve-sparing operations. The RCT from CTSN has contradicted many reports based on large observational studies that have reported a benefit with regard to outcomes after mitral-valve repair over replacement, including lower operative

311 mortality, improved LVEF, and higher rates of long-term survival[39-41]. These results were
312 confirmed in a meta-analysis showing the relative long-term risk of death was 35% higher in
313 patients who underwent mitral valve replacement than in those who underwent conservative
314 surgical repair[42]. One of the reasons for these conflicting results is that the superior clinical
315 outcomes associated with mitral valve repair that have been reported in registries have not
316 been replicated in the RCTs. There are concerns that observational studies may be biased in
317 favor of MV repair due to the presence of unmatched confounders related to the surgical
318 preference of dedicated MV surgeons alongside baseline characteristic of patients. For
319 example, patients who underwent MVRpl tended to be older and had more coexisting
320 illnesses than those who had surgical repair, thus adjustments for baseline differences are
321 essential in non-randomized studies. The RCTs that compared MV repair versus replacement
322 have not individually shown a difference in clinical outcomes. The present meta-analysis
323 aimed to overcome the limitations of individual reports by pooling the data from randomized
324 clinical trials and adjusted or matched observational studies. Although we observed no
325 differences in terms of long-term mortality, reoperation, readmission rates and composite end
326 point between patients who received mitral valve repair and those who had mitral valve
327 replacement, hospital mortality was higher in the MV repair group. In patients who are not
328 suitable for CABG and have reduced left ventricular function, the surgeon should ensure that
329 no more than trace-to-mild mitral regurgitation is present post-repair because the persistence
330 of moderate mitral regurgitation may worsen ventricular function.

331 In patients with moderate IMR observational, non-randomized studies, and single-center
332 experiences showed both heterogeneity and contained many confounders that limited the
333 quality of evidence. Concerns relating to the lack robustness in study design, including non-
334 rigorous definitions of the degree of MR especially in patients with moderate and severe
335 degrees were also noted[3, 6, 17, 18]. The RCT from CTSN[4] reported 301 patients with

moderate ischemic MR who underwent either CABG alone or combined with restrictive mitral annuloplasty (RMA). Results revealed no significant difference in mortality rate at 2-year follow-up (HR in the combined-procedure group 0.90; 95% CI: 0.45-1.83; 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+RMA suggesting that current evidence to support concomitant mitral valve repair during CABG for moderate IMR is weak[4]. As we noted, reoperation was only evaluated in two studies potentially influencing the results of combined CABG plus mitral valve repair showed in POINT[15] and RIME trials[14], which did not translate into a significant difference in survival rate. The traditional concept of a direct relationship between more viable LV segments, less dyssynchrony at baseline[4, 43], greater reverse remodeling, better wall motion scores and resolution of MR after CABG surgery alone[4, 5, 10, 43] is biologically and patho-anatomically plausible and is indirectly supported by studies that show a significantly lower prevalence of prior myocardial infarction while potentially resulting in less LV scar tissue[4, 5, 10, 43]. In addition, these patients had a baseline LV size that was less dilated and remodeled[4]. However, variables such as excessive scar tissue formation, more pronounced dyssynchrony, lack of improvement in reverse remodeling and wall motion score were clear demonstrations that CABG alone may not lead to an improvement in the LV function and thus negatively affects the reduction of the IMR burden. Instead, the combined restrictive mitral valve annuloplasty is more likely to cause a marked reduction in the size of the left ventricle by eliminating the risk of MR recurrence.

From valvular to subvalvular apparatus

More advanced repair techniques have been proposed for moderate-to-severe mitral regurgitation, extending the repair procedure to the surgical handling of subvalvular mitral valve apparatus. The objective of surgical correction of ischemic mitral valve failure is related to the restoration of an effective competent mitral valve with potential surgical manipulation of the subvalvular apparatus. Harmel et al, in a pooled outcome reported that the combination of subannular repair with ring annuloplasty was associated with a significantly lower rate of recurrence of mitral regurgitation ≥ 2 as compared to annuloplasty alone (OR 0.27, 95% CI 0.19-0.38, $P=0.0001$)[20]. This metanalysis studied a pooled sample size of 103 patients in each group who underwent either restrictive mitral valve repair alone or combined with surgery of papillary muscle of mitral valve. We reported no difference in survival rate, hospital mortality, and reoperation. RMA with subvalvular procedures showed a slightly lower rate of readmission for worsening NYHA class and adverse composite endpoint. Although surgery of papillary muscles may seem appropriate in patients with dilated a LV, with large areas of scar tissue formation, dyskinesia, or a basal aneurysm[44], prospective trials on the use of subvalvular surgery of MV are currently insufficient to highlight improvements in postoperative tethering among patients with LV lateral wall dysfunction, persistent LV dyskinesia, and predominant apical tethering of both leaflets due to symmetric tethering

Limitations

The present analysis has several limitations. Even when a combined-analysis approach is used to analyze different strategies, the overall number of patients remain relatively small considering the disease burden of moderate-to-severe IMR. In addition, patients who were enrolled in the 12 studies were highly selected. These aspects clearly limit the external validity of our work. The different RCTs and adjusted or matched observational studies used

various surgical techniques, harvesting protocols, and postoperative secondary prevention regimens. For example, in COAPT-RCT patients presented with a disproportionate number of secondary MR as opposed to MITRA-FR. Patients with disproportionate MR[11] have the mitral disease as the primary pathology, ensuring an effective and sustainable treatment may directly improve the prognosis. In patients with proportionate MR[12], the secondary MR is linked to the severity of LV disease and prognosis may not be linked to MR treatment. In the near future, a network meta-analysis might also include other heterogeneous studies such as the Coapsys trial, which has been excluded from this metanalysis as it implies off-pump CABG[45-47]. The number of studies for each comparison is limited as this is a study-level meta-analysis; some of the reported results are not robust (with few or zero events per group) and consequently the confidence interval of the summary measure is very high. There are also several limitations regarding long term follow-up analysis in our study mainly related to differences in echocardiographic follow up. Many studies[6, 7, 14-18] did not report hazard ratios or incidence rate ratios for long-term outcomes and such data could not be derived from the original publications; therefore, such endpoints were considered dichotomous and analyzed using odds ratios. The estimated rates of patients included in the subvalvular mitral valve procedure was scarce compared to those who had an evaluation of clinical outcome in other studies including reoperation for MR recurrence that may be over-represented. Finally, the lack of rigorous randomized trials of medical treatment versus surgery in patients not suitable for CABG with reduced LVEF and moderate-severe MR does not alleviate uncertainty for the optimal treatment in both populations with severe IMR.

Conclusion

This metanalysis showed that the MitraClip procedure does not confer a significant benefit in terms of mortality and repeated hospitalizations compared to medical therapy alone among patients with ischemic mitral regurgitation. In patients with moderate ischemic mitral regurgitation, the adjunct of mitral procedure over CABG is not associated with clinical improvements in early mortality, late mortality, readmission, reoperation and composite endpoints. For patients requiring surgery with moderate-to-severe IMR, MV replacement is associated with increased early mortality but reduced reoperation rate and readmission rate compared to MV repair using annuloplasty. Despite no significant benefit in isolated outcomes comparing annular and adjunct subvalvular procedures, the adjunct of subvalvular procedures reduces the risk of major postoperative adverse events.

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Conflict of interest: none.

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Table & Figure legends

Central picture. Treatment options for ischemic mitral regurgitation.

Video legend. Main results of the study.

Table 1. Patients' characteristics.

Table 2. Summary of the outcomes of the meta-analysis.

Table 3. Difference between the randomized clinical trials COAPT and MITRA-Fr.

Figure 1. Forest plot of comparison of MitraClip vs optimal medical therapy. The solid squares denote the odds ratios, the horizontal lines represent the 95% confidence intervals, and the diamonds denote the pooled odds ratios. M-H = Mantel-Haenszel.

Figure 2. Forest plot of comparison of CABG alone vs CABG associated with mitral valve procedure. The solid squares denote the odds ratios, the horizontal lines represent the 95% confidence intervals, and the diamonds denote the pooled odds ratios. M-H = Mantel-Haenszel.

Figure 3. Forest plot of comparison of mitral valve replacement vs mitral valve repair. The solid squares denote the odds ratios, the horizontal lines represent the 95% confidence intervals, and the diamonds denote the pooled odds ratios. M-H = Mantel-Haenszel.

Figure 4. Forest plot of comparison of restrictive annuloplasty vs restrictive annuloplasty with subvalvular repair. The solid squares denote the odds ratios, the horizontal lines represent the 95% confidence intervals, and the diamonds denote the pooled odds ratios. M-H = Mantel-Haenszel.

Figure 5. Summary of main outcomes of currently available strategies for ischemic mitral regurgitation.

Hospital mortality, death, hospital readmission, reoperation and freedom from adverse events are represented in different colors. The length of each band within any circle represents the absolute number of the different types of events. "No complications" represents the number of patients who did not experience any adverse event. Number of patients in each group are shown in parenthesis. Number of events are omitted for clarity of presentation and are shown in Figures 1 to 4.

Top-left panel: the MitraClip was not associated with benefit in mortality and repeated hospitalization compared to optimal medical therapy alone.

Top-right panel: the use of RMA over CABG does not result in clinical improvements.

Bottom-left panel: mitral valve repair was associated with higher early mortality compared with mitral valve replacement. Reoperation and readmission rates were lower in mitral valve replacement.

Bottom-right panel: Combined subvalvular repair (PMA) and RMA resulted in fewer adverse events compared to RMA alone.

GDMT: guideline-directed medical therapy; CABG: coronary artery bypass grafting; RMA: restrictive mitral annuloplasty (mitral valve repair); PMA: papillary muscle approximation.

Figure 6. Graphical abstract.

476 This study-level meta-analysis evaluates the currently available options for the treatment of
477 ischemic mitral regurgitation. CABG: coronary artery bypass graft. RCT: randomized
478 controlled trial. PSM: propensity score matched study.

479

Supplementary material

Supplementary file. Detailed methodology of meta-analysis.

Supplementary Table 1. Characteristics of the included studies.

Supplementary Table 2. PICOS, data items and eligibility criteria.

Supplementary Table 3. Methodological details of the included studies.

Supplementary Figure 1. Flowchart of literature search and selection process.

‘No intervention-control comparison’= no direct comparison of intervention of interest vs control; ‘no target population’= pediatric, adult congenital and cardiac cases were not part of the target population; ‘no target endpoints’= no clear quantification of end-points as described in the section ‘objectives’; ‘no target study design’= the study was not a randomized controlled trial or a propensity-score matched cohort.

Supplementary Figure 2. Cochrane risk of bias tool and Newcastle-Ottawa scale.

Cochrane risk of bias tool for the included randomized controlled trials. Criteria:

I=Random sequence generation (selection bias);

II= allocation concealment (selection bias);

III= Blinding of participants and personnel (performance bias);

IV= Blinding of outcome assessment (detection bias) (patient-reported outcomes);

V= Incomplete outcome data addressed (attrition bias) (Short-term outcomes 2-6 weeks);

VI= Incomplete outcome data addressed (attrition bias) (long-term outcomes > 6 weeks);

VII= Selective reporting (reporting bias).

Score; ‘+’ = low risk of bias; ‘-’ = high risk of bias; ‘?’ = unclear risk of bias.

505 Newcastle-Ottawa scale for the included propensity-score matched cohorts. Criteria:

506 IA= Representativeness of the exposed cohort,

507 IB= Selection of the non-exposed cohort,

508 IC: Ascertainment of exposure,

509 ID= Demonstration that outcome of interest was not present at start of study,

510 II= Comparability,

511 IIIA= Assessment of outcome,

512 IIIB= Was follow-up long enough for outcomes to occur,

513 IIIC= complete follow-up - all subjects accounted for,

514 IIID= subjects lost to follow-up unlikely to introduce bias.

515 Score: asterisk= the study meets the specified criterion; dash= the criterion is not applicable to

516 the study

517

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