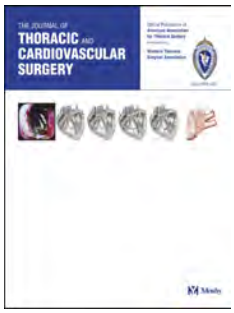
Journal Pre-proof



Treatment options for ischemic mitral regurgitation: a meta-analysis

Francesco Nappi, MD, George A. Antoniou, MD PhD MSc FEBVS, Antonio Nenna, MD, Robert Michler, MD, PhD, Umberto Benedetto, MD, PhD, Sanjeet Singh Avtaar Singh, MD, Ivan Carmine Gambardella, MD, Massimo Chello, MD

PII: S0022-5223(20)31262-9

DOI: https://doi.org/10.1016/j.jtcvs.2020.05.041

Reference: YMTC 16267

To appear in: *The Journal of Thoracic and Cardiovascular Surgery*

Received Date: 8 October 2019

Revised Date: 12 May 2020

Accepted Date: 15 May 2020

Please cite this article as: Nappi F, Antoniou GA, Nenna A, Michler R, Benedetto U, Avtaar Singh SS, Gambardella IC, Chello M, Treatment options for ischemic mitral regurgitation: a meta-analysis, *The Journal of Thoracic and Cardiovascular Surgery* (2020), doi: https://doi.org/10.1016/j.jtcvs.2020.05.041.

Treatment options for ischemic mitral regurgitation: a meta-analysis

Francesco Nappi, MD[1]; George A. Antoniou, MD PhD MSc FEBVS[2,3]; Antonio Nenna, MD[4]; Robert Michler MD, PhD[5], Umberto Benedetto, MD, PhD[6]; Sanjeet Singh Avtaar Singh, MD[7]; Ivan Carmine Gambardella, MD[8]; Massimo Chello, MD[4]

[1] Department of Cardiac Surgery, Centre Cardiologique du Nord de Saint-Denis, Paris, France

[2] Department of Vascular and Endovascular Surgery, The Royal Oldham Hospital, Pennine Acute Hospitals NHS Trust, Manchester, UK

[3] Division of Cardiovascular Sciences, School of Medical Sciences, University of Manchester, Manchester, UK

[4] Department of Cardiovascular Surgery, University Campus Bio-Medico of Rome, Italy.

[5]Department of Surgery and Cardiothoracic and Vascular Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, New York, NY.

[6]Department of Cardiothoracic Surgery, Bristol Heart Institute, University of Bristol, Bristol, United Kingdom

[7] Department of Cardiac Surgery, Golden Jubilee National Hospital, Glasgow, UK

[8] Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, USA

Funding Statement: None.

Conflict of interest Statement: None.

Article word count: 3726.

Corresponding author

Francesco Nappi, MD

Cardiac Surgery, Centre Cardiologique du Nord de Saint-Denis

36 Rue des Moulins Gémeaux, 93200 Saint-Denis, France

Tel: +33149334104

Fax: +33149334119

Email: francesconappi2@gmail.com

Treatment options for ischemic mitral regurgitation: a meta-analysis

Francesco Nappi, MD[1]; George A. Antoniou, MD PhD MSc FEBVS[2,3]; Antonio Nenna, MD[4]; Robert Michler MD, PhD[5], Umberto Benedetto, MD, PhD[6]; Sanjeet Singh Avtaar Singh, MD[7]; Ivan Carmine Gambardella, MD[8]; Massimo Chello, MD[4]

[1] Department of Cardiac Surgery, Centre Cardiologique du Nord de Saint-Denis, Paris, France

[2] Department of Vascular and Endovascular Surgery, The Royal Oldham Hospital, Pennine Acute Hospitals NHS Trust, Manchester, UK

[3] Division of Cardiovascular Sciences, School of Medical Sciences, University of Manchester, Manchester, UK

[4] Department of Cardiovascular Surgery, University Campus Bio-Medico of Rome, Italy.

[5]Department of Surgery and Cardiothoracic and Vascular Surgery, Montefiore Medical Center, Albert Einstein College of Medicine, New York, NY.

[6]Department of Cardiothoracic Surgery, Bristol Heart Institute, University of Bristol, Bristol, United Kingdom

[7] Department of Cardiac Surgery, Golden Jubilee National Hospital, Glasgow, UK

[8] Department of Cardiothoracic Surgery, Weill Cornell Medicine, New York, USA

Funding Statement: None.

Conflict of interest Statement: None.

Article word count: 3726.

Corresponding author

Francesco Nappi, MD

Cardiac Surgery, Centre Cardiologique du Nord de Saint-Denis

36 Rue des Moulins Gémeaux, 93200 Saint-Denis, France

Tel: +33149334104

Fax: +33149334119

Email: francesconappi2@gmail.com

Central Message

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

Perspective Statement

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

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.

Keyword: Mitral Valve, Mitral Valve Repair, Mitral Valve Replacement, Ischemic Mitral Regurgitation

Abbreviations list

ARB: angiotensin receptor blocker

CABG: coronary artery bypass graft

CI: confidence interval

EROA: effective regurgitant orifice area

GDMT: guideline directed medical therapy

HF: heart failure

IMR: ischemic mitral regurgitation

LVEDD: left ventricular end diastolic diameter

LVEDV: left ventricular end diastolic volume

LVEF: left ventricular ejection fraction

MACE: major adverse cardiovascular events

MI: myocardial infarction

MV: mitral valve

MVRpl: mitral valve replacement

PMA: papillary muscle approximation

RCT: randomized controlled trial

RMA: restrictive mitral annuloplasty

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. Results of reported outcomes were retrieved from the original publications or were calculated

by the authors after extracting numeric data, depending on the availability of each paper. In case of propensity score matched studies, only adjusted results were considered.

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 (with Mantel-Haenszel methods for combining results across studies) considering the clinical heterogeneity among the studies in terms of inclusion criteria, baseline characteristics and time frame of endpoints (**Supplementary file: "Detailed methodology of meta-analysis")**.

Assessment of heterogeneity

Inter-study heterogeneity was examined with the Cochrane's Q ($\chi 2$) 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. The confidence interval of I2 has been calculated and included in figures.

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≥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≥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-b) inhibition. This opposes mitral valve fibrosis post-MI which is associated with excessive endothelial-to-mesenchymal transition, driven by TGF-b 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 mortality, improved LVEF, and higher rates of long-term survival[39-41]. These results were confirmed in a meta-analysis showing the relative long-term risk of death was 35% higher in patients who underwent mitral valve replacement than in those who underwent conservative surgical repair[42]. One of the reasons for these conflicting results is that the superior clinical outcomes associated with mitral valve repair that have been reported in registries have not been replicated in the RCTs. There are concerns that observational studies may be biased in favor of MV repair due to the presence of unmatched confounders related to the surgical preference of dedicated MV surgeons alongside baseline characteristic of patients. For example, patients who underwent MVRpl tended to be older and had more coexisting illnesses than those who had surgical repair, thus adjustments for baseline differences are essential in non-randomized studies. The RCTs that compared MV repair versus replacement have not individually shown a difference in clinical outcomes. The present meta-analysis aimed to overcome the limitations of individual reports by pooling the data from randomized clinical trials and adjusted or matched observational studies. Although we observed no differences in terms of long-term mortality, reoperation, readmission rates and composite end point between patients who received mitral valve repair and those who had mitral valve replacement, hospital mortality was higher in the MV repair group. In patients who are not suitable for CABG and have reduced left ventricular function, the surgeon should ensure that

no more than trace-to-mild mitral regurgitation is present post-repair because the persistence of moderate mitral regurgitation may worsen ventricular function.

In patients with moderate IMR observational, non-randomized studies, and single-center experiences showed both heterogeneity and contained many confounders that limited the quality of evidence. Concerns relating to the lack robustness in study design, including non-rigorous definitions of the degree of MR especially in patients with moderate and severe 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 dyskinesis, 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; similarly, the wide confidence interval of the I^2 calculation for some outcomes cannot exclude potential significant heterogeneity among studies as the CI crossed the arbitrary thresholds for heterogeneity; also, the CI cannot be calculated for outcomes including 2 studies only because this implies only one degree of freedom. The outcomes were evaluated as defined in the original publications (**Supplementary Table 3**), with a significant between-study variation for the definitions of the outcomes, particularly for the composite endpoint. 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.

Acknowledgements: none.

Conflict of interest: none.

Financial support: none.

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.

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

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.

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

IA= Representativeness of the exposed cohort,

IB= Selection of the non-exposed cohort,

IC: Ascertainment of exposure,

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

II= Comparability,

IIIA= Assessment of outcome,

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

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

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

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

References

(1) Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159-e95.

(2) Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62:e147-239.

(3) Nappi F, Lusini M, Spadaccio C, Nenna A, Covino E, Acar C, et al. Papillary Muscle Approximation Versus Restrictive Annuloplasty Alone for Severe Ischemic Mitral Regurgitation. J Am Coll Cardiol 2016;67:2334-46.

(4) Goldstein D, Moskowitz AJ, Gelijns AC, Ailawadi G, Parides MK, Perrault LP, et al. Two-Year Outcomes of Surgical Treatment of Severe Ischemic Mitral Regurgitation. N Engl J Med 2016;374:344-53.

(5) Michler RE, Smith PK, Parides MK, Ailawadi G, Thourani V, Moskowitz AJ, et al. Two-Year Outcomes of Surgical Treatment of Moderate Ischemic Mitral Regurgitation. N Engl J Med 2016;374:1932-41.

(6) Mihaljevic T, Lam BK, Rajeswaran J, Takagaki M, Lauer MS, Gillinov AM, et al. Impact of mitral valve annuloplasty combined with revascularization in patients with functional ischemic mitral regurgitation. J Am Coll Cardiol 2007;49:2191-201.

(7) Fattouch K, Lancellotti P, Castrovinci S, Murana G, Sampognaro R, Corrado E, et al. Papillary muscle relocation in conjunction with valve annuloplasty improve repair

results in severe ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2012;143:1352-5.

(8) Wu AH, Aaronson KD, Bolling SF, Pagani FD, Welch K, Koelling TM. Impact of mitral valve annuloplasty on mortality risk in patients with mitral regurgitation and left ventricular systolic dysfunction. J Am Coll Cardiol 2005;45:381-7.

(9) Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, et al. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. N Engl J Med 2016;374:1511-20.

(10) Michler RE. Surgical management of moderate ischemic mitral regurgitation at the time of coronary artery bypass grafting remains controversial. J Thorac Cardiovasc Surg 2019;157:581.

(11) Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al. Transcatheter Mitral-Valve Repair in Patients with Heart Failure. N Engl J Med 2018;379:2307-18.

(12) Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al. Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation. N Engl J Med 2018;379:2297-306.

(13) Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. Jama 2000;283:2008-12.

(14) Chan KM, Punjabi PP, Flather M, Wage R, Symmonds K, Roussin I, et al. Coronary artery bypass surgery with or without mitral valve annuloplasty in moderate functional ischemic mitral regurgitation: final results of the Randomized Ischemic Mitral Evaluation (RIME) trial. Circulation 2012;126:2502-10.

(15) Fattouch K, Guccione F, Sampognaro R, Panzarella G, Corrado E, Navarra E, et al. POINT: Efficacy of adding mitral valve restrictive annuloplasty to coronary artery bypass grafting in patients with moderate ischemic mitral valve regurgitation: a randomized trial. J Thorac Cardiovasc Surg 2009;138:278-85.

(16) Bouchard D, Jensen H, Carrier M, Demers P, Pellerin M, Perrault LP, et al. Effect of systematic downsizing rigid ring annuloplasty in patients with moderate ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2014;147:1471-7.

(17) Magne J, Girerd N, Senechal M, Mathieu P, Dagenais F, Dumesnil JG, et al. Mitral repair versus replacement for ischemic mitral regurgitation: comparison of short-term and long-term survival. Circulation 2009;120:S104-11.

(18) Lorusso R, Gelsomino S, Vizzardi E, D'Aloia A, De Cicco G, Luca F, et al. Mitral valve repair or replacement for ischemic mitral regurgitation? The Italian Study on the Treatment of Ischemic Mitral Regurgitation (ISTIMIR). J Thorac Cardiovasc Surg 2013;145:128-39; discussion 37-8.

(19) Virk SA, Tian DH, Sriravindrarajah A, Dunn D, Wolfenden HD, Suri RM, et al. Mitral valve surgery and coronary artery bypass grafting for moderate-to-severe ischemic mitral regurgitation: Meta-analysis of clinical and echocardiographic outcomes. J Thorac Cardiovasc Surg 2017;154:127-36.

(20) Harmel EK, Reichenspurner H, Girdauskas E. Subannular reconstruction in secondary mitral regurgitation: a meta-analysis. Heart 2018;104:1783-90.

(21) Group CTS. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429-35.

(22) Evangelista-Masip A, Bruguera-Cortada J, Serrat-Serradell R, Robles-Castro A, Galve-Basilio E, Alijarde-Guimera M, et al. Influence of mitral regurgitation on the response

603 to captopril therapy for congestive heart failure caused by idiopathic dilated
604 cardiomyopathy. Am J Cardiol 1992;69:373-6.
605 (23) Seneviratne B, Moore GA, West PD. Effect of captopril on functional mitral
606 regurgitation in dilated heart failure: a randomised double blind placebo controlled trial.
607 Br Heart J 1994;72:63-8.
608 (24) He Z, Sun Y, Gao H, Zhang J, Lu Y, Feng J, et al. Efficacy and safety of supramaximal
609 titrated inhibition of renin-angiotensin-aldosterone system in idiopathic dilated
610 cardiomyopathy. ESC Heart Fail 2015;2:129-38.
611 (25) Kang DH, Park SJ, Shin SH, Hong GR, Lee S, Kim MS, et al. Angiotensin Receptor
612 Neprilysin Inhibitor for Functional Mitral Regurgitation. Circulation 2019;139:1354-65.
613 (26) Levine AB, Muller C, Levine TB. Effects of high-dose lisinopril-isosorbide dinitrate on
614 severe mitral regurgitation and heart failure remodeling. Am J Cardiol 1998;82:1299-
615 301, a10.
616 (27) Bartko PE, Dal-Bianco JP, Guerrero JL, Beaudoin J, Szymanski C, Kim DH, et al.
617 Effect of Losartan on Mitral Valve Changes After Myocardial Infarction. J Am Coll
618 Cardiol 2017;70:1232-44.
619 (28) Nasser R, Van Assche L, Vorlat A, Vermeulen T, Van Craenenbroeck E, Conraads V, et
620 al. Evolution of Functional Mitral Regurgitation and Prognosis in Medically Managed
621 Heart Failure Patients With Reduced Ejection Fraction. JACC Heart Fail 2017;5:652-9.
622 (29) Waagstein F, Caidahl K, Wallentin I, Bergh CH, Hjalmarson A. Long-term beta-
623 blockade in dilated cardiomyopathy. Effects of short- and long-term metoprolol
624 treatment followed by withdrawal and readministration of metoprolol. Circulation
625 1989;80:551-63.
626 (30) Waagstein F, Stromblad O, Andersson B, Bohm M, Darius M, Delius W, et al.
627 Increased exercise ejection fraction and reversed remodeling after long-term treatment

with metoprolol in congestive heart failure: a randomized, stratified, double-blind, placebo-controlled trial in mild to moderate heart failure due to ischemic or idiopathic dilated cardiomyopathy. Eur J Heart Fail 2003;5:679-91.

(31) Lowes BD, Gill EA, Abraham WT, Larrain JR, Robertson AD, Bristow MR, et al. Effects of carvedilol on left ventricular mass, chamber geometry, and mitral regurgitation in chronic heart failure. Am J Cardiol 1999;83:1201-5.

(32) Kotlyar E, Hayward CS, Keogh AM, Feneley M, Macdonald PS. The impact of baseline left ventricular size and mitral regurgitation on reverse left ventricular remodelling in response to carvedilol: size doesn't matter. Heart 2004;90:800-1.

(33) Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med 1996;334:1349-55.

(34) Comin-Colet J, Sanchez-Corral MA, Manito N, Gomez-Hospital JA, Roca J, Fernandez-Nofrerias E, et al. Effect of carvedilol therapy on functional mitral regurgitation, ventricular remodeling, and contractility in patients with heart failure due to left ventricular systolic dysfunction. Transplant Proc 2002;34:177-8.

(35) Capomolla S, Febo O, Gnemmi M, Riccardi G, Opasich C, Caporotondi A, et al. Beta-blockade therapy in chronic heart failure: diastolic function and mitral regurgitation improvement by carvedilol. Am Heart J 2000;139:596-608.

(36) McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803-69.

(37) Agricola E, Ielasi A, Oppizzi M, Faggiano P, Ferri L, Calabrese A, et al. Long-term prognosis of medically treated patients with functional mitral regurgitation and left ventricular dysfunction. Eur J Heart Fail 2009;11:581-7.

(38) Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999;341:709-17.

(39) Thourani VH, Weintraub WS, Guyton RA, Jones EL, Williams WH, Elkabbani S, et al. Outcomes and long-term survival for patients undergoing mitral valve repair versus replacement: effect of age and concomitant coronary artery bypass grafting. Circulation 2003;108:298-304.

(40) Micovic S, Milacic P, Otasevic P, Tasic N, Boskovic S, Nezic D, et al. Comparison of valve annuloplasty and replacement for ischemic mitral valve incompetence. Heart Surg Forum 2008;11:E340-5.

(41) Milano CA, Daneshmand MA, Rankin JS, Honeycutt E, Williams ML, Swaminathan M, et al. Survival prognosis and surgical management of ischemic mitral regurgitation. Ann Thorac Surg 2008;86:735-44.

(42) Vassileva CM, Boley T, Markwell S, Hazelrigg S. Meta-analysis of short-term and long-term survival following repair versus replacement for ischemic mitral regurgitation. Eur J Cardiothorac Surg 2011;39:295-303.

(43) Penicka M, Linkova H, Lang O, Fojt R, Kocka V, Vanderheyden M, et al. Predictors of improvement of unrepaired moderate ischemic mitral regurgitation in patients undergoing elective isolated coronary artery bypass graft surgery. Circulation 2009;120:1474-81.

(44) Nappi F, Spadaccio C, Nenna A, Lusini M, Fraldi M, Acar C, et al. Is subvalvular repair worthwhile in severe ischemic mitral regurgitation? Subanalysis of the Papillary Muscle Approximation trial. J Thorac Cardiovasc Surg 2017;153:286-95.e2.

(45) Grossi EA, Woo YJ, Patel N, Goldberg JD, Schwartz CF, Subramanian VA, et al. Outcomes of coronary artery bypass grafting and reduction annuloplasty for functional ischemic mitral regurgitation: a prospective multicenter study (Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve). J Thorac Cardiovasc Surg 2011;141:91-7.

(46) Grossi EA, Woo YJ, Schwartz CF, Gangahar DM, Subramanian VA, Patel N, et al. Comparison of Coapsys annuloplasty and internal reduction mitral annuloplasty in the randomized treatment of functional ischemic mitral regurgitation: impact on the left ventricle. J Thorac Cardiovasc Surg 2006;131:1095-8.

(47) Mishra YK, Mittal S, Jaguri P, Trehan N. Coapsys mitral annuloplasty for chronic functional ischemic mitral regurgitation: 1-year results. Ann Thorac Surg 2006;81:42-6.

Table 1. Patients' characteristics.

Author Year	Treatment Total Number		Age, y (Mean+/-SD)		Sex (Male)		Diabetes		Previous MI		NYHA Class I/II preop		NYHA Class I/II postop		LVEF Preop		LVEF Postop		LV Dimension preop		LV Dimension postop		Mean follow up duration
MitraClip vs optimal medical therapy																							
Obadia Mitra-Fr 2018	OMT 152	OMT + Mitraclip 152	70.6±9.9	70.1±10.1	107	120	39	50	52	75	40	35	84	80	32.9±6.7	33.3±6.5	34±6	30±6	LVEDV/ml		LVEDV/ml		12 months
																			134.5±33.1 LVEDD[e]: 52.7 mm	136.2±37.4 LVEDD[e]: 53.1 mm	141.5±42.5 LVEDD[e]: 53.9 mm	134.2±37 LVEDD[e]: 52.7 mm	
Stone Coapt 2018	OMT 312	OMT + Mitraclip 302	72.8±10.5	71.7±11.8	192	201	123	106	160	156	110	130	115	171	31.3±9.6	31.3±9.1	NR	NR	LVEDV/ml		LVEDV/ml		19.6 months
																			191.0±72.9 LVEDD[e]: 61.5 mm	194.4 ±69.2 LVEDD[e]: 61.9 mm	211.4 ±94.2 LVEDD[e]: 64.3 mm	192.2±76,5 LVEDD[e]: 61.7 mm	
CABG alone vs CABG associated with mitral valve procedure																							
Michler CTSN 2016	CABG 151	CABG + RMA 150	65.2±11.3	64.3±9.6	99	106	66	76	97	103	84	95	98	107	41.2±11.6	39.3±10.9	46.1±10.5	45.6±10.0	LVESVi /ml m^2		LVESVi /ml m^2		24 months
																			54.8±24.9 LVEDD[e]: 58.0 mm	59.6±25.7 LVEDD[e]: 59.5 mm	41.2±20.0 LVEDD[e]: 53.3 mm	43.2±20.6 LVEDD[e]: 54.2 mm	
Bouchard 2014	CABG 16	CABG + RMA 15	65 ±12	69 ±7	14	12	8	4	12	9	8	8	15	14	41.5±17.4	45.7±11.4	52±2	48±2	LVEDD /mm		LVEDD/mm		9 months
																			59±8	54±7	53±1	54±1	
Chan RIME 2012	CABG 39	CABG + RMA 34	70.4±7.9	70.9±10,5	29	25	15	12	28	27	26	23	30	32	40,3±16,1	40,0±17,3	NR	NR	LVEDD /mm		LVEDD/mm		12 months
																			56.5 ±12	56.5 ±12.6	NR	NR	
Fattouch Point 2009	CABG 54	CABG + RMA 48	66 ±7	64 ±9	35	30	32	28	54	48	15	13	27	38	43±9	42±10	45±7	48±8	LVEDD /mm		LVEDD /mm		32 months
																			58±7	59±2	56±8	52±7	
Mihaljevic 2007	CABG 54	CABG + RMA 54	66 ±9.2	66 ±9.6	32	37	54	53	31	34	NR	NR	NR	NR	NR	NR	NR	NR	LVEDD /mm		NR	NR	60 months
																			56 ±6	58 ±7			
Mitral valve replacement vs mitral valve repair																							
Goldstein CTSN 2015	MVRpl 125	RMA 126	68±9	69±10	78	77	41	48	88	99	48	54	93	100	40.0±11.0	42.4±12.0	37.6±11.8	42.5±11.8	LVESVi /ml m^2		LVESVi /ml m^2		24 months
																			65.7±27.4 LVEDD[e]: 62.4 mm	61.1±26.2 LVEDD[e]: 62.8 mm	60.6±39.0 LVEDD[e]: 59.1 mm	52.6±27.7 LVEDD[e]: 57.6 mm	
Lorusso ISTIMIR 2013	MVRpl 244	RMA 244	66,1±8	66 ±7,1	169	178	86	89	244	244	48	57	159	159	34.9±2.9	35±3.2	37.7±2.7	41.2±2.9	LVEDV/ml		LVEDV/ml		96 months
																			108±18.7 LVEDD[e]: 48.0 mm	108±16.6 LVEDD[e]: 48.0 mm	NR	NR	
Magne 2009	MVRpl 184	RMA 186	66 ±10	66 ±9	110	128	53	61	NR	NR	44	80	NR	NR	40±14	45±15	NR	NR	LVEDD /mm		LVEDD /mm		72 months
																			56 ±6	58 ±7	NR	NR	
Restrictive annuloplasty vs restrictive annuloplasty with subvalvular repair																							
Nappi 2016	RMA+ S-repair 48	RMA 48	62.9±7	64.6±7.4	28	30	18	20	48	48	0	0	29	26	35.0±.5.3	35.0±3.7	44.1±6	39.9±3.9	LVEDD /mm		LVEDD /mm		48 months
																			62.7±3.4	61.4±3.7	56.5±5.7	60.6±4.6	
Fattouch 2012	RMA+ S-repair 55	RMA 55	62 ±12	62 ±8	32	34	15	14	55	55	38	39	46	43	42±8	42±5	46±5	45±4	LVEDD /mm		LVEDD /mm		60 months
																			58 ±8	58 ±2	50 ±7	54 ±8	

LVEDD[e]: mean estimated left ventricular end diastolic diameter (based on Simpson's approximation). MI: myocardial infarction. LVEF: left ventricular ejection fraction. NR: not reported. LVESV: left ventricular end systolic volume. LVEDD: left ventricular end diastolic diameter. LVEDV: left ventricular end diastolic volume. RMA: restrictive mitral annuloplasty. S-repair: subvalvular repair. MVRpl: mitral valve replacement. CABG: coronary artery bypass grafting. OMT: optimal medical therapy.

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

	Long-term mortality	Hospital mortality	Reoperation	Readmission	Composite endpoint
MitraClip (N=454) vs optimal medical therapy (N=464)	0.77 (0.40-1.49) P=0.44	3.35 (0.25-44.7) P=0.36	**0.40 (0.22-0.72) P=0.003**	0.35 (0.04-3.06) P=0.34	0.39 (0.09-1.73) P=0.21
CABG associated with mitral valve procedure (N=301) vs CABG alone (N=314)	1.10 (0.67-1.79) P=0.71	0.84 (0.31-2.24) P=0.73	2.96 (0.64-13.63) P=0.16	0.53 (0.05-5.07) P=0.58	0.72 (0.33-1.56) P=0.40
Mitral valve replacement (N=553) vs mitral valve repair (N=556)	1.12 (0.85-1.48) P=0.43	**1.91 (1.18-3.12) P=0.009**	**0.60 (0.36-1.00) P=0.05**	**0.45 (0.23-0.87) P=0.02**	0.95 (0.74-1.21) P=0.68
Restrictive annuloplasty with subvalvular repair (N=103) vs restrictive annuloplasty alone (N=103)	0.78 (0.35-1.73) P=0.55	0.70 (0.21-2.28) P=0.55	0.39 (0.09-1.61) P=0.19	**0.50 (0.24-1.02) P=0.06**	**0.30 (0.12-0.74) P=0.009**

In table, data are presented as odds ratio (OR) with 95% confidence interval, with the corresponding overall P value. OR refer to the comparison between the first group and the second group in the treatment group.

a) an OR > 1 favors optimal medical therapy, an OR < 1 favors optimal medical therapy plus MitraClip

b) an OR > 1 favors CABG alone, an OR < 1 favors CABG associated with mitral valve procedure

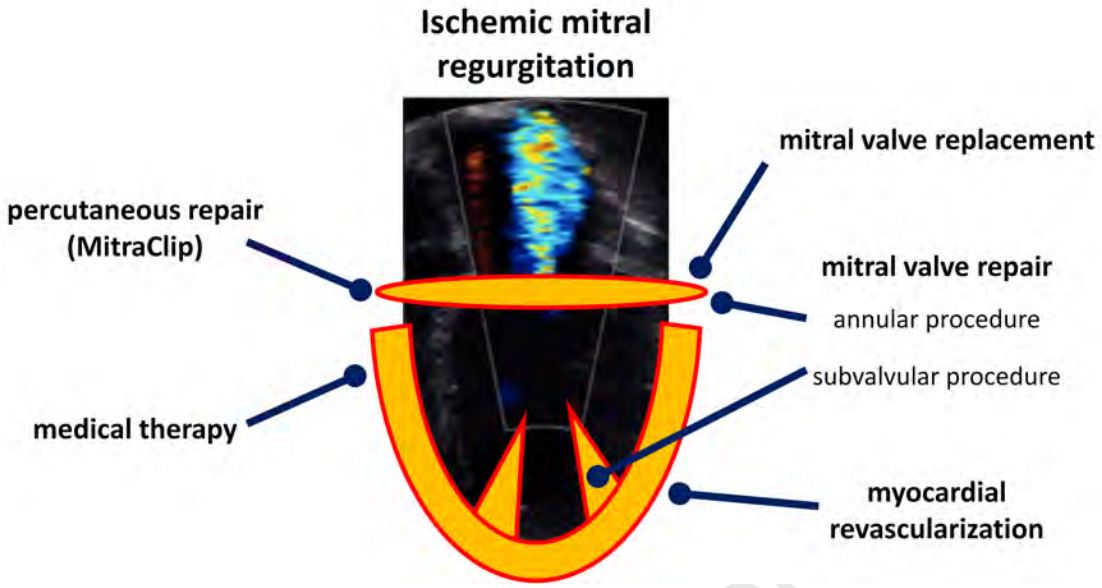
c) an OR > 1 favors MV repair, an OR < 1 favors MV replacement

d) an OR > 1 favors restrictive annuloplasty alone, an OR < 1 favors restrictive annuloplasty with subvalvular repair

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

	Mitra-FR (n=304)	COAPT (n=614)
Type of study	Institutional RCT	Sponsored by Abbott
Year of enrollment	2013-2017 (3 years and 4 months)	2012-2017 (3 years and 4 months)
Number of centers	37 (France)	89 (US et Canada)
Inclusion criteria		
Criteria for severe functional mitral regurgitation	EROA> 0.2 cm^2 or Regurgitant Volume > 30 ml (ESC guidelines). EROA mean value 0.31 cm2, 50% EROA <0.3 cm^2, 16% >/=0.4 cm^2	MR Grade 3/4 EROA > 30 mm^2 or Regurgitant Volume > 45 ml (ACC/AHA guidelines) EROA mean value 0.41 cm^2; 14 % EROA <0.3 cm^2; 41% >/=0.4 cm^2
At least 1 hospitalization for heart failure in the year	100% (inclusion criteria)	58,3% device group vs 56.1% OMT
Mode of inclusion	Practitioners in charge of the patient	External adjudication committee (OMT check, drug doses +++)
Patients Included		
EROA	0.31 ± 0.10 cm^2	0.41 ± 0.15 cm^2
Of which EROA <0.3 cm2	52%	14%
LVEDV indexed	135 mL ± 35 mL/m^2	101 mL ± 34 mL/m^2
LVEF	33 ± 7 % (all LVEF ≤ 40%)	31 ± 9 % (of which18% LVEF > 40%)
LVEDD		62 mm
LVESD		55 mm
Optimal medical treatment		
	Real life treatment, adjustments according to the patient's clinical condition	Baseline: optimal dose medical treatment. Few changes during follow-up
MitraClip Procedure		
Immediate results: failure	9%	5%
Immediate Outcomes: Residual MR ≥ Grade 3/4	9%	5%
Number of Clips	**46% treated with a single clip,** 45% with 2 clips, 9% by 3 or more clips	36% treated with a single clip, **54% with 2 clips**, 8.2% by 3 or more clips
Peri-procedural complications	14.6%	8.5%
Mortality at 30 days	3.3%	2.3%
Recurrent MR ≥ grade 3/4 at 1 year	17%	5%
Main Findings		
Follow-up	12 months	24 months
Death	Slightly higher in device group. MitraClip 24,3% vs OMT 22,4%. HR; 1.11; 95% CI,0.69 to 1.77	Lower rate with device treatment. MitraClip 29,1% vs OMT 46,1%. HR, 0.62;95% CI, 0.46 to 0.82; P<0.001
Hospitalization for heart failure	No difference in unplanned hospitalization rate. MitraClip 48.7% vs OMT 47.4%. HR 1.13; 95% CI 0.81 to 1.56.	Lower rate of unplanned hospitalization in device group. MitraClip 35.8% vs OMT 67.9%. HR 0.53; 95% CI 0.40 to 0.70; P<0.001
Death or Hospitalization for heart failure	Slightly higher in device group. MitraClip 54,6% vs OMT 51,3%. HR,1.16; 95% CI,0.73 to 1.84; P=0.53	

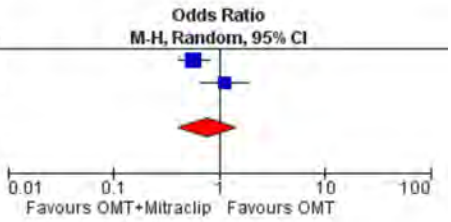
Mitra-FR MR proportionate MR	**COAPT Disproportionate MR**
Average patients' value. LVEDV 252 ml; EROA 0.31 cm^2	Average patients' value. LVEDV 192 ml; EROA 0.41 cm^2.



Mortality

Study or Subgroup	OMT+Mitraclip Events	Total	OMT Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Stone	80	302	121	312	54.7%	0.57 [0.40, 0.80]	2018
Obadia	37	152	34	152	45.3%	1.12 [0.66, 1.90]	2018
Total (95% CI)		**454**		**464**	**100.0%**	**0.77 [0.40, 1.49]**	
Total events	117		155				

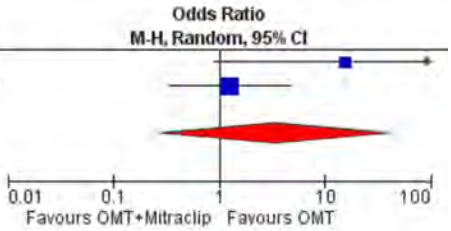
Heterogeneity: Tau² = 0.18; Chi² = 4.37, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 0.77 (P = 0.44)



Hospital mortality

Study or Subgroup	OMT+Mitraclip Events	Total	OMT Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Stone	7	302	0	312	38.6%	15.86 [0.90, 278.97]	2018
Obadia	5	152	4	152	61.4%	1.26 [0.33, 4.78]	2018
Total (95% CI)		**454**		**464**	**100.0%**	**3.35 [0.25, 44.70]**	
Total events	12		4				

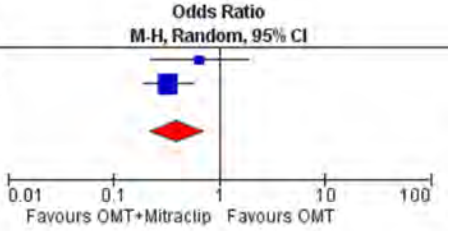
Heterogeneity: Tau² = 2.38; Chi² = 2.83, df = 1 (P = 0.09); I² = 65%
Test for overall effect: Z = 0.91 (P = 0.36)



Reoperation

Study or Subgroup	OMT+Mitraclip Events	Total	OMT Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Obadia	6	152	9	152	27.6%	0.65 [0.23, 1.88]	2018
Stone	19	302	53	312	72.4%	0.33 [0.19, 0.57]	2018
Total (95% CI)		**454**		**464**	**100.0%**	**0.40 [0.22, 0.72]**	
Total events	25		62				

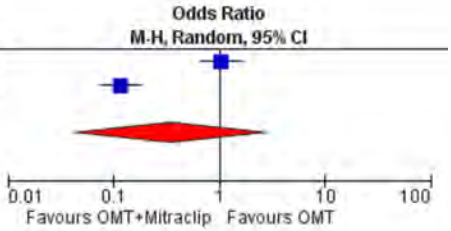
Heterogeneity: Tau² = 0.05; Chi² = 1.28, df = 1 (P = 0.26); I² = 22%
Test for overall effect: Z = 3.01 (P = 0.003)



Readmission

Study or Subgroup	OMT+Mitraclip Events	Total	OMT Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Obadia	74	152	72	152	50.0%	1.05 [0.67, 1.65]	2018
Stone	160	302	283	312	50.0%	0.12 [0.07, 0.18]	2018
Total (95% CI)		**454**		**464**	**100.0%**	**0.35 [0.04, 3.06]**	
Total events	234		355				

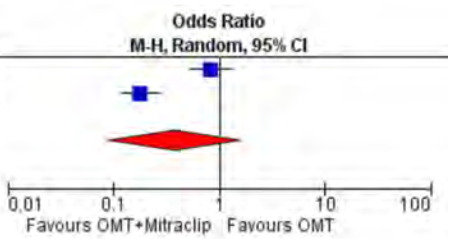
Heterogeneity: Tau² = 2.40; Chi² = 47.17, df = 1 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.95 (P = 0.34)



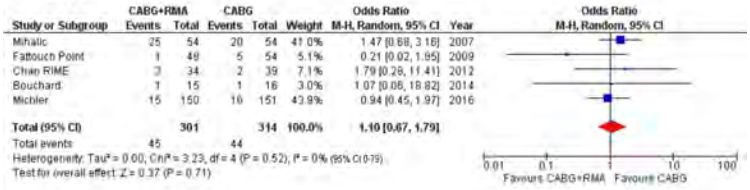
Composite endpoint

Study or Subgroup	OMT+Mitraclip Events	Total	OMT Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Obadia	65	152	72	152	49.8%	0.83 [0.53, 1.30]	2018
Stone	175	302	276	312	50.2%	0.18 [0.12, 0.27]	2018
Total (95% CI)		**454**		**464**	**100.0%**	**0.39 [0.09, 1.73]**	
Total events	240		348				

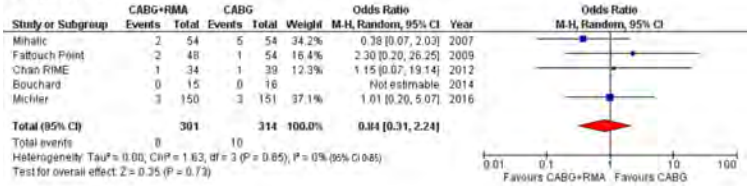
Heterogeneity: Tau² = 1.12; Chi² = 23.86, df = 1 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.25 (P = 0.21)



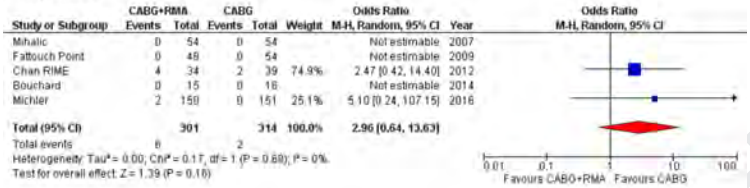
Mortality



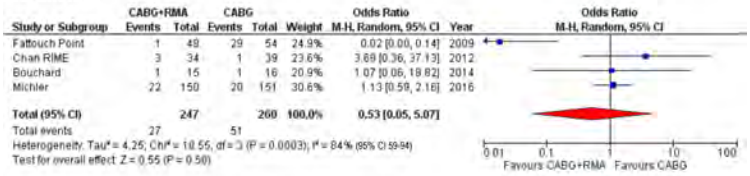
Hospital mortality



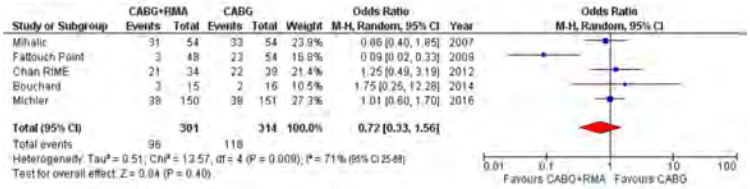
Reoperation



Readmission



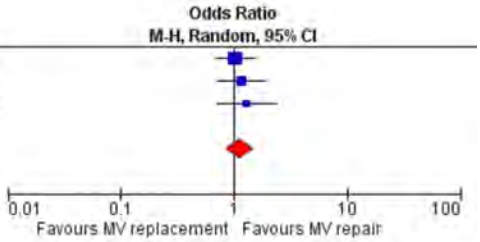
Composite endpoint



Mortality

Study or Subgroup	MV replacement Events	Total	MV repair Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Magne	96	184	96	186	46.5%	1.02 [0.68, 1.54]	2009
Lorusso	41	244	36	244	32.6%	1.17 [0.72, 1.90]	2013
Goldstein	29	125	24	126	20.9%	1.28 [0.70, 2.36]	2015
Total (95% CI)		**553**		**556**	**100.0%**	**1.12 [0.85, 1.48]**	
Total events	166		156				

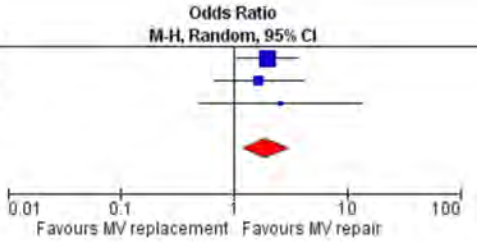
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 2 (P = 0.81); I² = 0% (95% CI 0-90)
Test for overall effect: Z = 0.80 (P = 0.43)



Hospital mortality

Study or Subgroup	MV replacement Events	Total	MV repair Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Magne	32	184	18	186	62.1%	1.96 [1.06, 3.64]	2009
Lorusso	13	244	8	244	29.3%	1.66 [0.68, 4.08]	2013
Goldstein	5	125	2	126	8.6%	2.58 [0.49, 13.57]	2015
Total (95% CI)		**553**		**556**	**100.0%**	**1.91 [1.18, 3.12]**	
Total events	50		28				

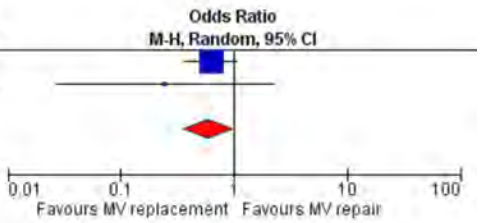
Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 2 (P = 0.89); I² = 0% (95% CI 0-90)
Test for overall effect: Z = 2.62 (P = 0.009)



Reoperation

Study or Subgroup	MV replacement Events	Total	MV repair Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Lorusso	26	244	39	244	94.5%	0.63 [0.37, 1.07]	2013
Goldstein	1	125	4	126	5.5%	0.25 [0.03, 2.23]	2015
Total (95% CI)		**369**		**370**	**100.0%**	**0.60 [0.36, 1.00]**	
Total events	27		43				

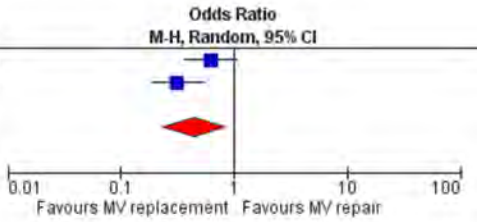
Heterogeneity: Tau² = 0.00; Chi² = 0.66, df = 1 (P = 0.42); I² = 0%
Test for overall effect: Z = 1.97 (P = 0.05)



Readmission

Study or Subgroup	MV replacement Events	Total	MV repair Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Lorusso	26	244	39	244	50.0%	0.63 [0.37, 1.07]	2013
Goldstein	59	125	93	126	50.0%	0.32 [0.19, 0.54]	2015
Total (95% CI)		**369**		**370**	**100.0%**	**0.45 [0.23, 0.87]**	
Total events	85		132				

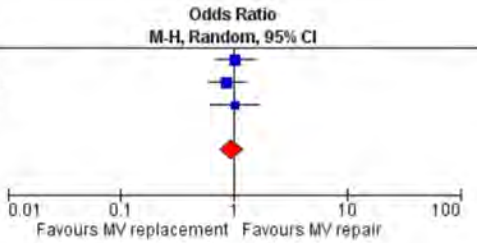
Heterogeneity: Tau² = 0.16; Chi² = 3.16, df = 1 (P = 0.08); I² = 68%
Test for overall effect: Z = 2.37 (P = 0.02)



Composite endpoint

Study or Subgroup	MV replacement Events	Total	MV repair Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Magne	97	184	97	186	36.3%	1.02 [0.68, 1.54]	2009
Lorusso	67	244	75	244	39.6%	0.85 [0.58, 1.26]	2013
Goldstein	53	125	53	126	24.1%	1.01 [0.61, 1.67]	2015
Total (95% CI)		**553**		**556**	**100.0%**	**0.95 [0.74, 1.21]**	
Total events	217		225				

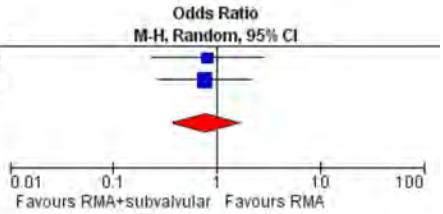
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 2 (P = 0.79); I² = 0% (95% CI 0-90)
Test for overall effect: Z = 0.41 (P = 0.68)



Mortality

Study or Subgroup	RMA+subvalvular repair Events	Total	RMA Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Fattouch	5	55	6	55	40.4%	0.82 [0.23, 2.85]	2012
Nappi	8	48	10	48	59.6%	0.76 [0.27, 2.13]	2016
Total (95% CI)		**103**		**103**	**100.0%**	**0.78 [0.35, 1.73]**	
Total events	13		16				

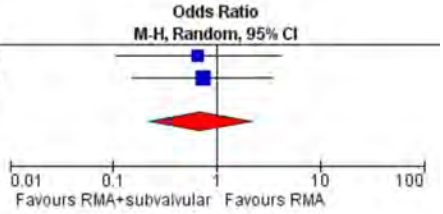
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)



Hospital mortality

Study or Subgroup	RMA+subvalvular repair Events	Total	RMA Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Fattouch	2	55	3	55	41.9%	0.65 [0.10, 4.08]	2012
Nappi	3	48	4	48	58.1%	0.73 [0.16, 3.47]	2016
Total (95% CI)		**103**		**103**	**100.0%**	**0.70 [0.21, 2.28]**	
Total events	5		7				

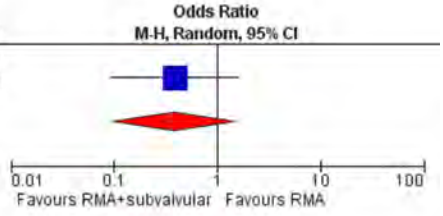
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.55)



Reoperation

Study or Subgroup	RMA+subvalvular repair Events	Total	RMA Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Fattouch	0	55	0	55		Not estimable	2012
Nappi	3	48	7	48	100.0%	0.39 [0.09, 1.61]	2016
Total (95% CI)		**103**		**103**	**100.0%**	**0.39 [0.09, 1.61]**	
Total events	3		7				

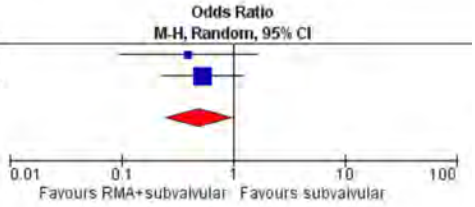
Heterogeneity: Not applicable
Test for overall effect: Z = 1.30 (P = 0.19)



Readmission

Study or Subgroup	RMA+subvalvular repair Events	Total	RMA Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Fattouch	3	55	7	55	25.9%	0.40 [0.10, 1.62]	2012
Nappi	15	48	22	48	74.1%	0.54 [0.23, 1.24]	2016
Total (95% CI)		**103**		**103**	**100.0%**	**0.50 [0.24, 1.02]**	
Total events	18		29				

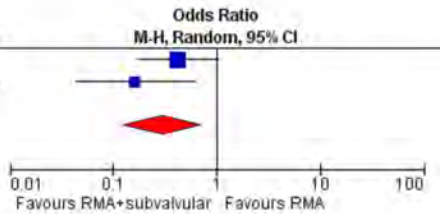
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.91 (P = 0.06)

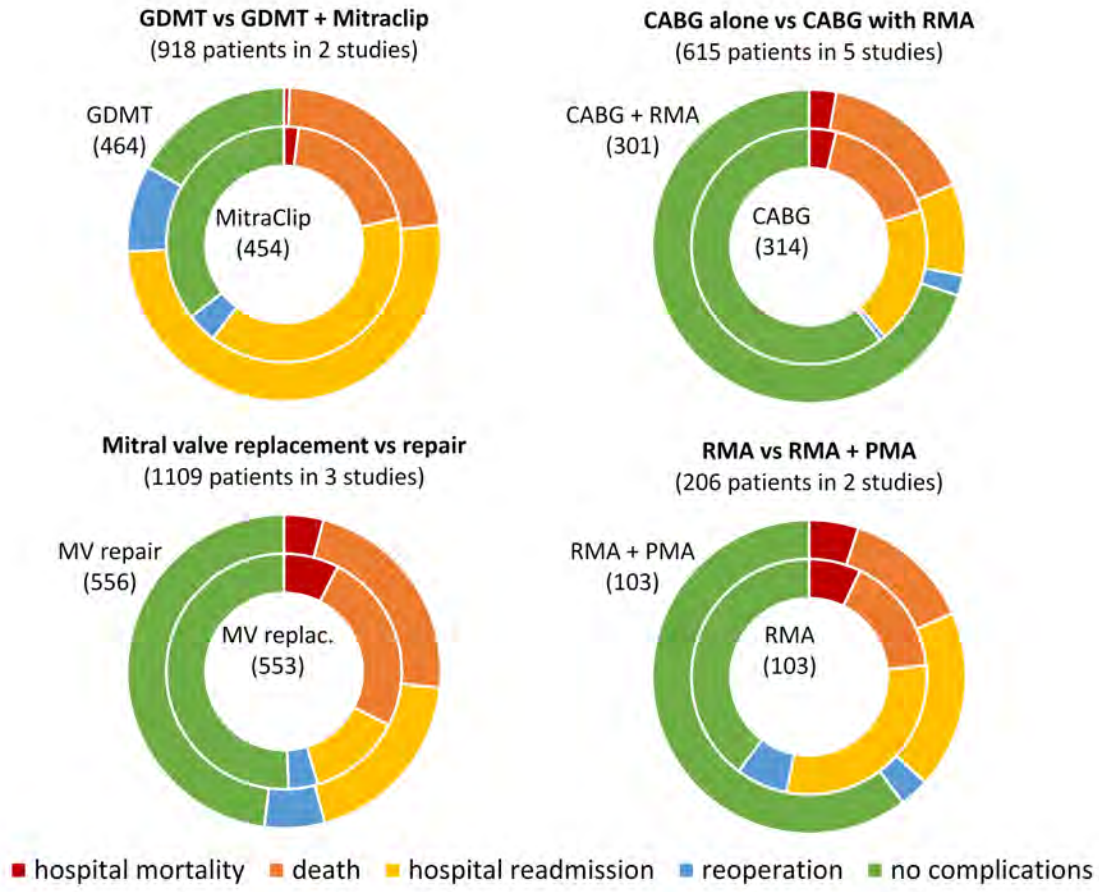


Composite endpoint

Study or Subgroup	RMA+subvalvular repair Events	Total	RMA Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Fattouch	10	55	19	55	63.8%	0.42 [0.17, 1.02]	2012
Nappi	34	48	45	48	36.2%	0.16 [0.04, 0.61]	2016
Total (95% CI)		**103**		**103**	**100.0%**	**0.30 [0.12, 0.74]**	
Total events	44		64				

Heterogeneity: Tau² = 0.13; Chi² = 1.40, df = 1 (P = 0.24); I² = 28%
Test for overall effect: Z = 2.63 (P = 0.009)




GDMT vs GDMT + Mitraclip
(918 patients in 2 studies)
GDMT
(464)
MitraClip
(454)
CABG alone vs CABG with RMA
(615 patients in 5 studies)
CABG + RMA
(301)
CABG
(314)
Mitral valve replacement vs repair
(1109 patients in 3 studies)
MV repair
(556)
MV replac.
(553)
RMA vs RMA + PMA
(206 patients in 2 studies)
RMA + PMA
(103)
RMA
(103)
hospital mortality
death
hospital readmission
reoperation
no complications

Treatment options for ischemic mitral regurgitation

- medical therapy
- percutaneous repair (MitraClip)
- CABG
- CABG + mitral valve replacement
- CABG + mitral valve repair
  - annular
  - annular + subvalvular

meta-analysis of high-quality evidences
12 studies (8 RCTs and 4 PSMs)
2848 patients

	Long-term mortality	Hospital mortality	Reoperation	Readmission	Composite endpoint
MitraClip (N=454) vs optimal medical therapy (N=464)	=	=	Mitraclip better	=	=
CABG associated with mitral valve procedure (N=301) vs CABG alone (N=314)	=	=	=	=	=
Mitral valve replacement (N=553) vs mitral valve repair (N=556)	=	Repair better	Replacement better	Replacement better	=
Restrictive annuloplasty with subvalvular repair (N=103) vs restrictive annuloplasty alone (N=103)	=	=	=	Subvalvular repair better	Subvalvular repair better

Mitral valve repair has better short-term outcomes than replacement.
The adjunct of subvalvular procedures reduces the risk of major postoperative adverse events.

Treatment options for ischemic mitral regurgitation

- medical therapy
- percutaneous repair (MitraClip)
- CABG
- CABG + mitral valve replacement
- CABG + mitral valve repair
  - annular
  - annular + subvalvular

meta-analysis of high-quality evidences
12 studies (8 RCTs and 4 PSMs)
2848 patients

	Long-term mortality	Hospital mortality	Reoperation	Readmission	Composite endpoint
MitraClip (N=454) vs optimal medical therapy (N=464)	=	=	Mitraclip better	=	=
CABG associated with mitral valve procedure (N=301) vs CABG alone (N=314)	=	=	=	=	=
Mitral valve replacement (N=553) vs mitral valve repair (N=556)	=	Repair better	Replacement better	Replacement better	=
Restrictive annuloplasty with subvalvular repair (N=103) vs restrictive annuloplasty alone (N=103)	=	=	=	Subvalvular repair better	Subvalvular repair better

Mitral valve repair has better short-term outcomes than replacement.
The adjunct of subvalvular procedures reduces the risk of major postoperative adverse events.