

# ISCHEMIC MITRAL REGURGITATION – TO REPAIR OR REPLACE? LOOKING BEYOND THE VALVE.

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## Abstract

**Introduction:** Ischemic mitral regurgitation (IMR) is a frequent and serious complication of coronary artery disease, associated with considerable patient increased mortality and morbidity. While the benefits of optimal medical therapy and surgical revascularization, when indicated, are uncontested in moderate to severe cases, the ideal surgical approach to the valve, if any, is yet to be established.

Mitral valve repair has established benefits over replacement in primary mitral regurgitation, but its superiority in the treatment of functional regurgitation has not been replicated.

Differing outcomes likely stem from the distinct IMR pathophysiology. Unlike its degenerative counterparts, IMR does not derive from direct damage to the valve leaflets, but rather from dysfunction of its sub-valvular apparatus and the left ventricular wall, in the context of acute or chronic ischaemia. Echocardiographic data points to remodelling of the left ventricle, with subsequent papillary muscle displacement, increased leaflet tethering and inefficient coaptation, as the main responsible mechanism for ischemic mitral regurgitation. Neither mitral valve repair nor replacement directly address these issues, with the appearance of the first randomized trials supporting replacement as the more durable option. However, new subvalvular procedures are improving the stability of repair techniques and the debate is long from settled.

The purpose of this review is to analyse the currently available data, couple it with our understanding of IMR's pathophysiology and compare the different outcomes for mitral valve repair and replacement.

## INTRODUCTION

Ischemic mitral regurgitation (IMR) is a frequent and serious complication of coronary artery disease (CAD).<sup>1-5</sup> Unlike primary mitral regurgitation (MR), where the mitral leaflets are diseased, IMR is grouped within the secondary mitral regurgitation (SMR) group (sometimes referred to as functional mitral regurgitation). In this subset of patients, while the leaflets are structurally normal, pathological changes in the left ventricle (LV) result in significant mitral regurgitation. Secondary MR can further be divided symmetric and asymmetric, in patients with dilated cardiomyopathy or IMR. In the case of IMR, a combination of LV abnormal regional wall motility, papillary muscle displacement

(with resulting apical tethering of the leaflets) and annular dilation contribute to this "functional" regurgitation. At its core, ischemic myocardial injury is responsible for these pathophysiological changes.

It is independently associated with increased cardiac mortality rates, even in mild cases, with direct correlation between severity and reduced survival.<sup>3</sup> Its importance to patient prognosis and difficult clinical recognisability makes it an important factor to monitor in patients with acute or chronic coronary artery disease.

The optimal treatment strategy for IMR has long remained controversial. Because the leaflets themselves are not the cause of the disease, but rather the dilated left ventricle and displaced papillary muscles, valvular surgery

does not in itself resolve the underlying mechanism of the disease. This is perhaps better illustrated by the fact that, even in the case of severe IMR, isolated valvular intervention is mired with high procedural risk, significant rates of recurrence and an absence of clear survival benefit.<sup>6,7</sup>

Another debated topic is the choice of valvular intervention. Restrictive mitral annuloplasty repair (RMA) has been touted to have lower operative mortality but has been hindered by significantly higher rates of recurrence when compared to chordal-sparing valve replacement (MVR). Studies comparing the two techniques demonstrate differing results and have contributed to the heterogenous clinical approach used in different heart centres and by different surgeons.

### The Mitral Valve Apparatus – Anatomy and Function

It is paramount to recall that the function of the mitral valve depends not only on the function of its leaflets but on the integrity and fine coordination of all the structures that make up the Mitral Valve Complex: the left atrial wall, the two mitral leaflets, the mitral annulus, the chordae tendineae and papillary muscles, as well as the left ventricular wall.<sup>8</sup> Dysfunction of the arterial blood supply to these structures is at the core of IMR.

**Chordae Tendinae and Papillary Muscles – The Subvalvular Apparatus**

The edges of the mitral valve are held below the level of the mitral orifice by the chordae tendinae, drawing the leaflets to closure and helping in the maintenance of competence. The majority of chordae tendineae originate from the anterolateral and the posteromedial papillary muscles of the left ventricle and attach mostly to the free edges of both the leaflets.<sup>9</sup>

The anterolateral papillary muscle of the left ventricle possesses a double blood supply through one or more branches from the left anterior descending coronary artery and marginal branches of the circumflex coronary artery. The arterial supply of the posteromedial papillary muscle, on the other hand, is mediated solely by branches of the posterior descending coronary artery (which arises from either the right main coronary or left circumflex coronary arteries, according to the coronary artery dominance).<sup>10</sup> This results in a greater likelihood of ischemia for the posteromedial papillary muscle, as compared to its anteromedial counterpart, in acute ischemic events.<sup>11–13</sup>

### Left Ventricular Wall

The superficial and deep layers of the myocardium are anchored at the ventricular orifices to fibrous structures of the central fibrous skeleton of the heart, suggesting that myocardial contraction plays an active role in valvular function. Changes in the left ventricular wall (such as dilatation

or akinesia) can negatively impact the function of the mitral valve, both through its connection to the fibrous structures of the heart and through the displacement of the region of myocardium immediately underlying the papillary muscles.<sup>10</sup>

### Ischemic Mitral Regurgitation - Definition

Ischemic Mitral Regurgitation is a subset of secondary mitral regurgitation. It stems from an imbalance between closing and tethering forces due to changes in the LV and LA structure and function, resulting from ischemic myocardial injury.<sup>14</sup> IMR may present acutely in the setting of myocardial infarction (MI), usually from regional wall dysfunction with papillary muscle displacement and unusually secondary to papillary muscle rupture, presenting with cardiogenic shock and hemodynamic instability. It also presents chronically, with long-standing CAD and in the absence of acute ischemia.<sup>15</sup> The remainder of this article refers to chronic IMR.

In IMR the leaflets and chordae and papillary muscle are structurally normal. It must not be confused with mitral regurgitation from other causes that coexists with ischemic heart disease (such as rheumatic heart disease or myxomatous mitral degeneration). As such, a careful clinical history and echocardiographic description of the lesions are essential to determine whether a regurgitant lesion is truly ischemic.

### Pathophysiology and Echocardiographic Diagnosis

As previously stated, ischemic myocardial injury results in reduced closing forces acting on the mitral valve, whilst geometrical changes to the LV result in increased tethering forces acting on the leaflets, the combination of the two preventing the effective coaptation of the mitral valve.

Mechanisms that generate reduced closing forces include: reduction in LV contractility, altered systolic annular contraction, reduced synchronicity between the two papillary muscles and global LV dyssynchrony (especially in basal segments).<sup>16,17</sup>

The main mechanism responsible for increased tethering forces are changes in LV configuration (remodelling).<sup>18–23</sup> The most common pattern observed involves a posterior infarction, usually transmural, leading to local LV remodelling and distortion, contributing to apical, posterior, and lateral displacement of the posterior papillary muscle. Through its chordal attachments, this displacement results in a more apical position of the leaflets and preventing correct coaptation (type IIIb dysfunction in the Carpentier's Surgical Classification of Mitral Valve Pathology).<sup>24,25</sup> In other patients, LV remodelling occurs globally, with a more spherical LV where both papillary muscles are displaced, and in which annular dilatation (type I dysfunction) also plays an important role.<sup>26</sup>

## TREATMENT

### Medical Therapy and Cardiac Resynchronization Therapy (CRT)

Optimal medical therapy (OMT) is the first-line therapy in the management of all patients with secondary MR and should be administered in accordance with the available guidelines for the management of heart failure. These include ACE inhibitors, neprilysin inhibitors, beta-blockers, sodium-glucose co-transporter 2 inhibitors, ivabradine and aldosterone antagonists. The purpose of medical treatment is to prevent further myocardial ischemia, reduce and revert LV pathological remodelling, thereby decreasing the degree of ischemic mitral regurgitation.<sup>27,28</sup>

The use of CRT should also be considered in line with the related guidelines and may result in reduction of MR severity through increased closed forces and resynchronization of papillary muscles.<sup>29</sup> It is also possible that some of the reduction in tethering forces may result from LV reverse remodelling. The decrease in severity of regurgitation in responders may correlate with increased survival.<sup>30</sup>

In case of refractory clinical symptoms despite OMT, surgical intervention should be promptly considered so as to avoid further deterioration of LV function and adverse remodelling.

## SURGICAL INTERVENTION - INDICATIONS

### Severe IMR

Current guidelines recommend valvular surgery for patients with severe IMR refractory to OMT, or those undergoing coronary artery bypass graft surgery (CABG) or other cardiac surgery.<sup>28,31</sup> These indications are restrictive when compared with primary MR, due to the high surgical risk and absence of proven survival benefit.<sup>6,7</sup>

Recently, the 2021 ESC guidelines have changed the severity criteria for IMR to meet those of the primary variant (EROA > 40 mm<sup>2</sup>; Regurgitant volume > 60 mL; Regurgitant fraction > 50%). Earlier lower thresholds (EROA > 20 mm<sup>2</sup>) were based on the poor prognosis of the disease, even in cases of mild regurgitation. However, the absence of improvement in patient outcomes with surgical and transcatheter interventions motivated a review of these numbers and a more restrictive approach was used. The paper still acknowledges that lower thresholds may be used for IMR when dealing with a more crescent shaped regurgitant orifice.<sup>28</sup>

While European guidelines do not make any recommendations as to the specific valvular procedure to perform, the ACC/AHA Guidelines for Valvular Heart Disease have since 2017 updated to recommend the choice of chordal-sparing valve replacement over restrictive mitral

annuloplasty repair (RMA) for selected patients, in light of the first randomized trial data.

Patients who are not surgical candidates should be considered for transcatheter edge-to-edge repair, the particulars of which are outside the scope of this paper.

### Moderate IMR

The optimal surgical strategy for moderate ischemic mitral regurgitation has long remained a challenge. Since a lot of patients with IMR also suffer from multivessel coronary artery disease, a lot of the discussion has revolved around whether or not to perform mitral valve surgery at the time of coronary artery bypass grafting (CABG).

The idea would be that correcting mitral regurgitation directly (either with restrictive mitral annuloplasty or mitral valve replacement) would prevent further adverse ventricular remodelling and decrease the progression of heart failure, despite the obvious added risks of open-heart surgery and longer clamping times. However, some experts believe that, given the ventricular pathophysiology of the disease (as opposed to diseased leaflets), that revascularization alone could lead to improved ventricular geometry and reduction of the regurgitation by itself.

The first randomized clinical trials (RCTs) comparing isolated CABG with combined surgery (CABG + valve procedure) for moderate IMR failed to demonstrate an improvement in hard endpoints such as all-cause mortality, major adverse events and hospital readmissions with the addition of a mitral valve procedure.<sup>32-34</sup> It is important to note that these trials were not adequately powered to evaluate mortality, although studies previously found significant correlation between reverse LV remodelling and the improvement in survival of patients with secondary MR.<sup>35,36</sup> Therefore, other endpoint such as improvements in LV remodelling, LV ejection fraction, functional class of the patients and prevalence of MR after 2 years were primarily evaluated. Interestingly enough, results were varied, with the RIME and POINT trial demonstrating improvements in LV remodelling, LVEF, MR grade and functional class with the addition of RMA. In contrast, the CTSN trial only reproduced improvements in MR prevalence after 2 years, with no statistical difference between the 2 groups in the degree of LV reverse remodelling (LV end-systolic volume index/LVESVI), New York Heart Association functional class, LV ejection fraction or major adverse cardiac and cerebrovascular events at 1 and 2 years. In this last study, RMA was associated with a longer hospital stay after surgery, a higher incidence of post-operative supraventricular arrhythmias and more postoperative neurologic events.

Several experts have analysed these discrepancies and the differences in the study sample population have been pointed out as the probable cause. Compared to the RIME and POINT trial, CTSN participants had significantly lower rate of previous MI (therefore likely to have less scar tissue), as well as significantly smaller LV size (mean base-

line of 78 mL/m<sup>2</sup> for the RIME trial vs 57 mL/m<sup>2</sup> on the CTSN trial). In the RIME trial, a 28% reduction in LVESVI from baseline was achieved with a combined procedure, as opposed to only 9% in the CTSN trial. This suggests that patients in the CTSN trial were likely to possess less scar tissue, more myocardial viability and lower degrees of LV remodelling. Therefore, they were the patients most likely to improve with CABG alone, as opposed to the patients from the RIME and POINT trials, who were more likely to benefit from the addition of a valvular intervention.<sup>37,38</sup>

The decision process for patients with moderate IMR could therefore be improved by preoperative screening of myocardial viability and papillary muscle desynchrony, though this would also require confirmation trials.

The potential for LV reverse remodelling after surgical intervention has been shown to be correlated with preoperative echocardiographic LV dimensions and has been established as quite low once a threshold of 65mm for LV end-diastolic diameter has been surpassed.<sup>39</sup> For patients where surgery seems devoid of benefit, other interventions should be considered (including left-ventricular assist devices and cardiac transplantation).

### Valve Surgery – Repair vs Replacement

Although mitral valve repair has proven benefits over replacement in primary MR, its superiority over replacement in patients with IMR has not been established.<sup>28</sup>

The most commonly used technique is the undersized/restrictive annuloplasty repair. It uses a complete rigid ring, undersized by one or two numbers with the objective of reducing the medial-lateral ventricular diameter and restoring the coaptation plane. Its proponents argue for it over lower operative mortality, preservation of ventricular geometry and avoidance of anticoagulation. However, the use of an undersized ring, whilst correcting potential annular dilations (type I mechanism), fails to address the

underlying ventricular pathology (IIIb mechanism) and the reported rate of recurrence after RMA has ranged from 15-30%.<sup>40,41</sup>

Mitral valve replacement, while also not addressing ventricular remodelling and being typically associated with increased perioperative mortality, avoids this increased risk of recurrence. Current replacement techniques also preserve the subvalvular apparatus contributing to increased preservation of LV geometry, which could nullify some of the benefits previously attributed only to valve repair. Given the poor long-term prognosis of IMR patients, the use of a bioprosthetic valve would also circumvent the need for long-term anticoagulation in patients without severely dilated LV and in the absence of atrial fibrillation.

There have been several observational studies published in the past, which have acted as the first evidence-based support for the decision-making process in patients with moderate-to-severe IMR. This evidence has been difficult to interpret given its lack of randomization, heterogeneous study populations, different endpoints and selection bias affecting the majority of retrospective studies. The use of unequal definitions of severity, varied surgical strategies, including methods employed to measure the mitral ring, as well as the diverse type of annuloplasty ring used, all introduce heterogeneity to the evaluation of these results (especially for RMA). Propensity scoring has been used in an attempt to resolve these shortcomings, with several meta-analysis having been carried out. To date, the CTSN trial remains the only randomized clinical trial comparing RMA with MVR in IMR patients.

### Peri-operative mortality

The majority of observational studies point toward inferior 30-day mortality rates in patients undergoing RMA as compared to MVR.<sup>1,42-47</sup> The same trend has been confirmed by virtually all subsequent meta-analysis.<sup>48-51</sup>

**Table 1** IMR study

Outcome evaluated	No. of studies	No. of patients	ORWMD	95% CI	p-Value
Operative mortality	10	2162	0.45	0.31, 0.65	<0.0001
5-y survival rate	9	1640	1.20	0.88, 1.65	0.25
Reoperation rate	4	839	1.25	0.34, 4.62	0.73
Recurrence of MR	4	772	5.89	3.34, 10.39	<0.00001
Acute renal failure	4	560	0.95	0.42, 2.13	0.90
Acute respiratory failure	4	560	1.20	0.59, 2.44	0.62
ICU stay (h)	2	320	-10.38	-34.26, 13.4	0.39
In-hospital stay (h)	2	320	-0.98	-2.56, 0.61	0.23

Outcomes of the meta-analysis comparing RMA with MVR for patients with IMR (adapted from Yun-Dan et al.52).

However, the single randomized clinical trial by Ack-er et al. comparing these techniques did not find a significant difference in 30-day mortality.<sup>52</sup> This discrepancy might be justified by the small number of enrolled patients, which did not confer power to the study to determine mortality as a primary endpoint, or by baseline differences in comorbidities and selection bias in the observational studies.

### Late mortality

In studies with median follow-up ranging between 12 and 36 months, the differences in late mortality between RMA and MVR were found to not be statistically significant.<sup>43,44,53,54</sup> However, other studies with follow-up length beyond 36 months demonstrated significantly reduced late mortality for the RMA arm.<sup>42,45,46,55,56</sup>

A lot of the authors of these observational studies recognize that, on par with operative mortality, the difference in long-term survival might correlate with the baseline differences in comorbidities and selection bias, with the sickest patients undergoing MVR.<sup>42,54</sup> Moreover, when propensity scoring is used to account for different baseline comorbidities, the difference is then deemed not statistically significant.<sup>47,57,58</sup> The results of the latest meta-analysis, with follow-up periods of 5 years for the included studies supports these findings.<sup>51</sup> The 2-year results on the randomized clinical trial by Goldstein et al. also concluded that there was no significant cumulative mortality difference between treatment groups, with a rate of 19.0% in the repair group and 23.2% in the replacement group (HR for RMA of 0.79; 95% [CI], 0.46 to 1.35;  $P = 0.39$ ).<sup>59</sup>

### Regurgitation recurrence

One of the main drawbacks of RMA has been the significantly higher rates of at least moderate mitral regurgitation recurrence at mid-term follow-up, which has been shown to affect survival.<sup>60,61</sup>

In virtually every observational study comparing the two techniques, replacement has been superior to repair in this aspect, offering a more durable solution, with several meta-analysis supporting these findings.<sup>48-51</sup> The results from randomized patients corroborate these results, with 58.8% of RMA patients recurring with moderate-to-severe regurgitation vs. 3.8% of MVR patients ( $P < 0.001$ ) at the two-year follow-up mark.<sup>59</sup>

While the annular downsizing procedure reduces the effective regurgitation area, it does not correct the underlying pathophysiology of ongoing LV wall remodelling (localized or generalized) and subsequent leaflet tethering resulting, in time, in recurrent regurgitation.<sup>62</sup> There have been some studies that attempted to pinpoint predictors of regurgitation recurrence. Ciarka and colleagues<sup>63</sup> studied LV and left atrial volumes and dimensions, LV sphericity index, mitral annular area, as well as mitral valve geometry parameters in patients undergoing CABG + RMA. They

concluded that, of the studied parameters, the distal mitral anterior leaflet angle (hazard ratio 1.48, 95% confidence interval 1.32 to 1.66,  $p < 0.001$ ) and posterior leaflet angle (hazard ratio 1.13, 95% confidence interval 1.07 to 1.19,  $p < 0.001$ ) were independent determinants of MR recurrence at mid-term follow-up. However, it is of note that the study included both idiopathic dilated cardiomyopathy and IMR patients. Kron et al. reviewed 116 IMR patients that underwent CABG + RMA in the randomized trial for the CTSN, using logistic regression in an attempt to determine probability of recurrence based on echocardiographic measurements or clinical characteristics. They concluded that the presence of basal aneurysms and dyskinesia were the only characteristics strongly associated with recurrent moderate or severe MR.<sup>64</sup>

The CTSN authors themselves concluded in univariable logistic regression analysis that larger LV end-systolic diameters (LVESD) ( $P = 0.02$ ) and LVESD/ring size ratio of at least 2 ( $P = 0.007$ ) were associated with recurrent MR. In multivariable models only the LVESD/ring size ratio (OR per 0.5 increase, 2.20; 95% CI, 1.05–4.62;  $P = 0.038$ ) remained significantly associated MR recurrence. According to the authors, RMA has the potential to disrupt the balance of the LV-mitral valve geometry. With the reduction of the mitral annulus relative to the LV, tethering of the MV posterior leaflet can be exacerbated after restrictive ring annuloplasty if the papillary muscles remain laterally displaced relative to the mitral annulus. Therefore, insertion of an excessively small ring could increase the LVESD/ring size ratio and lead to persistent MR or even mitral stenosis.<sup>65</sup>

Some authors suggest that a tenting height  $> 10$ mm is highly predictive of MR recurrence for isolated RMA and a subvalvular procedure should be pondered in these cases.<sup>66</sup>

### Mitral valve re-operations

Despite the higher rates of regurgitation recurrence associated with RMA, these do not correlate, in the majority of studies, with significantly higher reoperation rates. The meta-analysis by Virk et al. noted an increased trend towards reoperation among RMA patients, when earlier studies with low use of subvalvular apparatus preservation were excluded from the sensitivity analysis.<sup>50</sup> However, a more recent meta-analysis failed to reach conclusive results after pooling the results, with noted heterogeneity between studies.<sup>51</sup>

### Ecocardiographic dimensions

Given their retrospective nature, the majority of published papers do not possess comprehensive reports on echocardiographic measurements (LVEF, LVESD, LVEDD) and even fewer report on post-operative evolution. The lack of raw data has also made it impossible to conduct meta-analysis for these endpoints.<sup>50</sup> However, the few that do report on left ventricular ejection fraction and end-sys-

tolic and end-diastolic diameters after surgery, reported no significant difference between techniques in post-operative geometric improvement.<sup>55,67,68</sup> The CTSN trials reported no significant between-group difference in LVESVI at 2 years (z score = -1.32, P = 0.19).<sup>59</sup> Interestingly, the patients that underwent RMA that did NOT develop recurrent MR experienced greater reverse LV remodelling (23% in LVESVI vs 8%) compared to the MVR group.

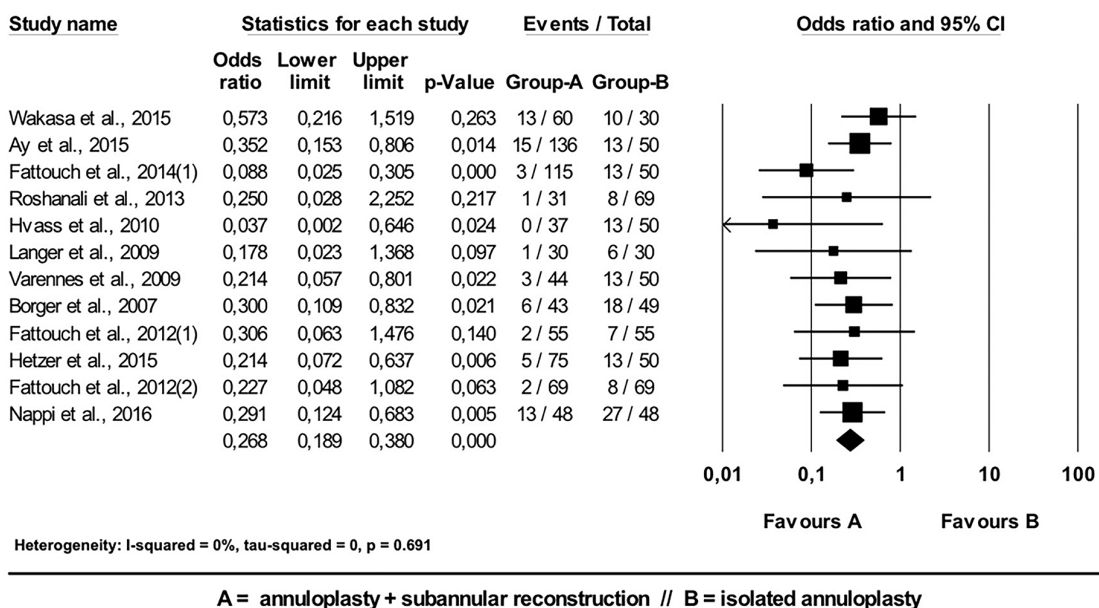
**Quality of life**

Perhaps insufficiently investigated as an outcome, there have been few noted differences in quality-of-life scores between patients undergoing different techniques. The CTSN trial reported greater overall improvement on the Minnesota Living with Heart Failure questionnaire scores among patients undergoing MVR (mean change in heart-failure symptoms from baseline was 20.0 in the repair group versus 27.9 in the replacement group [P = 0.07]). It is of note that there was greater improvement from baseline scores among patients who did not have regurgitation recurrence (26.6 for patients without recurrence vs 16.2 those with recurrence), which may justify the difference between techniques. These differences only became apparent after the 12-month mark. However, in terms of NYHA class, there were no significant differences in improvement between the different techniques.<sup>59</sup>

**Valve Surgery – Subvalvular procedures**

In order to address the shortcomings of isolated RMA and improve the stability of the repair, several subvalvular techniques have been developed to use in adjunction with annuloplasty. These are heterogenous interventions and include papillary muscle (PM) approximation, relocation, the ‘ring and string technique’, chordal cutting, posterior annulus shortening, posterior leaflet augmentation and LV ventriculoplasty. Generally speaking, they aim to reduce tethering forces acting on the valve by restoring the geometry of the subvalvular apparatus.

PM relocation: Suture anchorage (polytetrafluoroethylene) at the head of the PMs and then through ipsilateral mitral annulus. Subsequently, both PMs are relocated so as to minimise tenting. PM approximation: performed with either pledgetted mattress sutures (3–0) or with a polypropylene 4 mm Gore-Tex tube, the latter encircling the bodies of posteriormedial and anterolateral PMs, which are then drawn together. Ring and string: A Teflon-pledgetted suture (3–0 polytetrafluoroethylene) is anchored in the head of the posterior PM and then passed through the mitroaortic fibrosa, between the non-coronary and left coronary aortic cusps, exiting through the aortic wall. The suture is then tied under echocardiographical guidance. Chordal cutting: preoperative identification of the affected PM by echocardiography followed by division and cutting of secondary



**Figure 1**

Meta-analysis of late recurrence of mitral regurgitation after surgical mitral valve repair (RMA + subvalvular procedure vs isolated RMA). (adapte from Harmel et al.70).

chords from the same PM.<sup>69-72</sup>

In a recent meta-analysis of these techniques by Harmel et al., regardless of the technique used, the combination of a subvalvular procedures with RMA was associated with a 4-time lower rate of MR recurrence, compared with isolated repair, after 3 years follow-up (OR 0.27, 95% CI 0.19 to 0.38, P=0.0001).<sup>73</sup> Their evaluation of the effect on reverse LV remodelling was restricted by the limited follow-up information concerning LV geometry variables.

As evidenced in a review by Mihos and Santana, none of the studies included reported a significant increment in mortality with the addition of subvalvular procedures.<sup>74</sup>

### CONCLUSION AND FUTURE PERSPECTIVE

The best surgical approach to IMR remains a subject of considerable debate.

RMA has demonstrated clinical and echocardiographic benefits over replacement, without a clear benefit in hard endpoints, such as long-term mortality. Furthermore, a rather important subset of patients suffers from recurrent MR, which signifies demonstrated worse outcomes for the patient. This has led to replacement being recommended over repair in American guidelines. However, much of the comparison done between RMA and MVR has involved isolated annuloplasty for the majority of repair cases, with few studies including subvalvular procedures, which actually act on the diseased portion of the valvular apparatus. For those patients that exhibit predictors of MR failure/recurrence, the addition of a subvalvular procedure or the performance of replacement must be considered. It is important to better define the patients which will benefit from RMA, with an improved recognition of preoperative image-study features and patient characteristics that predict durable long-term results, as well as improved outcomes.

The search for answers remains cumbersome, as the IMR population is significantly heterogenous and their reduced prevalence makes it difficult to achieve the needed sample sizes in individual centres. Multicentred prospective trials are thus needed to adequately power studies for hard endpoints such as mortality and major adverse events, not only for the comparison of replacement vs repair techniques, but also for the ideal surgical approach in moderate IMR patients undergoing CABG. Nevertheless, the heterogeneity of this population will always require an individualized and multidisciplinary approach for each patient.

Prospective studies are also warranted to determine when and which subvalvular procedures should be used in combination with RMA. If a technique is demonstrated as replicable, it would be important to assess how the combined repair procedure compares with MVR, as it might significantly reduce the need for MVR and the latter's inherent disadvantages can be avoided.

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