The unfinished saga of invasive procedures for secondary mitral regurgitation

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Secondary mitral regurgitation (MR) is a common valvular heart disease. Its prognostic burden in patients suffering from idiopathic or ischemic cardiomyopathy (ICM) with left ventricular (LV) dysfunction/dilation has been clearly demonstrated. Severe secondary MR is associated with an increased mortality and frequent heart failure hospitalizations. Although guideline-directed medical therapy (GDMT) is the cornerstone of the management of secondary MR, a certain proportion of patients remain symptomatic. For these patients, several surgical techniques have been progressively developed during the last few decades (replacement, repair, sub-valvular apparatus interventions and other ventricular approaches). In the absence of evidence-based medicine, the benefits of these surgical procedures remains controversial, leading to a low level of recommendation in the guidelines. One way to anticipate the future is to look to the past. Recent prospective randomized trials evaluated surgical and percutaneous techniques and led to a better understanding of how best to treat this disease. In this article, we aim to describe the saga of the surgical and percutaneous treatments for secondary MR throughout the previous decades.

Keywords: Secondary mitral regurgitation (secondary MR); mitral valve repair (MVr); mitral valve replacement (MVR); percutaneous procedures; MitraClip

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Introduction

The ancient functional mitral regurgitation (MR), today defined as secondary MR, is a common valvular heart disease resulting from idiopathic or ischemic cardiomyopathy (ICM) with left ventricular (LV) dysfunction/dilation (1). The prognostic implications of secondary MR have been clearly demonstrated showing a strong association between the severity of MR and mortality as well as heart failure hospitalizations (2,3). Although guideline-directed medical therapy (GDMT) is the cornerstone of the management of secondary MR, a high proportion of patients remain quite symptomatic despite a maximal GDMT. The role of mitral valve (MV) surgery is still controversial as a consequence of limited available data, which has resulted in guidelines recommending surgery with low levels of evidence (4,5). Nevertheless, several techniques (replacement, repair, subvalvular apparatus interventions and other ventricular approaches) have been adopted over time, however, no solution has proved superior to another or altered the natural history of the underlying cardiomyopathy (6).

The best way to anticipate the future is to look to the past. In this article, we aim to describe the saga of the surgical and percutaneous treatments for secondary MR throughout the previous decades.

1990s: the "pop-off valve" theory

For many years, it was believed that the MV anatomo-functional complex had a beneficial "pop-off" function in advanced heart failure, which should be preserved. Surgical correction of MR in end-stage LV dysfunction was considered deleterious and responsible for prohibitive morbidity and mortality (7).

Early 2000s: "undersized rigid annuloplasty for everybody"

The "pop-off valve" hypothesis was soon challenged by "the Bolling theory", which promoted the efficiency of undersized annuloplasty. In 1996, Bolling's team showed for the first-time reasonable mortality when a surgical undersized annuloplasty was performed for severely symptomatic patients with LV ejection fraction (LVEF) <25%. The technique was deemed to reverse the vicious cycle while restoring valvular competency, alleviating the excessive ventricular workload and improving ventricular function (8). All cohort studies conducted during this decade revealed reasonable operative mortality in this population (1.6% to 8.2% 30-day mortality) (9,10). The technique also should have promoted durable LV reverse remodelling and improved functional class. This theory was reinforced by the results of *in vivo* studies (ischemic sheep model) showing a decrease in LV radius curvature at the basal, equatorial and apical levels following restrictive annuloplasty. Thus, for the first time, the paramount importance of maintaining the integrity of annular and subvalvular continuity during MV surgery was highlighted and it was assumed that prohibitive morbidity associated with surgical correction could be attributed to the loss of the subvalvular apparatus (rather than the loss of the "pop-off valve"). Therefore, MV repair (MVr) was always recommended over replacement. This benefit was reported (I) in both ischemic and non-ischemic patients and (II) when MV surgery was associated with coronary artery bypass grafting (CABG) surgery (11).

In this specific setting, rigid rings were preferred to fix both inter-trigonal distance and septal-lateral dimension (12). Indeed, in the mid 2000s, the gold standard in functional MR (which, later, was reclassified as secondary MR) was the annulus remodelling by a restrictive annuloplasty (downsized by 2 to 4 sizes) with a nonflexible ring (rather than flexible band) regardless of the cardiomyopathy etiology. This position was supported by both American and European guidelines in 2006 and 2007 despite a total lack of analysis comparing surgery in conjunction with medical treatment versus medical treatment alone (class IC and IIaC, respectively) (13,14).

Late 2000s: disappointing time for surgical MVr

As early as 2005, Bolling's team raised initial doubts concerning the real benefits for survival conferred by MV annuloplasty (MVA) for significant MR with severe LV dysfunction after 10 years of promoting a proactive approach in patients with secondary MR (15). The promising initial results were discounted by arguments of heterogeneous ring selection, an insufficient annular downsizing and the lack of reported data on the presence of recurrent MR at follow-up (16).

In the late 2000s, Magne *et al.* compared MV replacement (MVR) versus MVr, both associated with CABG surgery, in ischemic patients (17). Data suggested that MVr was not superior to MVR with regard to operative and overall mortality. Most importantly, this survival equivalence at long-term follow-up (12 years) was found regardless of the MR recurrence rate in the repair group—45% of MVr patients had at least mild MR (*Figure 1*). Since patients with persistent MR despite MVr had the same survival rate as patients with no recurrent MR, the question of the clinical impact of treating secondary MR was raised. Additional doubts were set forth by large retrospective studies analysing CABG alone versus CABG in conjunction with MVA in ischemic patients who were candidates for CABG surgery. Several studies suggested no clear demonstrable survival benefit conferred by MVA as the poor prognosis was related to the underlying cardiomyopathy rather than to the mitral surgery (21,22). A sudden shock wave passed through the cardiovascular surgery field and it became increasingly questionable if modern surgical strategies could really improve patients' prognosis when compared to medical therapy alone. Finally, most of the publications that shaped recommendations (even the current ones) were single-centre, retrospective studies including small populations with heterogeneous patients (primary and secondary MR, ischemic and non-ischemic secondary MR, broad inclusion criteria regardless of selection on LV dimensions). Moreover, most studies reported the retrospective results of a single treatment (surgery) with no control group. Thus, "evidence based medicine" had not yet reached the surgical world.

Early 2010s: surgeons want to understand, but...

In order to provide strong evidence-based recommendations and possibly stimulated by the fast development of percutaneous techniques, considerable efforts were made

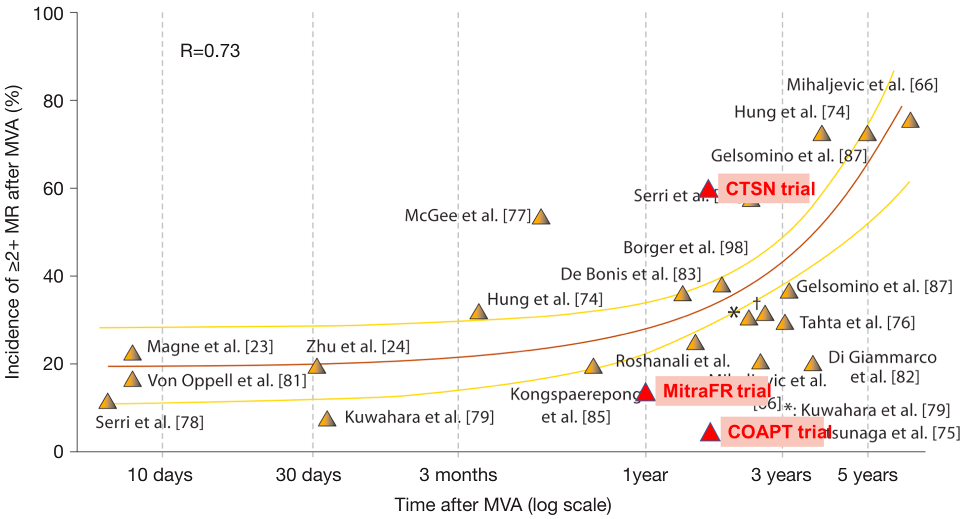

Figure 1 The Achilles' heel of MVr: the recurrence of MR after MVr increases with time. In this figure, adapted from Magne *et al.* (17), we have added in red the high recurrence of MR after surgical repair [60% in the CTSN trial (18)] and the lower recurrence after percutaneous repair [17% in MITRA.FR and 5% in COAPT (19,20)]. MVr, mitral valve repair; MR, mitral regurgitation.

Table 1 Ischemic and non-ischemic secondary MR

	Ischemic	Non-ischemic
Mechanism	LV remodelling and dysfunction; annular dilation/ dysfunction; mechanical dyssynchrony	LV remodelling; annular dilation
Natural history	It remains hard to determine if secondary MR occurs when cardiomyopathies are more severe or if the occurrence of a secondary MR makes the underlying cardiomyopathy more severe	
Common features	Up to 50% of cases after AMI	Up to 75% of patients with heart-failure symptoms
	Moderate or severe in only 10–12%	Moderate to severe in only 25%
	Independent of initial LVEF or LV dimensions	More LV dilatation and worse LVEF

MR, mitral regurgitation; LV, left ventricular; AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction.

by surgeons to identify the best candidates for the invasive correction of secondary MR and to choose the best surgical strategies for this population. *Table 1* shows the differences between ischemic and non-ischemic secondary MR.

Secondary MR complicating ICM

Most data concerned patients with ICM, especially patients awaiting surgical coronary revascularization, since adding a mitral procedure during CABG surgery had been the standard of care for decades (23). Three subsets of ischemic patients were identified:

(I) Candidates for CABG with severe secondary MR: a randomized study was performed in the US by the Cardiothoracic Surgical Trials Network (CTSN) to compare MVr and MVR over a 12-month follow-up period (18). The authors found no significant difference in LV end-systolic volume index (LVESVI), remodelling or survival between both groups. Two other major takeaways were also identified: (I) the composite major adverse event (rate of death, stroke, subsequent MV surgery, hospitalization for heart failure or an increase in New York Heart Association class of ≥1) occurred in up to 30% of patients at 1-year follow-up, highlighting the large potential for improvement in the therapy of ischemic secondary MR; and (II) the investigators found a MR recurrence (≥ grade 2) rate at 2 years of 60% after MVr. Thus, if the persistence of MR had no impact on the survival, the usefulness of treating secondary MR would be challenged. In the subgroup of CABG surgery candidates with severe ischemic MR, no prospective study compared CABG surgery with MR correction versus CABG surgery without MR correction for understandable ethical reasons.

(II) Candidates for CABG with moderate secondary MR [defined as an effective regurgitant orifice (ERO) area of 0.20 to 0.39 cm^2] and good LV ejection function (LVEF >30%): in 2012, the Randomized Ischemic Mitral Evaluation (RIME) investigators in Europe proposed to randomize patients referred for CABG surgery with moderate ischemic MR to undergo CABG + MVr or CABG alone (24). The study was stopped early after the 1-year interim data analysis showed a greater improvement in the primary endpoint (peak oxygen consumption) in the CABG + MVr group. In these patients, adding a mitral annuloplasty to CABG was also associated with a greater LV reverse remodelling and a decrease in MR severity. However, no improvement of survival at 1 year could be identified. In the subgroup of patients with mild ischemic MR, there was no evidence that adding a MVr to surgical revascularization improved the long-term survival (25).

(III) Candidates for CABG with poor LV function: in patients with LV dysfunction and moderate to severe MR, adding a MVr to CABG may improve survival compared with CABG alone or medical therapy alone (26).

Secondary MR in non-ICM (N-ICM)

Conversely, secondary MR in non-ischemic patients occurs more often where there is a reduced LVEF. This population is less studied probably because proposing a surgery to frail patients without CABG indication appears to be risky. Preliminary results comparing mitral surgery and medical therapy in "historical patients" with catastrophic LV parameters suggested a benefit of surgical correction of MR in terms of survival and LV remodelling (11). Thus, both patients' characteristics and modern non-surgical therapy dramatically changed in the last 15 years and this literature should be carefully interpreted. Recent retrospective data showed that postoperative survival was conditioned by the restoration of a LV forward stroke volume (27). Thus, no specific preoperative clinical or echocardiographic prognostic parameters were identified. As of today, surgery is an option with a IIb class of recommendation. This subset of patients probably will be less often referred to surgery and is a possible target for innovative therapies.

Finally, after more than 20 years of fine-tuning, no significant evidence supports a systematic adoption of surgical treatment of secondary MR. Table S1 summarizes the most significant published studies regarding secondary MR.

Late 2010s: one confirmation (MITRA.FR) and one cat among pigeons (COAPT)

Based on the encouraging results of the surgical edge-to-edge technique (28-30), percutaneous, transcatheter procedures with the MitraClip (Abbott Vascular, Santa Clara, California) were proposed (31).

In 2011, the EVEREST II trial concluded that MitraClip implantation is safe and feasible and further concluded that MitraClip implication reduced symptoms and improved the clinical status of secondary MR in a series with only 30% of secondary MR patients (32). Due to the design of the study, the efficacy of the MitraClip was judged non-inferior to MVr despite a reoperation rate of 22% in the MitraClip group *vs.* 2% in the surgical group (33). Thus, by 2012, the potential use of percutaneous edge-to-edge procedures in secondary MR was mentioned in European guidelines (without specific indications) (34).

In August 2018, the results of the MITRA.FR randomized controlled trial were presented, comparing a group receiving GDMT versus a group of MitraClip + GDMT in a population of heart failure patients with secondary MR (19). The study showed an absence of benefit in the primary endpoint (death from any cause or rehospitalisation for heart failure) and in any sub-group analysis. These results were in total accordance with all previous literature and, in particular, when we compared the curve of MITRA.FR with the propensity matched series of Wu *et al.* (15) (*Figure 2*).

In November 2018, surprising results were announced in the COAPT study showing for the first time in the history of secondary MR treatment a major benefit of MitraClip implantation on the primary endpoint (cumulative incidence of rehospitalisation for heart failure), on mortality and in

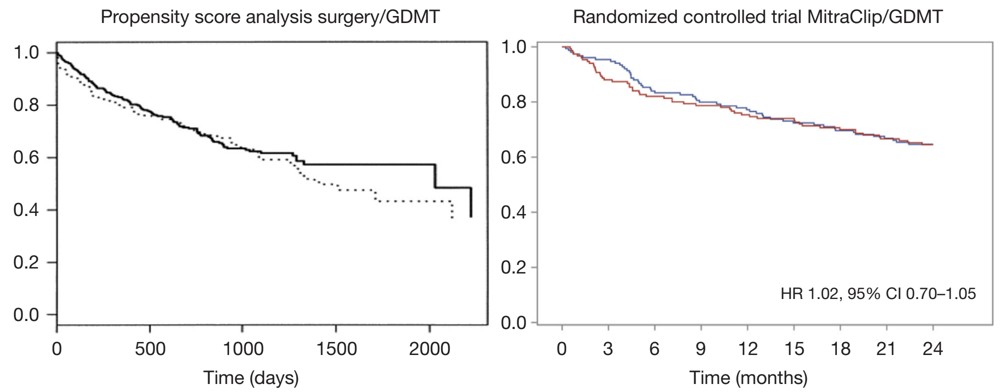

Figure 2 Similarity of results after surgery in 2005 (left) and percutaneous treatment in 2018 (right) of secondary MR. (Left) In 2005, the results in terms of morbidity and mortality of the surgical correction of secondary MR in addition to GDMT (solid line) were not better in a propensity score analysis of a comparative group of patients treated with GDMT only (dotted line) (15); (right) in 2018, the MITRA.FR randomized controlled trial seems to confirm this result with no benefit in adding the percutaneous treatment (red line) to GDMT (blue line) (19). MR, mitral regurgitation; GDMT, guideline-directed medical therapy.

any sub-group analysis (20).

These apparently contradictory results created a "buzz" in the cardiology community. Hundreds of publications were subsequently published to analyze this discrepancy. Despite similar LVEFs (33.3% *vs.* 31.3% in MITRA.FR and COAPT, respectively), the severity of regurgitation was higher in the COAPT study (0.31 *vs.* 0.41 cm^2) and LV volumes less dilated (192 *vs.* 251 mL). This apparent discrepancy led to the rethinking of the definition of secondary MR with the proportionate/disproportionate concept, which had the advantage of reconciling the results of the two studies (35).

After the publication of the COAPT study, in March 2019, the Food and Drug Administration (FDA) approved the MitraClip for the treatment of secondary MR in the U.S. and implantations of MitraClip increased dramatically worldwide. Currently, implantation of MitraClip is the only procedure (surgical or percutaneous) with a proven benefit; in addition to medical treatment, in the treatment of secondary MR. It now is the gold standard against which any new device will be compared. Several new percutaneous repair or replacement techniques (36-43) are the subject of a dedicated keynote lecture and will not be discussed herein, but will be discussed in detail in another chapter of this issue.

What's next?

There is no doubt that GDMT, including cardiac resynchronization therapy and myocardial revascularization, should systematically be considered as the first line of treatment in patients with secondary MR complicating heart failure regardless of the LVEF (44). The remaining patients unresponsive to GDMT (60%) as well as those developing secondary MR despite GDMT have the worst prognosis and should be evaluated by a "Valvular Heart Team" and possibly recommended to correct their secondary MR. Every case must be analyzed by integrating both MR quantification and LV analysis (etiology, viability, function, volume). The old definitions of secondary MR, as described in the previous guidelines, should be revisited taking into account the LV geometry ("proportionate/disproportionate theory") (45). Although very appealing, this classification model is yet to be validated and, even more important, it is necessary to understand how it will help the decision-making for every single patient.

The proper recommendations summarized in *Figure 3* should be revisited. New Guidelines are expected in the U.S. in 2020 and in Europe in 2021 and they should take into account the main lessons of the past decades, which are as follows:

(I) Heart failure with secondary MR is a severe disease with a prognosis worsening with the severity of the regurgitation;
(II) All literature strongly suggests that GDMT including cardiac resynchronization therapy and myocardial revascularization should be the first line of treatment for any secondary MR;

<table>
<tr><th colspan="4"></th><th>ESC 2012</th><th>ESC 2017</th><th>AHA/ACC 2014</th><th>AHA/ACC 2017</th></tr>
<tr><td rowspan="5">Severe SMR</td><td rowspan="3">LVEF >30%</td><td colspan="2">Patient undergoing CABG surgery</td><td colspan="2">SURGERY
I - C</td><td colspan="2">SURGERY
IIa - C</td></tr>
<tr><td rowspan="2">No option for revascularization
BUT
symptoms despite GDMT</td><td>Low surgical risk</td><td colspan="2">SURGERY
IIb - C</td><td rowspan="4">SURGERY
(MVR = MVr)
IIb - C</td><td rowspan="4">SURGERY
(MVR > annuloplasty)
IIb - C</td></tr>
<tr><td>No low surgical risk AND suitable morphology</td><td></td><td>E2E
IIb - C</td></tr>
<tr><td rowspan="2">LVEF <30%</td><td colspan="2">Viability with Option for revascularization AND symptoms despite GDMT</td><td colspan="2">SURGERY
IIa - C</td></tr>
<tr><td colspan="2">No option for revascularization</td><td></td><td>E2E
IIb - C</td></tr>
<tr><td>Moderate SMR</td><td colspan="3">Patient undergoing CABG</td><td>SURGERY considered
IIa - C</td><td></td><td>MVr my be considered
IIb - C</td><td>Usefulness of MVr UNCERTAIN
IIb - B-R</td></tr>
</table>

Figure 3 Evolution of European and American guidelines in the management of secondary MR. ACC, American College of Cardiology; AHA, American Heart Association; CABG, coronary artery bypass graft; ESC, European Society of Cardiology; GDMT, guideline-directed medical therapy; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MVR, mitral valve replacement; OMM, optimal medical management; SMR, secondary mitral regurgitation.

(III) The definition of secondary MR should be revisited, integrating the regurgitation in its ventricular environment (size and function);

(IV) In candidates for surgical myocardial revascularization, the indication for treating severe secondary MR with such surgical procedure is still recommended by the guidelines, which seems logical, but one must note that we have no trials supporting this recommendation and we probably will never have such support;

(V) With respect to N-ICM, the benefit of the surgical treatment of secondary MR has never been confirmed by evidence-based medicine, so that such surgery will probably be rare and limited (i) to significant secondary MR associated with other surgical procedures or (ii) when other percutaneous procedures are impossible and when LV function is not too low or (iii) as an alternative to transplantation or long-term mechanical circulatory support;

(VI) In patients contraindicated for surgery, COAPT indicates that the treatment of secondary MR can save lives and improve quality of life in a highly selective group of secondary MR patients. COAPT and MITRA.FR confirm that the MitraClip technique is safe and efficient in reducing the severity of the regurgitation and better than the majority of the surgical series suggesting that the edge-to-edge technique is particularly adapted for the treatment of this disease (*Figure 2*). MITRA. FR shows the limits of over indication of MitraClip implantation, in particular, when the ventricles are too dilated and the regurgitation too low (the best way to kill a technique is to overuse it);

(VII) The Achilles' heel of valve repair being the high risk of recurrence of MR, a wider place for MVR (surgical or percutaneous) is expected, in particular, when the tethering is important and the edge-to-edge technique is unsuitable.

Conclusions

Looking back through the past decades of the history of secondary MR shows the progress in understanding this complex disease and better defines its phenotype and treatment. The poor prognosis of secondary MR is confirmed and directly linked to the severity of the regurgitation, justifying an aggressive approach starting with a GDMT. The place of surgical treatment has always been a matter of controversy as reflected in recent studies which have never been able to confirm its efficacy. Conversely, percutaneous treatment has, for the first time, established the concept of a possible virtuous cycle after correction of a severe secondary MR. An opposite randomized controlled trial shows that this benefit is possible only in a very accurately selected population. The challenge for the future will be to define which phenotype of patients and which definition of secondary MR (severity of MR/ventricular remodelling) could actually benefit from correction. New randomized controlled studies are expected to answer these questions, in particular, at an earlier phase of the disease.

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Footnote

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Table S1 Details chart of some of the most significant published studies about secondary MR

Author (ref.)	Study frame			Etiology			Severity			LVEF			LV dilatation			Conclusion
	Design	Groups	Population	ICM	N-ICM	Comment	Moderate (ERO 0.2–0.4)	Severe (ERO ≥0.4)	Comment	Good (≥35%)	Poor (<35%)	Comment	Yes	No	Comments	
Bax *et al.* (9)	Retrospective	Single arm	51 patients underwent CABG and restrictive annuloplasty	X			X	X	Mean grade 3.4		X	Mean 31%	X		Mean LVEDD 59 and 61 mm	Excellent results of combined restrictive annuloplasty and CABG
Badhwar *et al.* (10)	Retrospective	Single arm	125 patients manage with restrictive annuloplasty	X	X	N/A			N/A		X	Mean 16%	X		Mean LVEDV 281 mL	Mitral reconstruction offers a new treatment strategy for patients with MR and end-stage heart failure
Acker *et al.* (11)	Retrospective	Comparative	193 patients with MR surgery (84% annuloplasty and 15% MVR). Corecap in 50%		X	6.2% are ICM	X	X	58% ≥ grade 2		X	Mean 23.9%	X		Mean LVEDV 270.1 mL	Clear benefit to the surgical elimination of MR
Spoor *et al.* (12)	Retrospective	Comparative	289 patients: BAND *vs.* RING			N/A			N/A		X	Mean LVEF 17% and 21%		X	LVIDd 60 mm	Use of a nonflexible ring appears to significantly reduce the need for repeat surgical procedures
McGee *et al.* (16)	Retrospective	Single arm	257 consecutive patients undergoing MVr	X		95% CABG associate	X	X	≥3+ in 98.4%	X	X	Mean 35%			N/A	Development of additional techniques is necessary to achieve more secure repair of functional ischemic MR
Mihaljevic *et al.* (21)	Retrospective	Comparative	CABG alone (100 patients) and CABG + MVA (290 patients)	X		100% CABG associate	X	X	≥3+ in 100%	X	X	All <45%			N/A	MVA does not improve long-term functional status or survival in patients with severe functional ischemic MR
Wu *et al.* (15)	Retrospective	Comparative	126 MVA, 263 no MVA, 293 candidates for MVA but not performed	X	X	CABG associate from 51 to 71%			N/A		X	Mean LVEF 19% to 23%	X		Mean LVEDD 65 mm	No clearly demonstrable mortality benefit conferred by MVA for significant MR with severe LV dysfunction
Crabtree *et al.* (22)	Retrospective	Single arm	257 patients undergoing MVr for secondary MR	X		85% CABG associate			N/A	X	X	Mean 35%			N/A	Mortality for ischemic MR remains high despite surgical management and may be related to risk factors for progression of CAD
Castleberry *et al.* (23)	Retrospective	Comparative	4,989 patients with CAD and MR (36% medical treatment, 25% PCI, 34% CABG, 5% CABG + MV surgery)	X		100% significant CAD	X	X	≥2+ in 100%	X	X	Mean from 45% to 50%			N/A	Medical treatment alone had poor results (performed in more seek patients) CABG > PCI if mild MR CABG + MVR associated with poor prognosis but more severe patients
Salmasi *et al.* (46)	Meta-analysis	Comparative	CABG alone *vs.* CABG + MV surgery	X		Only ICM	X		Only moderate			N/A			N/A	MV surgery is not associate with any improvement in long-term survival or functional class
Chan *et al.* (24)	Randomized	Comparative	CABG alone (39 patients) *vs.* CABG + MVr (34 patients)	X		Only ICM	X		Mean ERO 0.18–0.21 cm^2	X	X	Mean 40%		X	Mean LVEDD 56 mm	Greater improvement in peak oxygen consumption, greater LV reverse remodeling but no improvement of survival at 1 year
Michler *et al.* (47)	Randomized	Comparative	CABG alone (151 patients) *vs.* CABG + MVr (150 patients)	X		Only ICM	X		Mean ERO 0.2 cm^2	X	X	Mean 40%		X	Mean LVESVi 54 and 50 mL/m^2	Combined strategy did not result in a higher degree of LV reverse remodeling. Increased number of untoward events and survival was not different
Kang *et al.* (25)	Prospective	Comparative	CABG alone (5 patients) *vs.* CABG + MVr (50 patients)	X		Only ICM	X		Mean MR grade 2.5 and 2.8		X	Mean LVEF 36.2% and 33.8%		X	Mean LVEDD 59 and 61 mm	No improvement in long-term survival when mitral repair is associated with CABG surgery
Deja *et al.* (26)	Randomized	Comparative	CAD amenable to CABG randomized to medial therapy with (613 patients) or without CABG (599 patients)	X		Only ICM	X	X	Mild in 46% ≥3+ in 18%		X	Only LVEF ≤35%	X	X	Mean LVESVi 72 to 89 mL/m^2	In mild MR : CABG = medical treatment; in moderate to severe MR (104 patients): surgery may improve survival but it remains unclear if this advantage is due to the CABG itself or the treatment of the associated MR
Kamperidis *et al.* (27)	Retrospective	Single arm	130 patients treated with surgical MVr		X	78% non-ischemic	X	X	Severe define as ERO ≥0.2 cm^2		X	Mean 31%	X		Mean LVEDV 188 mL	MVr help reducing LV volumes, increase LV forward stroke volume and LV forward ejection fraction but not LVEF
Kamperidis *et al.* (48)	Retrospective	Single arm	76 patients underwent surgical repair (71%) or MitraClip repair (29%)		X	100% non-ischemic	X	X	Mean ERO 0.21 cm^2		X	Mean 34%		X	Mean LVEDVi 87 mL/m^2	Repair improved LV forward flow and induced LV reverse remodelling but did not change LV systolic function (no survival data)
Obadia *et al.* (19)	Randomized	Comparative	Medical therapy alone (155 patients) or associated with MitraClip (152 patients) in patients not considered to be candidates for MV surgery	X	X	ICM in 60%	X	X	Mean ERO 0.31 cm^2		X	Mean 33%	X		Mean LVEDVi 134 and 136 mL/m^2	Survival and hospitalization rate for heart failure at 1 year did not differ significantly between patients who underwent MitraClip therapy and those who received medical therapy alone
Stone *et al.* (20)	Randomized	Comparative	Medical therapy alone (312 patients) or associated with MitraClip (302 patients) in patients with STS score ≥8%	X	X	ICM in 60%		X	Mean ERO 0.4 cm^2		X	Mean 31%	X		Mean LVEDV 191 and 194 mL	Transcatheter MVr resulted in a lower rate of hospitalization for heart failure and lower all-cause mortality within 24 months of follow-up
Magne *et al.* (17)	Retrospective	Comparative	MVR (184 patients) *vs.* MVr (186 patients)	X		CABG associate in 84% (MVr) and 94% (MVR)		X	Severe in 88% (MVr) and 97% MVR	X		Mean LVEF 43% and 45%		X	Mean LVEDD 57 and 58 mm	MVr is not superior to replacement with regard to operative and overall mortality in patients with ischemic MR
Acker *et al.* (18)	Randomized	Comparative	MVR (125 patients) *vs.* MVr (126 patients)	X		CABG associate in 75%		X	Mean ERO 0.4 and 0.39 cm^2	X		Mean LVEF 42% and 40%		X	Mean LVESVi 61 and 67 mL/mm^2	No significant difference in LV reverse remodeling or survival at 12 months between
Calafiore *et al.* (49)	Retrospective	Comparative	82 repairs and 20 replacements (depending on end-systolic distance between the coaptation point of mitral leaflets and the plane of mitral annulus)	X		CABG associate in 92%		X	≥3+ in 82% and 84%	X	X	Mean 37%	X		Mean LVEDVi 116 and 109 mL/m^2	Correction of chronic ischemic MR through either repair or replacement provides a good 5-year survival rate
Lee *et al.* (50)	Retrospective	Single arm	Risk of MR recurrence in 104 patients who underwent annuloplasty for nonischemic dilated cardiomyopathy		X		X	X	≥3+ in 82% and 84%	X	X	Mean LVEF 28% and 24%	X		Mean LVEDV 242 and 349 mL	Postoperative mitral competence highly dependent on preoperative distal anterior leaflet mobility
Magne *et al.* (51)	Retrospective	Comparative	Risk of MR recurrence in 51 consecutive patients undergoing restrictive annuloplasty with or without CABG for ischemic MR	X		CABG associated in >90%	X	X	Vena contracta width 5.4 and 5.9 mm	X	X	Mean LVEF 37% and 34%		X	Mean LVEDV 168 and 180 mL	Patients with high posterior leaflet restriction should thus be considered poor candidates for restrictive MVA

CABG, coronary artery bypass graft; CAD, coronary artery disease; ERO, effective regurgitant orifice; ICM, ischemic cardiomyopathy; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEDVi, left ventricular end-diastolic volume indexed; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end-systolic volume indexed; LVIDd, left ventricular internal diameter in diastole; MR, mitral regurgitation; MV, mitral valve; MVA, mitral valve annuloplasty; MVR, mitral valve replacement; N-ICM, non-ischemic cardiomyopathy; PCI, percutaneous coronary intervention; MVr, mitral valve repair.

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