Personalised surgical treatment of functional mitral regurgitation
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Citation
Petrus, A. H. J. (2020, June 23). *Personalised surgical treatment of functional mitral regurgitation*. Retrieved from https://hdl.handle.net/1887/123058

Cover Page

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Author: Petrus, A.H.J.
Title: Personalised surgical treatment of functional mitral regurgitation
Issue Date: 2020-06-23

Chapter 2

The optimal treatment strategy for secondary mitral regurgitation: A subject of ongoing debate

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Introduction

Secondary mitral regurgitation (MR) is a disease condition in which the mitral valve (MV) becomes insufficient as a result of left ventricular (LV) dysfunction. As such, it is also referred to as functional MR. A thorough comprehension of the forces involved in MV opening and closing is necessary to understand the mechanism of secondary MR, which in turn has implications for the (interventional) treatment of this condition.

In secondary MR (as opposed to primary MR), the MV is macroscopically normal, and incomplete mitral leaflet closure results from a combination of annular dilatation, papillary muscle displacement with increased systolic leaflet tethering, and reduced closing forces due to regional or global LV remodelling (**Figure 1**).[1]
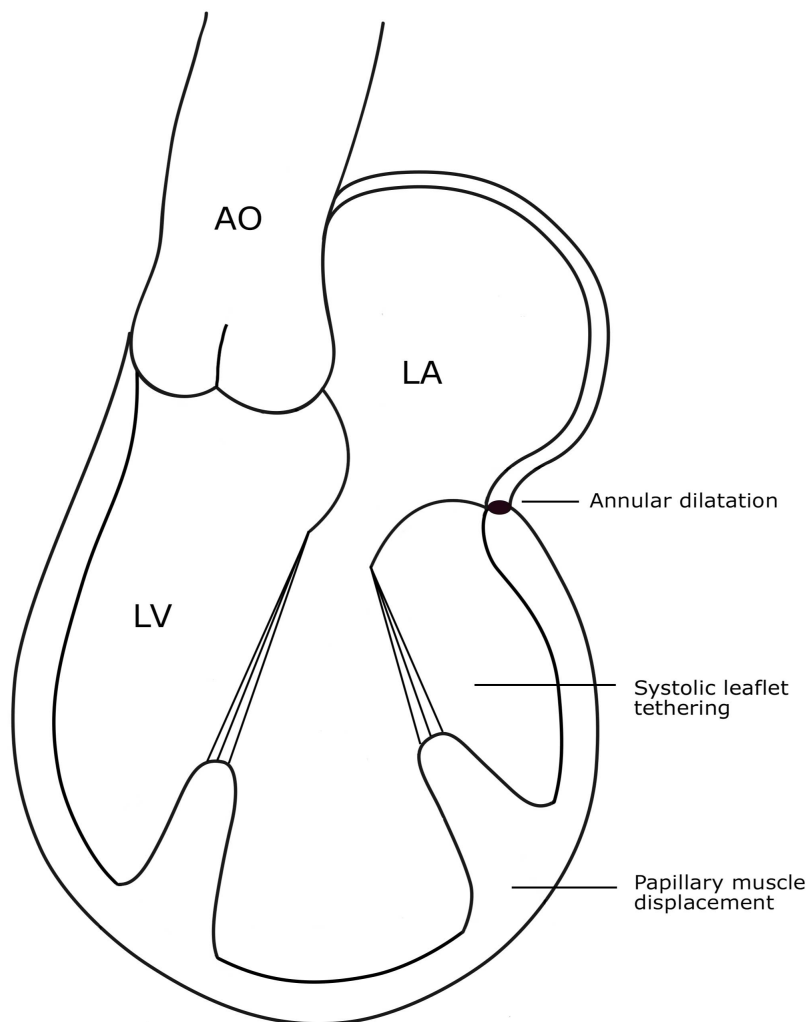

Figure 1. Pathophysiology of secondary mitral regurgitation.
AO = aorta, LA = left atrium, LV = left ventricle

Secondary MR is a common phenomenon and can be classified based on the aetiology of LV dysfunction as either ischaemic or non-ischaemic. Although there are many similarities between ischaemic and non-ischaemic MR, there are also distinct differences. In non-ischaemic cardiomyopathy, MR develops when considerable LV remodelling has taken place and is therefore always accompanied by heart failure with reduced ejection fraction. Ischaemic MR may develop in the same way when diffuse ischaemia or extensive infarction leads to global LV remodelling. However, more frequently ischaemic MR results from local LV remodelling, following local myocardial infarction or ischaemia. In this situation, LV ejection fraction can be relatively preserved and symptoms of heart failure may not yet have become manifest.

Echocardiography is the recommended imaging technique to evaluate secondary MR and its severity should be assessed using an integrative approach consisting of a combination of qualitative, quantitative and additional supportive echocardiographic parameters.[2, 3] The threshold for the definition of severe secondary MR is a topic of debate. Currently, severe secondary MR is defined as an effective regurgitant orifice area (EROA) of ≥40 mm^2 and a regurgitant volume of ≥60 ml in the American Heart Association (AHA)/American College of Cardiology (ACC) guidelines,[3] whereas the European Society of Cardiology (ESC) guidelines use an EROA of ≥20 mm^2 and regurgitant volume of ≥30 ml.[2]

Secondary MR, regardless of its aetiology, has a poor prognosis.[4, 5] This is easily explained by the fact that the LV suffers from both intrinsic myocardial disease and volume overload that ensues with MR, resulting in a vicious cycle of progressive LV remodelling and worsening MR (**Figure 2**). In the past decades, many treatment options have been proposed to break this vicious cycle. The common goal is two-fold: to restore MV competence and to initiate sustained LV reverse remodelling, in order to improve clinical outcome.
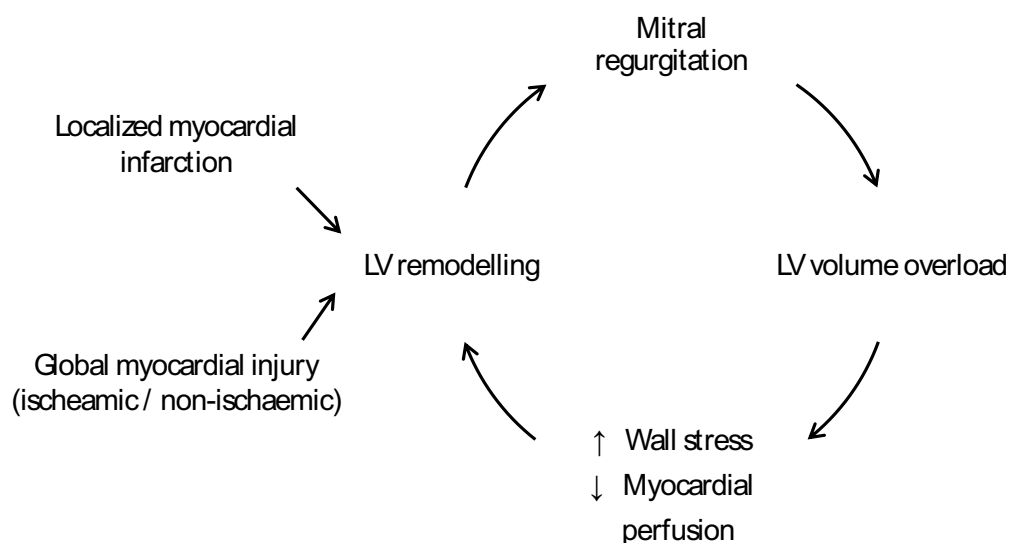
Figure 2. Vicious cycle of secondary mitral regurgitation.

The treatment of secondary MR is included in many guidelines.[2, 3, 6–13] Optimal guideline-directed medical therapy (GDMT) is the cornerstone in the treatment of patients with secondary MR. Effective medical therapy lowers LV afterload, reverses LV remodelling and consequently reduces MR. Cardiac resynchronization therapy improves LV systolic function in selected patients — both acute-term (by reduction of dyssynchrony) and long-term (by means of LV reverse remodelling) — resulting in increased closing forces and reduced tethering forces acting on the MV.[7, 11] In patients with persisting MR despite GDMT (including cardiac resynchronization therapy, when indicated), more invasive treatment options may be considered. In line with the broad spectrum of disease manifestations and the different aetiologies, many different interventions have been proposed, aiming at the valve (surgical MV repair, MV replacement and percutaneous approaches), at the subvalvular apparatus, at the ventricle (coronary revascularization, surgical ventricular restoration and external cardiac constraint devices), or a combination thereof. In patients who are unlikely to benefit from these interventions, implantation of an LV assist device (LVAD) may be considered.

This vast array of interventional treatment options reflects the fact that the optimal treatment strategy for patients with secondary MR is a topic of ongoing debate, also in current guidelines (**Table 1**).[2, 3, 6–13] Guideline recommendations are not unequivocal and are based on the results of many studies — predominantly observational in nature — with conflicting outcomes, whereas data from randomized controlled trials (RCTs) on the surgical treatment of secondary MR is scarce, and only available for ischaemic MR.[2, 3, 6–13] In this Great Debate, different approaches for the treatment of secondary MR, their rationale, outcomes and limitations are described by experts in this field.

Mitral valve repair

Annelieke Petrus, Jerry Braun, Robert Klautz, Leiden, The Netherlands

Rationale and indication

Bolling and Bach introduced the concept of MV repair using an undersized (or: restrictive) annuloplasty ring.[14, 15] Undersizing corrects mitral annular dilatation and enforces leaflet coaptation, thereby abolishing MR, and reduces the size of the LV base, consequently lowering LV wall stress and initiating LV reverse remodelling.[16] This technique can be considered in both patients with ischaemic and non-ischaemic MR.

Theoretically, secondary MR in patients with ischaemic cardiomyopathy may improve after coronary artery bypass grafting (CABG) due to improvement in LV geometry and function. In practice, the outcome after CABG alone is highly unpredictable, with MR severity being

Table 1. Guidelines' recommendations for the surgical treatment of secondary MR.

Guideline	Recommendations	LOE	COR
ESC and EACTS[5]	Surgery is indicated in patients with severe secondary MR undergoing CABG and LVEF >30%	C	I
	Surgery should be considered in symptomatic patients with severe secondary MR, LVEF <30% but with an option for revascularization and evidence of myocardial viability.	C	IIa
	When revascularization is not indicated, surgery may be considered in patients with severe secondary MR and LVEF >30% who remain symptomatic despite OMT (including CRT if indicated) and have a low surgical risk.	C	IIb
	When revascularization is not indicated and surgical risk is not low, a percutaneous edge-to-edge procedure may be considered in patients with severe secondary MR and LVEF >30% who remain symptomatic despite OMT (including CRT if indicated) and who have a suitable valve morphology by echocardiography, avoiding futility.	C	IIb
	In patients with severe secondary MR and LVEF <30% who remain symptomatic despite OMT (including CRT if indicated) and who have no option for revascularization, the Heart Team may consider a percutaneous edge-to-edge procedure or valve surgery after careful evaluation for a ventricular assist device or heart transplant according to individual patient characteristics.	C	IIb
AHA and ACC[8, 9]	In patients with moderate ischemic MR undergoing CABG, the usefulness of mitral valve repair is uncertain.	B-R	IIb
	MV surgery is reasonable for patients with severe secondary MR who are undergoing CABG or AVR.	C	IIa
	It is reasonable to choose chordal-sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA III to IV) with severe ischemic MR and persistent symptoms despite OMT for heart failure.	B-R	IIa
	MV repair or replacement may be considered for severely symptomatic patients (NYHA class III-IV) with severe secondary MR who have persistent symptoms despite OMT for heart failure.	B	IIb
AATS[12, 13]	In patients with moderate ischemic MR undergoing CABG, MV repair with an undersized complete rigid annuloplasty ring may be considered.	B	IIIb
	MV replacement is reasonable in patients with severe ischemic MR who remain symptomatic despite OMT and cardiac device therapy and who have a basal aneurysm/dyskinesis, significant leaflet tethering and/or severe LV dilatation (LVEDD >65mm).	B	IIa
	MV repair with an undersized complete rigid annuloplasty ring may be considered in patients with severe ischemic MR who remain symptomatic despite OMT and cardiac device therapy and no basal aneurysm/dyskinesis, significant leaflet tethering, or severe LV enlargement.	B	IIb

ACC = American College of Cardiology, AHA = American Heart Association, AATS = American Association of Thoracic Surgery, CABG = coronary artery bypass grafting, COR = classification of recommendations, CRT = cardiac resynchronization therapy, EACTS = European Association for Cardio-Thoracic Surgery, ESC = European Society of Cardiology, LOE = level of evidence, LV = left ventricle, LVEDD = left ventricular end-diastolic diameter, LVEF = left ventricular ejection fraction, MR = mitral regurgitation, MV = mitral valve, OMT = optimal medical therapy.

unchanged or worse in 31–50% of patients undergoing surgical revascularization only.[17–20] The combination of MV repair and CABG addresses both the valve and the underlying ventricular component in patients with ischaemic MR. In patients with non-ischaemic MR, the intrinsic ventricular disease cannot be addressed, which therefore remains an uncovered area.

Surgical technique

In our institution, the ring size is carefully determined by measuring the anterior leaflet height and then downsizing by 2 ring sizes (i.e. size 26 when measuring size 30). Restrictive mitral annuloplasty (RMA) is performed with a complete rigid or semirigid ring to reduce the septal-to-lateral dimension of the mitral annulus; using a complete ring also accounts for dilatation of the anterior mitral annulus. Repair is considered successful in case no or mild MR and a leaflet coaptation length ≥8 mm are observed on intraoperative transoesophageal echocardiography. If these criteria are not met, further downsizing is performed. In ischaemic MR patients, we always aim at complete revascularization.[21]

Results - Mitral valve repair for ischaemic mitral regurgitation

Several observational studies showed that RMA results in durable correction of MR, LV reverse remodelling and beneficial clinical outcomes in patients with ischaemic MR,[18, 21–23] whereas others negated these benefits.[24–26] Outcomes of observational studies are difficult to compare due to differences in baseline characteristics, completeness of revascularization and technique of MV repair. Therefore, we will focus on 2 RCTs — the Randomized Ischaemic Mitral Evaluation (RIME) and Cardiothoracic Surgical Trials Network (CTSN) trial — comparing CABG alone versus CABG + RMA for moderate ischaemic MR.[18–20, 27] The CTSN trial regarding RMA versus MV replacement for severe MR will be discussed later.[28, 29]

In both the RIME and CTSN trial patients with coronary artery disease and moderate secondary MR were randomized to undergo CABG alone or CABG + RMA. RMA was performed using a complete (semi-)rigid ring in both trials, but downsizing by 2 ring sizes was mandated in the RIME trial whereas the degree of downsizing and addition of supplementary repair techniques were left at the discretion of the surgeon in the CTSN trial. No difference in 30-day mortality was observed in both trials (RIME: 3% in both groups, p = 1.00; CTSN: 2.7% after CABG vs 1.3% after CABG + RMA, p = 0.68). One year after CABG, moderate-to-severe residual MR was observed in 50% of patients in the RIME trial and in 31% in the CTSN trial. After CABG + RMA, recurrent MR was observed in 4% in the RIME trial, compared with 11% in the CTSN trial. LV reverse remodelling 1 year after surgery was defined as an endpoint in both trials. The RIME trial demonstrated a significantly better decrease in indexed LVESV after CABG + RMA (-28%)

compared with CABG alone (-6%). By contrast, in the CTSN trial change in indexed LVESV was similar for both groups (-16% after the combined procedure vs -17% after CABG alone), with comparable results at 2-year follow-up (-25% vs -26%, respectively). Mortality at 1-year was equal between treatment groups in both trials (RIME: 9% after CABG + RMA vs 5% after CABG, p = 0.66; CTSN: 6.7% vs 7.3%, respectively, p = 0.81). However, neither trial was powered to detect a mortality difference. The RIME trial showed a higher increase in peak oxygen consumption (defined as primary endpoint) after CABG + RMA compared with CABG alone, but no difference in readmissions for heart failure. In the CTSN trial, no differences in major adverse cardiac or cerebrovascular events or hospital readmissions were demonstrated. However, more serious adverse neurological events and supraventricular arrhythmias were observed in patients after the combined procedure.

How can we explain the fact that the RIME trial observed a difference in LV reverse remodelling in favour of CABG + RMA, whereas the CTSN trial did not? First, LV reverse remodelling after CABG alone was better in the CTSN trial. This may be explained by the lower rate of previous myocardial infarction and smaller indexed LVESV at baseline, indicating that MR was most likely caused by reversible ischaemia rather than scar tissue in a large proportion of patients in this trial. Second, less LV reverse remodelling was observed after CABG + RMA in the CTSN compared with the RIME trial. Since MR recurrence was higher in the CTSN trial, the degree of LV reverse remodelling seems to be related to the durability of MV repair. Indeed, patients without recurrent MR after CABG + RMA showed a 29% reduction in indexed LVESV, compared with only 6% in patients with recurrent MR.

Results - Mitral valve repair for non-ischaemic mitral regurgitation

Data regarding RMA for MR due to non-ischaemic cardiomyopathy are limited. Observational studies report improved New York Heart Association (NYHA) functional class, better quality of life and LV reverse remodelling after RMA.[30–33] Much information regarding the effect of RMA in non-ischaemic cardiomyopathy has been obtained from the Acorn trial.[34, 35] Primary objective of this RCT was to examine the effect of an external cardiac support device (CSD). The trial enrolled 300 patients with non-ischaemic cardiomyopathy and heart failure into a no MV surgery (n = 107) or MV surgery stratum (n = 192), based on the presence of significant MR. Patients in the MV surgery stratum were then randomized to MV surgery + CSD (n = 91), or MV surgery alone (n = 102). In the MV surgery stratum, baseline LV end-diastolic volume was 270 ml, ejection fraction 24% and all patients had MR ≥ grade 3. The MV was replaced in 16% of patients; the remainder underwent MV repair by RMA. Perioperative mortality was low (1.6% at 30-day). Echocardiography 1 year after surgery demonstrated recurrent MR ≥ grade 2 in 16.5% of patients and a decrease in LVESV of approximately -25 ml. LV reverse remodelling

remained stable at 5-year follow-up. Cumulative mortality was 13% at 1-year, 15% at 2-year and 30% at 5-year follow-up. Concomitant implantation of a CSD resulted in an additional decrease in LVESV (15 ml on average), whereas change in MR and ejection fraction was similar between both groups; addition of the CSD did not improve survival.

Limitations and pitfalls

Reported incidences of MR recurrence after RMA highly differ between studies.[24–26] Although this difference can be partly explained by surgical technique — whether RMA was performed using stringent downsizing and aiming at a coaptation length of ≥8 mm — a subgroup of patients may develop recurrent MR despite a well-conducted MV repair.[21, 33, 36] Several echocardiographic parameters can be used to identify these patients (**Table 2**).[36–39] Furthermore, some surgeons are reluctant to perform RMA due to the risk of inducing functional MV stenosis. However, recent exercise echocardiography studies challenge the concept that functional mitral stenosis — when present after RMA — simply results from implantation of a downsized ring, and demonstrated that MV area during exercise is associated with diastolic tethering and LV geometrical and functional changes after surgery.[40, 41]

Table 2. Predictors for recurrence of MR after mitral valve repair by restrictive mitral annuloplasty, assessed by transthoracic echocardiography.[36, 40, 59, 81]

Valvular parameters
MR grade ≥3.5
Central or complex regurgitant jet
Tenting area ≥2.5 cm^2
Coaptation distance (= tenting height) ≥10 mm
Posterior leaflet angle ≥45º
Posterior leaflet tethering distance ≥40 mm
Mitral annulus diameter ≥37 mm*

Ventricular parameters
LV end-diastolic diameter ≥65 mm
LV end-systolic diameter ≥51 mm
LV end-systolic volume ≥145 ml
Presence of a basal aneurysm/dyskinesis
Systolic sphericity index ≥0.7
Myocardial performance index ≥0.9
Wall motion score index ≥1.5
Interpapillary muscle distance >20 mm
Diastolic dysfunction (restrictive filling pattern)

*Assessed by transoesophageal echocardiography. LV = left ventricle, MR = mitral regurgitation.

Edge-to-edge procedure
Michele De Bonis, Milan, Italy

Rationale and indication

The idea for using the edge-to-edge procedure in addition to implantation of an RMA ring in patients with secondary MR is that it will enhance durability of MV repair and prevent MR recurrence. The edge-to-edge technique involves suturing the edges of the MV leaflets together at the site of regurgitation, specifically addressing the site of the regurgitant jet. This ensures early valve closure and abolishes occurrence of the 'loitering effect' (delayed mitral leaflet coaptation in early systole, due to mitral annulus dilatation and circularization, and posterior papillary muscle displacement).[42] Moreover, anchoring the leaflets together might exert an upward tension on the chordae tendinae and therefore on the papillary muscles and the adjacent LV wall (a kind of 'reins' effect), potentially counteracting progression of LV remodelling.

The edge-to-edge procedure can be considered in patients with both ischaemic and non-ischaemic MR, who are at increased risk of MR recurrence after repair (**Table 2**).[36–39] Tenting height (TH; also known as coaptation depth) is defined as the distance from the annular plane of the MV to the leaflet coaptation point and represents the degree of mitral leaflet tethering, independent of LV function and shape. In patients with annular dilatation and moderate leaflet tethering (TH <10 mm), isolated RMA with a complete rigid or semi-rigid ring can be performed. However, when tethering is more pronounced (TH >10 mm), addition of the edge-to-edge technique to RMA is preferred.

Surgical technique

To perform the edge-to-edge procedure, the location of the regurgitant jet should be identified on preoperative echocardiography, to choose the site of the approximating stitch. In case of a central jet (between A2 and P2), a central edge-to-edge repair is performed leading to a double-orifice MV configuration (**Figure 3**). When the regurgitant jet is located at the posterior commissure, as in some cases of ischaemic MR, a commissural edge-to-edge suture is applied, resulting in a single orifice MV with a relatively smaller area. The length of the suture is always kept as short as possible to minimize the risk of postoperative MV stenosis: in most patients between a few millimetres and 1 cm. A complete rigid or semi-rigid prosthetic ring is invariably implanted and is usually 1 or 2 sizes smaller than the anterior leaflet surface.

Results

Outcomes of the edge-to-edge procedure have been investigated in several retrospective observational studies.[43–47] The earliest reports were disappointing; however, these studies described the edge-to-edge procedure without concomitant annuloplasty or combined with a flexible band, which could not prevent progression of annular dilatation.[43–45] In more recent studies,[46, 47] we described outcomes of patients with moderately severe to severe ischaemic and non-ischaemic MR and LV ejection fraction ≤35%, who underwent either a combination of RMA with edge-to-edge procedure (in case of a TH ≥10 mm) or RMA alone (in case of a TH <10 mm). In-hospital mortality was not significantly different between both groups (2.5% after RMA alone vs 3% after RMA with edge-to-edge procedure, p = 1.0).[47] Cumulative incidence of recurrent MR ≥ grade 3 was significantly lower after the combined procedure compared with RMA alone, both at 18 months (5% vs 23%, respectively, p = 0.04)[46] and 10 years after surgery (10% vs 31%, p = 0.01).[47] In both groups, LV end-diastolic dimensions decreased (67 to 58 mm after RMA and 68 to 62 mm after RMA with edge-to-edge procedure) and NYHA functional class improved after surgery.[46, 47] Although addition of the edge-to-edge technique to RMA significantly decreased the rate of recurrent MR, the improved repair durability did not translate into better LV reverse remodelling or improved long-term survival (55% after RMA alone compared to 42% after RMA with edge-to-edge procedure at 10-year follow-up, p = 0.2).[47]
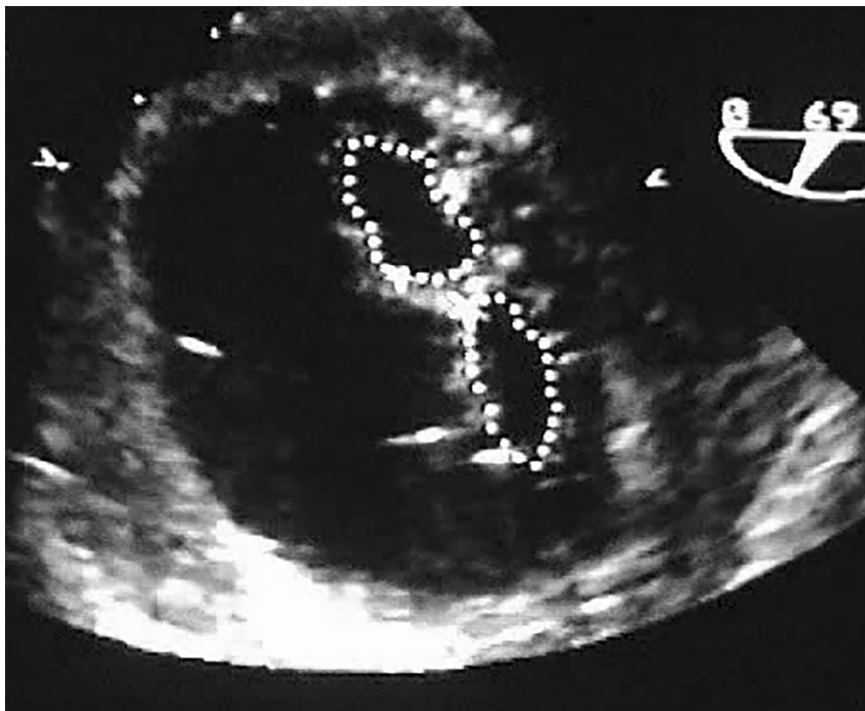

Figure 3. Echocardiographic image of the edge-to-edge procedure.

Limitations and pitfalls of the technique

The edge-to-edge procedure restricts the MV orifice area, which may potentially induce a stenosis. Although a clinically relevant MV stenosis has not been observed in any of the patients, experience and careful choice of the annuloplasty ring size are mandatory in order to avoid significant MV stenosis. The edge-to-edge technique should be avoided in rare instances where leaflet tethering is associated with only mild annular dilatation. Finally, unsatisfactory results can be expected, even with the edge-to-edge technique, in the case of extreme mitral leaflet tethering or extremely advanced LV remodelling.

Subvalvular procedures

Subvalvular procedures, which are generally used as an adjunct to annuloplasty, aim at restoring the configuration of the subvalvular apparatus and subsequently reduce tethering forces on the MV. In addition, these techniques provide a direct change in LV geometry. Both contribute to the durability of MV repair. Subvalvular procedures include various techniques with different concepts[48] and each procedure should be selected considering the direction of MV tethering (apical, outward or posterior).[49] Two of these techniques will be discussed.

Subvalvular procedures: RING + STRING
Frank Langer, Hans-Joachim Schäfers, Homburg/Saar, Germany

Rationale and indication

The RING + STRING technique combines implantation of an RMA ring (RING) with papillary muscle repositioning (STRING). This approach addresses annular dilatation as well as subvalvular systolic leaflet tethering and LV geometry — serving as an internal LV restraint.

Indication for papillary muscle repositioning in our practice is dictated by the degree of LV remodelling, for which TH is one of the more easily determined quantitative parameters.[36] If TH exceeds 10 mm, almost all patients develop recurrent MR with absence of reverse remodelling.[50] Consequently, we add papillary muscle repositioning to mitral annuloplasty in patients with secondary MR ≥ grade 3 and TH ≥10 mm.[51]

Surgical technique

Standard MV repair (RING) is performed with a moderately undersized ring (by 1 to 2 sizes in relation to the intertrigonal distance). Thereafter, a horizontal aortotomy is performed and a

double-armed Teflon pledgeted 3-0 polytetrafluoroethylene (PTFE) suture (STRING) is passed through the head of the papillary muscle and then passed from the LV cavity through the aorto-mitral continuity underneath the commissure between the non-coronary and left coronary aortic cusps and exteriorized. In patients with ischaemic MR due to local LV remodelling, a string for the posterior papillary muscle often suffices. In patients with ischaemic MR due to global LV remodelling and in patients with non-ischaemic MR we use 2 strings, one for each papillary muscle. During termination of cardiopulmonary bypass, the STRING-suture is tied under transoesophageal echocardiography guidance in the loaded beating heart. Tension on the suture is titrated under direct echocardiographic control in 2-dimensional-mode, achieving the most physiological shape of the anterior mitral leaflet along its entire body and bringing the coaptation point as close to the annular plane as possible (**Figure 4**).

Results

Studies describing outcomes regarding the RING + STRING procedure are limited.[51, 52] In our institution, 224 patients with ischaemic (n = 148) or non-ischaemic (n = 76) MR and TH ≥10 mm have undergone papillary muscle repositioning in addition to a moderately undersized RMA. The in-hospital mortality was 8%. During follow-up (median 50 months), 11% of patients developed recurrent MR ≥ grade 3. MV reoperation was performed in 15 patients (rerepair in 6 and MV replacement in 9). Decreased LV end-diastolic diameter was observed in 60% of patients (mean -7 mm change in LV end-diastolic diameter from baseline) and NYHA functional class significantly improved. Overall freedom from death, LVAD or heart transplantation was 57% at 5 years after surgery.
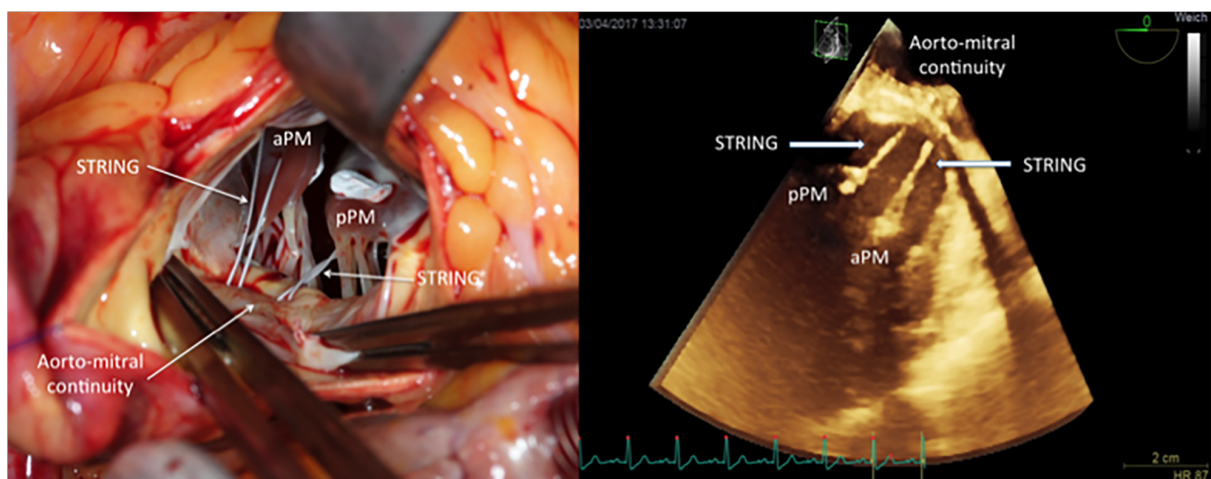
Figure 4. Intraoperative and echocardiographic image of the RING + STRING procedure.
Left: Intraoperative view via horizontal aortotomy: 2 PTFE sutures ('STRING') anchored in heads of both papillary muscles (aPM = anterior papillary muscle; pPM = posterior papillary muscle) and exteriorized through the aorto-mitral continuity. Right: 3-dimensional-transesophageal echocardiography: 2 PTFE sutures ('STRING') anchored in heads of both papillary muscles fixed at the aorto-mitral continuity.

Limitations and pitfalls of the technique

Ring dehiscence may occur after RMA — even after moderate downsizing. Since February 2008 we have eliminated this clinical problem by modifying our suturing technique. After the annular mattress sutures were tied, they were then passed around the annuloplasty ring once more, taking additional bites of atrial tissue and tied again (double-suture technique). Furthermore, in a limited proportion we have observed residual/recurrent tethering, most likely resulting from inadequate tension on the PTFE sutures. Finally, LV reverse remodelling could not be achieved in all patients; further research should be directed towards identifying patients who will not have recovery of LV function.

Subvalvular procedures: Papillary muscle approximation
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Rationale and indication

Papillary muscle approximation (PMA) aims at restoring configuration of the subvalvular apparatus and subsequently reducing tethering forces on the MV. This obviates the need for a downsized annuloplasty ring, and consequently dispels the potential risk of inducing functional mitral stenosis.[53]

We typically add PMA and anterior suspension for patients with moderate-to-severe (≥ grade 2) secondary MR and TH ≥10 mm or diastolic inter-papillary muscle distance ≥30 mm.[54]

Surgical technique

The extent of PMA is determined by the degree of LV remodelling (presence of scar). Incomplete PMA is performed by partial approximation from the tips to the mid-parts of the papillary muscles (using pledgeted mattress sutures of 3-0 polypropylene), through the mitral or aortic valve (**Figure 5**). In the presence of a transmural scar of the anterior LV wall, we perform a complete side-by-side PMA through an anterior LV incision (**Figure 5**). In all patients, concomitant MV annuloplasty with a true- or undersized semi-rigid or rigid ring is performed.[55]

Results

The efficacy of PMA has been investigated in several observational studies and 1 RCT.[55–59] The RCT compared RMA + PMA (n = 48) to RMA alone (n = 48) for patients with severe ischaemic MR.[59] This trial demonstrated no difference in 30-day mortality (6.2% after RMA + PMA compared with 8.3% after RMA alone). Recurrence of MR ≥ grade 3 at 5-year follow-up was

significantly higher in the RMA alone group (56%) compared with the combined procedure (27%; p = 0.013). Furthermore, patients with RMA + PMA showed more LV reverse remodelling (-5.8 mm change in LV end-diastolic diameter from baseline to 5 years follow-up, vs -0.2mm after RMA alone, p <0.001). There was no significant difference in mortality at 5 years (23% after RMA + PMA vs 29% after RMA alone, p = 0.496), but a trend towards better freedom from major adverse cardiac and cerebrovascular events (MACCE) was observed after RMA + PMA [HR 0.66 (0.42 – 1.04), p = 0.073].

The vast majority of studies regarding subvalvular procedures have been conducted in patients with ischaemic MR. However, a propensity matched study including both patients with ischaemic and non-ischaemic MR demonstrated more LV reverse remodelling after RMA + PMA compared with RMA alone.[60] Therefore, subvalvular techniques may be considered in patients with non-ischaemic MR, although more research is needed to establish the beneficial effect in this subgroup of patients.
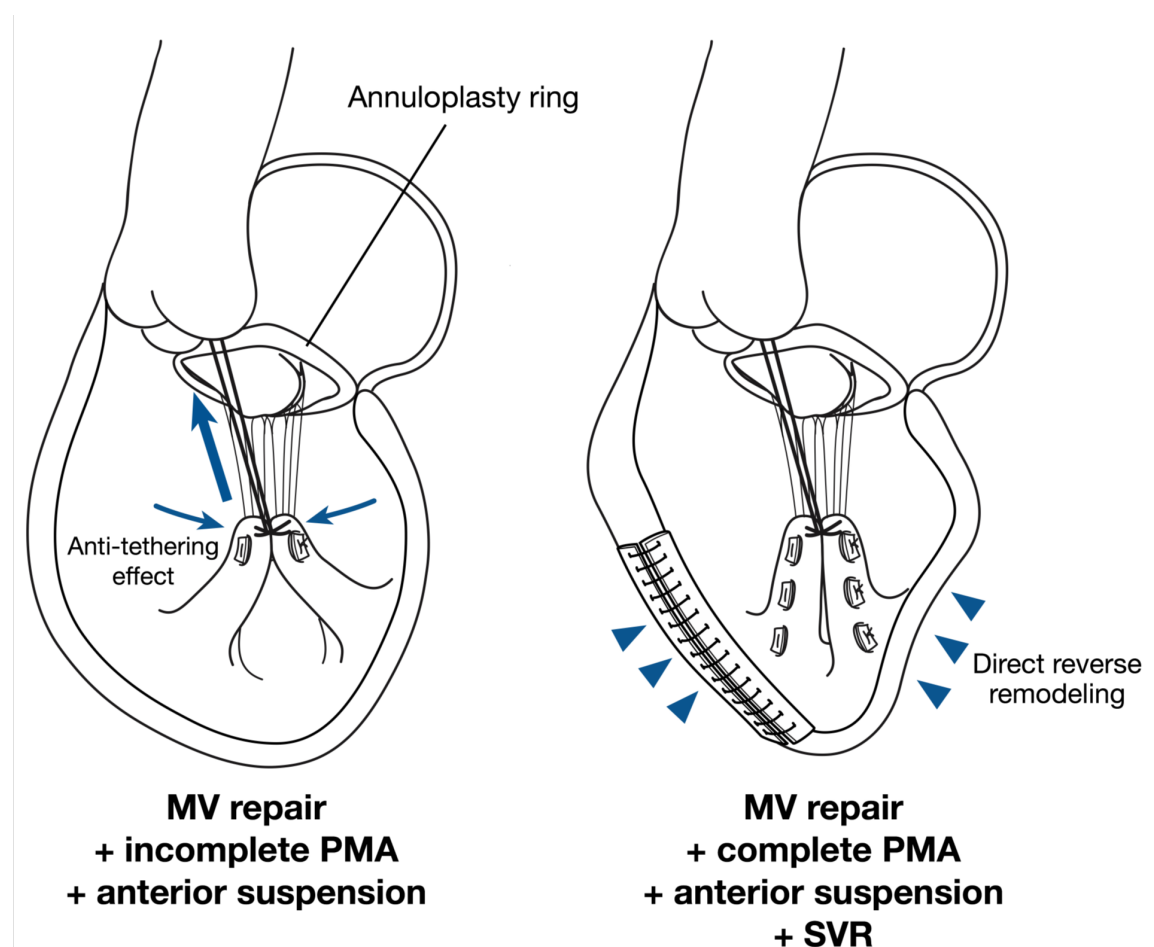

Figure 5. Schematic image of papillary muscle approximation and concomitant procedures.
MV = mitral valve, PMA = papillary muscle approximation, SVR = surgical ventricular reconstruction.

Limitations and pitfalls

PMA in addition to RMA, addressing the specific direction of MV tethering (apical, outward or posterior), reduces the risk of recurrent MR compared to RMA alone. However, in a subgroup of patients, elimination of MV tethering by subvalvular procedures is not sufficient to ensure durability of repair.

Mitral valve replacement

Michael Acker, Roland Assi, Philadelphia, PA, USA

Rationale and indication

The rationale for replacing rather than repairing the MV in patients with secondary MR stems from the high rates of MR recurrence observed after MV repair.[38] MV replacement may improve outcomes by providing a more predictable and durable correction of MR and can be considered in patients with severe ischaemic MR and echocardiographic parameters that are associated with an increased risk of MV repair failure.[12, 13] Furthermore, mortality rates for MV replacement have significantly improved from 10–20% in older series to 4–5% in contemporary series utilizing complete chordal sparing technique.[61] Therefore, the common belief that MV replacement is associated with a higher operative mortality than MV repair is not true today.[28, 29, 62–64]

Results

The strongest evidence to date supporting MV replacement for patients with severe ischaemic MR comes from the multicentre RCT sponsored by the CTSN, where MV repair using an undersized rigid complete annuloplasty ring (and additional subvalvular procedures performed according to surgeon's discretion) was compared with MV replacement with complete chordal sparing.[28, 29] Recurrence of moderate or severe MR was significantly greater in the repair than in the replacement group (33% vs 2% at 1 year; 59% vs 3.8% at 2 years). The primary endpoint of LV reverse remodelling was similar between the groups at both the first- (indexed LVESV -6.6 ml/m^2 after repair vs -6.8 ml/m^2 after replacement, respectively) and second year after surgery (-9.0 vs -6.5ml/m^2, respectively). Mortality at 30 days, 1 year and 2 years was statistically equivalent between both groups (1.6% after repair vs 4% after replacement; 14% vs 18%; 19% vs 23%), as was MACCE. At 1 year, no difference in clinical outcomes was seen, but after 2 years, patients who underwent repair had more heart failure events (24 per 100 patients years vs 15.5 per 100 patients years, p = 0.05) as well as a significantly higher rate of readmissions for cardiovascular causes (48 vs 32 per 100 patient years, p = 0.01). In addition,

there was a trend for greater improvement in quality of life (p = 0.07) as measured by the Minnesota Living with Heart Failure Questionnaire of patients who had a MV replacement. Interestingly, a subgroup analysis demonstrated that patients who underwent MV repair and did not develop recurrent MR had a greater degree of LV reverse remodelling (23% decrease in indexed LVESV) 1 year after surgery than patients who underwent MV replacement (8% decrease in indexed LVESV).[28, 29]

Limitations and pitfalls

MV replacement for severe ischaemic MR has the limitations and pitfalls of any MV replacement, including the risk of infection, thromboembolism and structural valve deterioration over time. Given the observation that patients without recurrent MR after MV repair have more LV reverse remodelling than patients after MV replacement, it is imperative that we learn how to predict the subgroup of patients who can have a durable MV repair.

MitraClip
Alec Vahanian, Paris, France; Jean-Francois Obadia, Lyon, France

Rationale and indication

The rationale for the development of transcatheter techniques in patients with severe secondary MR comes from the fact that secondary MR carries a poor prognosis, patients are often older with several comorbidities, and surgery may be high-risk or even contraindicated; in addition, the benefit of surgery with regard to survival is largely unproven.

The MitraClip technique represents the largest experience available in the domain of transcatheter MV interventions. This technique has been used for more than 10 years, treating >80.000 patients worldwide, of which two thirds had secondary MR. MitraClip replicates the surgical edge-to-edge technique, creating a 'double-orifice' MV.[65]

Recommendations for the use of MitraClip in the current guidelines[2, 9] are of low-level evidence (**Table 1**) and based on 1 RCT (EVEREST II), including a mix of patients with organic and secondary MR, and a number of registries, including mostly, but not exclusively, patients with secondary MR.[66–73] Recently, 2 RCTs have been performed regarding the use of MitraClip in patients with secondary MR.[74, 75]

Results

Registries on outcomes regarding MitraClip for the treatment of secondary MR have inherent limitations. Therefore, we shall focus on 2 RCTs (the MITRA-FR and COAPT trial), which were recently reported and bring important, even if apparently contradictory, information.[74, 75]

Both RCTs only included patients with MR due to ischaemic or non-ischaemic cardiomyopathy and compared optimal GDMT with GDMT + MitraClip implantation. Outcomes were assessed at 1-year follow-up in the MITRA-FR and at 2-year follow-up in the COAPT trial. There are some differences in baseline characteristics between the patients in the 2 trials. First, patients in the MITRA-FR trial were at a more advanced stage of disease: all had a previous heart failure hospitalization and the left ventricles were larger. Furthermore, the initial degree of MR was lower in the MITRA-FR (EROA 31 mm^2) than in the COAPT trial (EROA 41 mm^2), due to differences in thresholds for MR severity between European and US guidelines. Finally, in the COAPT trial, medical therapy was optimized before randomization by a central selection committee (which has methodological advantages but may limit the applicability of the findings), whereas in the MITRA-FR trial this evaluation was based on the local Heart Team decision (which may be suboptimal but represents more 'real-life' practice). Both RCTs confirmed low procedural risk; urgent surgery was not needed in MITRA-FR and in 0.3% in the COAPT trial; 30-day mortality was 3.3% and 2.3%, respectively. Procedural success was high in both studies (91% in MITRA-FR and 95% in the COAPT) and residual MR ≥ grade 2 at discharge was observed in 24% of patients in MITRA-FR and 18% in COAPT. After 1 year, approximately 30% of patients had MR ≥ grade 2 in COAPT compared with approximately 50% in MITRA-FR, which has more missing data. However, it should be kept in mind that the grading of MR was different between the 2 trials and none of the RCTs provided precise figures concerning 'recurrence of MR', which is a concern in surgical publications. In COAPT, LV volumes slightly decreased between the baseline and 2 years follow-up in the intervention group (-3.7 ml), compared with an increase in the control group (+17.1 ml). LV reverse remodelling was not observed in MITRA-FR. Improvement in clinical outcomes was the primary endpoint of both trials: death or heart failure rehospitalizations at 12 months in the MITRA-FR and all heart failure hospitalizations at 24 months in COAPT. There were no differences between groups in MITRA-FR, whereas MitraClip reduced the rate of heart failure hospitalizations, and improved survival, quality of life and functional capacity in the COAPT trial.

The striking differences between the outcomes in the 2 trials are difficult to explain. The most likely explanation is that patients in the MITRA-FR trial were treated at a more advanced stage of LV disease with less MR, where the role of LV dysfunction predominates over the valve dysfunction[76]: COAPT patients had disproportionate MR in relation to LV dysfunction and

derived benefit from valve intervention; MITRA-FR patients had proportionate MR and did not benefit from valve intervention.

Limitations and pitfalls of the technique

Development of MV stenosis is a potential complication of MitraClip implantation. Although mitral stenosis was not observed in either RCT, careful haemodynamic assessment should be performed to avoid such complication. The edge-to-edge transcatheter technique shares the limitations of the isolated surgical technique where the combination with annuloplasty is associated with better outcomes.[65] Currently, other transcatheter techniques such as annuloplasty (as stand-alone procedure or combined with the edge-to-edge technique) and transcatheter MV replacement are at an early stage of development but may be useful in the future.

Left ventricular assist device
Matthias Siepe, Freiburg, Germany

Rationale and indication

The existing evidence on patients with secondary MR and severe LV dysfunction highlights an overall very poor prognosis. Choosing the optimal treatment strategy for these patients is difficult, as reflected by this Great Debate article. MV procedures may not improve outcome, since the underlying disease is not addressed, and ongoing LV remodelling may result in further deterioration of LV function and recurrence of MR. Transcatheter procedures avoid the perioperative risks associated with surgery. However, the recently published MITRA-FR and COAPT trials presented contrasting outcomes regarding efficacy of the MitraClip compared with GDMT.[74, 75] For patients with severe secondary MR and more severe LV dysfunction — like those included in the MITRA-FR trial — each Heart Team should consider allocating patients to LVAD implantation as a valid alternative.

Results

Survival after LVAD implantation has steadily improved over the years, due to improvements in LVAD devices, patient selection, perioperative management and outpatient treatment. There is convincing evidence that in severe end-stage heart failure, the use of ventricular assist devices leads to remarkable improvement of life expectancy compared with GDMT.[77, 78] Nowadays, LVAD therapy has a 1-year survival of approximately 75%.[79] Concomitant MV repair is sometimes considered in patients with severe MR undergoing LVAD implantation.[80] During

LVAD support, MR seems to be irrelevant due to the continuous suction of the device in the LV, which leads to unloading of the LA and pulmonary veins, resulting in a permanently open MV. MR might become relevant again when weaning from the device or a pulsatile mode of the device is anticipated. However, since the likelihood of either of these circumstances is rather low, almost all centres prefer not to address the MR in patients undergoing LVAD implantation.

Limitations and pitfalls

LVAD implantation in patients with secondary MR might be an acceptable solution for those secondary MR patients with the worst left ventricles, but carries the risks of any LVAD implantation, i.e. thrombo-embolic events, anticoagulation-related haemorrhage and infection. Furthermore, patients with severe right ventricular dysfunction are not eligible for LVAD therapy. Therefore, LVAD implantation should be considered before right ventricular function deteriorates.
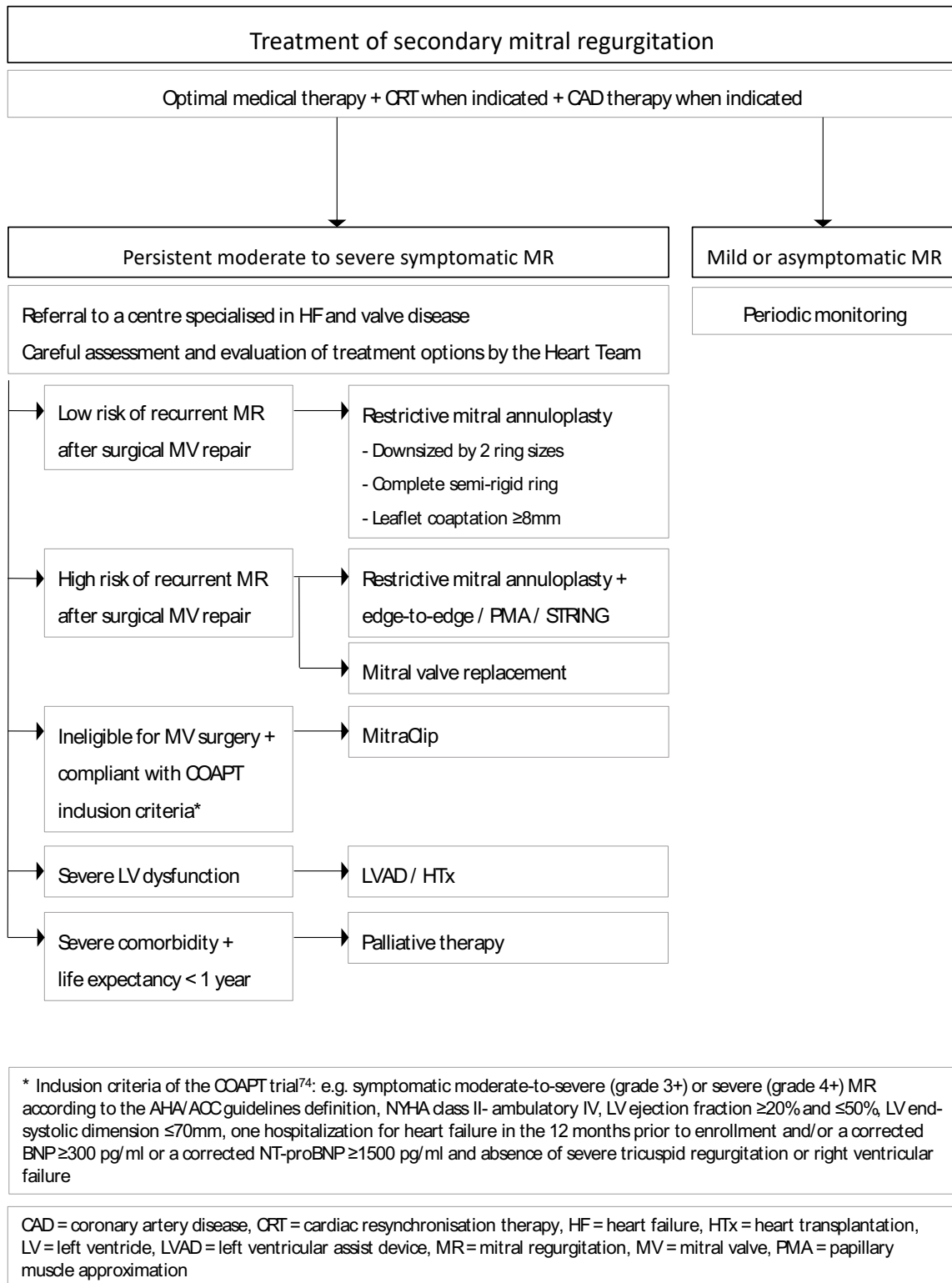
Treatment of secondary mitral regurgitation

Optimal medical therapy + CRT when indicated + CAD therapy when indicated

Persistent moderate to severe symptomatic MR

Referral to a centre specialised in HF and valve disease

Careful assessment and evaluation of treatment options by the Heart Team

Low risk of recurrent MR after surgical MV repair → Restrictive mitral annuloplasty
- Downsized by 2 ring sizes
- Complete semi-rigid ring
- Leaflet coaptation ≥8mm

High risk of recurrent MR after surgical MV repair → Restrictive mitral annuloplasty + edge-to-edge / PMA / STRING

Mitral valve replacement

Ineligible for MV surgery + compliant with COAPT inclusion criteria* → MitraClip

Severe LV dysfunction → LVAD / HTx

Severe comorbidity + life expectancy < 1 year → Palliative therapy

Mild or asymptomatic MR

Periodic monitoring

* Inclusion criteria of the COAPT trial[74]: e.g. symptomatic moderate-to-severe (grade 3+) or severe (grade 4+) MR according to the AHA/ACC guidelines definition, NYHA class II- ambulatory IV, LV ejection fraction ≥20% and ≤50%, LV end-systolic dimension ≤70mm, one hospitalization for heart failure in the 12 months prior to enrollment and/or a corrected BNP ≥300 pg/ml or a corrected NT-proBNP ≥1500 pg/ml and absence of severe tricuspid regurgitation or right ventricular failure

CAD = coronary artery disease, CRT = cardiac resynchronisation therapy, HF = heart failure, HTx = heart transplantation, LV = left ventricle, LVAD = left ventricular assist device, MR = mitral regurgitation, MV = mitral valve, PMA = papillary muscle approximation

Figure 6. Flowchart regarding the treatment of secondary mitral regurgitation.

Conclusion and future implications

The optimal treatment strategy for patients with secondary MR is the subject of ongoing debate. The cornerstone in the management of these patients remains optimal guideline-directed pharmacological and device therapy. Care for patients with persistence of secondary MR despite optimal medical therapy should be concentrated in specialized centres with expertise in heart failure and valve disease.

For patients with severe comorbidity — limiting life expectancy to <1 year — palliative therapy is warranted. For all other patients, the Heart Team — consisting of heart failure specialists, interventional cardiologists, arrhythmia cardiologists and cardiac surgeons — should carefully balance the different available treatment options.[2, 7] A flowchart regarding these treatment options is shown in **Figure 6**.

The benefit of percutaneous MV repair using MitraClip has recently been investigated in 2 RCTs. Results of these trials demonstrated that patients in whom heart failure is predominantly related to valvular dysfunction with relatively preserved LV function — included in the COAPT trial — derived benefit from MitraClip implantation.[74, 75] Therefore, it seems reasonable to try a transcatheter procedure in the highly selected subgroup of patients with secondary MR who fall within the inclusion criteria of this trial (as specified in **Figure 6**).[75]

Several surgical MV procedures have evolved over the years. Mitral valve surgery has the advantage that not only the MV can be addressed, but concomitant procedures can be performed as well, e.g. CABG, tricuspid valve repair and arrhythmia surgery. However, thus far, a survival benefit could not be observed in any of the surgical trials.

Mitral valve repair by RMA has demonstrated beneficial clinical and echocardiographic results in the majority of patients in several studies.[18, 21–23, 27] However, even in the most successful series a subgroup of patients does not show LV reverse remodelling and/or develops recurrent MR.[21, 33, 81] Since recurrence of MR is associated with significantly higher mortality[81], additional valvular or subvalvular techniques may be considered in patients with a high-risk of MV repair failure. These patients can be identified by sophisticated echocardiographic parameters (**Table 2**),[36–39] but a practical guide remains the tenting height. If TH exceeds 10mm, additional procedures — edge-to-edge repair, RING + STRING or PMA — can improve the outcome in terms of freedom from MR recurrence and LV reverse remodelling.

Alternatively, MV replacement can be considered to avoid MR recurrence. Mitral valve replacement provides a durable correction of MR and the CTSN trial found a reduction of heart failure events and cardiovascular hospital readmissions compared with MV repair. However,

the absence of recurrent MR after MV replacement did not translate into better LV reverse remodelling or survival.[28, 29]

Finally, in the subgroup of patients with secondary MR in whom LV dysfunction is too advanced and who most likely will not benefit from any MV procedure, the Heart Team should consider heart transplantation or LVAD therapy.

Patients with secondary MR comprise a highly heterogeneous population and should be treated in specialized centres with expertise in heart failure and valve disease. Dissatisfying outcomes are mainly associated with MR recurrence and/or absence of LV reverse remodelling—which are interrelated in a complex way. Recurrent MR may lead to absence of LV reverse remodelling and adverse clinical outcome, while the absence of LV reverse remodelling may lead to recurrence of MR and again adverse clinical outcome. Since merely resolving MR — by MV replacement — does not offer a definitive solution, the extent of LV dysfunction, rather than abolishment of MR, seems to ultimately determine the fate of patients with secondary MR — or at least for some of them. Most likely a subgroup of patients is already at a stage of LV disease where reverse remodelling and consequently better clinical outcome are no longer attainable at the time of intervention. This specific subgroup of patients will not benefit from any MV procedure, but requires an intervention addressing the underlying ventricular component. We should appreciate that the same limitations will apply to outcomes after percutaneous MV replacement — by some offered as a promising future therapy for secondary MR.

For now, the main challenge for cardiologists and cardiothoracic surgeons remains identifying the individual patients who are most likely to benefit from a MV procedure, and to select the appropriate procedure for each of them. The currently available imaging techniques primarily focus on MV configuration and LV parameters: size, geometry and function. Using these techniques, we can quite adequately predict the probability of recurrent MR after MV interventions.[36–39] However, prediction of the ability to reverse LV remodelling — which seems crucial for recovery after MV interventions — remains an area largely uncovered. Our focus should therefore be to improve imaging techniques assessing the underlying LV disease and its expected functional recovery after MV interventions, and to further improve the different percutaneous and surgical procedures, so that we are able to provide patients with secondary MR a timely and truly tailor-made treatment which optimizes their outcomes.

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