European Journal of Cardio-Thoracic Surgery 56 (2019) 631–642
doi:10.1093/ejcts/ezz238

Cite this article as: Petrus AHJ, Klautz RJM, De Bonis M, Langer F, Schäfers H-J, Wakasa S *et al*. The optimal treatment strategy for secondary mitral regurgitation: a subject of ongoing debate. Eur J Cardiothorac Surg 2019;56:631–42.

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

Annelieke H.J. Petrus [a], Robert J.M. Klautz [a], Michele De Bonis [b], Frank Langer [c], Hans-Joachim Schäfers[d], Satoru Wakasa [e], Alec Vahanian [f], Jean-Francois Obadia [g], Roland Assi [h], Michael Acker [h], Matthias Siepe [i] and Jerry Braun [a,*]

[a] Department of Cardiothoracic Surgery, Leiden University Medical Centre, Leiden, Netherlands
[b] Department of Cardiac Surgery, San Raffaele Hospital, Milan, Italy
[c] Department of Thoracic and Cardiovascular Surgery, University Hospital Homburg, Homburg, Germany
[d] Department of Thoracic and Cardiovascular Surgery, Saarland University Medical Center, Homburg/Saar, Germany
[e] Department of Cardiovascular and Thoracic Surgery, Hokkaido University Hospital, Sapporo, Japan
[f] Department of Cardiology, University Paris Diderot, Paris, France
[g] Department of Cardiac Surgery, Louis Pradel Hospital, Lyon, France
[h] Department of Cardiovascular Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA, USA
[i] Department of Cardiovascular Surgery, University Heart Centre, Freiburg, Germany

* Corresponding author. Department of Cardiothoracic Surgery, Leiden University Medical Centre, Albinusdreef 2, PO Box 9600, 2300 ZA Leiden, Netherlands. Tel: +31-71-5264022; e-mail: j.braun@lumc.nl (J. Braun).

Received 30 May 2019; received in revised form 17 July 2019; accepted 31 July 2019

Keywords: Secondary mitral regurgitation • Mitral valve repair • Subvalvular procedures • Mitral valve replacement • Percutaneous mitral valve procedures

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 (Fig. 1) [1].

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 $\geq$40 mm^2 and a regurgitant volume of $\geq$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 $\geq$20 mm^2 and regurgitant volume of $\geq$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 (Fig. 2). In the past decades, many treatment options have been proposed to break this vicious cycle. The common goal is 2-fold: to restore MV competence and to initiate sustained LV reverse remodelling, in order to improve clinical outcome.

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

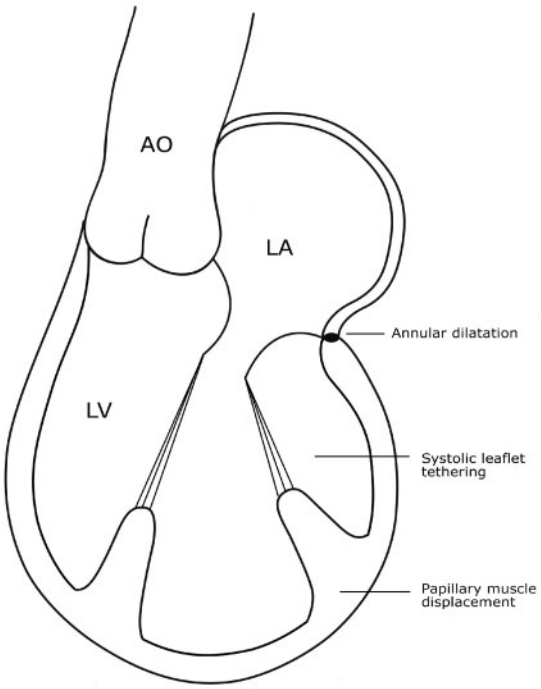

Figure 1: Pathophysiology of secondary mitral regurgitation. AO: aorta, LA: left atrium; LV: left ventricle.

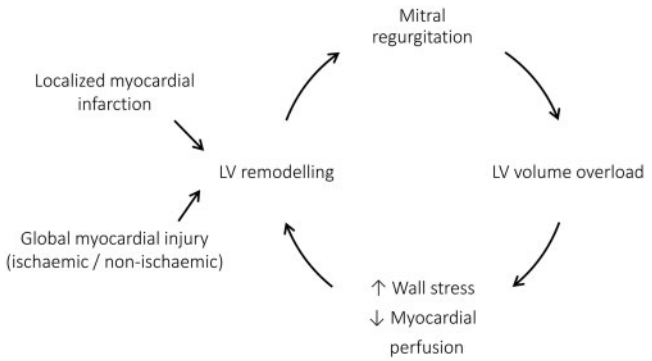

Figure 2: Vicious cycle of secondary mitral regurgitation.

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 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 semi-rigid 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 $\geq$8mm 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

Table 1: Guidelines' recommendations for the surgical treatment of patients with secondary MR

Guideline	Recommendations	LOE	COR
Guidelines on valvular heart disease of the ESC and EACTS [2]	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 optimal medical management (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 optimal medical management (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 optimal medical management (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
Guidelines on valvular heart disease of the AHA and ACC [3, 9]	In patients with moderate ischaemic 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 aortic valve replacement	C	IIa
	It is reasonable to choose chordal sparing mitral valve replacement over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA III to IV) with severe ischaemic MR and persistent symptoms despite GDMT for heart failure	B-R	IIa
	MV repair or replacement may be considered for severely symptomatic patients (NYHA class III to IV) with severe secondary MR who have persistent symptoms despite optimal GDMT for heart failure	B	IIb
Guidelines on ischaemic MV surgery of the AATS [12, 13]	In patients with moderate ischaemic MR undergoing CABG, MV repair with and undersized complete rigid annuloplasty ring may be considered	B	IIIb
	MV replacement is reasonable in patients with severe ischaemic MR who remain symptomatic despite guideline-directed medical and cardiac device therapy and who have a basal aneurysm/dyskinesis, significant leaflet tethering and/or severe LV dilatation (LVEDD >65 mm)	B	IIa
	MV repair with an undersized complete rigid annuloplasty ring may be considered in patients with severe ischaemic MR who remain symptomatic despite guideline-directed medical and cardiac device therapy and who do not have a basal aneurysm/dyskinesis, significant leaflet tethering or severe LV enlargement	B	IIb

AATS: American Association of Thoracic Surgery; ACC: American College of Cardiology; AHA: American Heart Association; 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; GDMT: guideline-directed medical therapy; LOE: level of evidence; LV: left ventricle; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; MR: mitral regurgitation; MV: mitral valve; NYHA: New York Heart Association.

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 end point 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 end point) 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

Table 2: Predictors for recurrence of MR after mitral valve repair by restrictive mitral annuloplasty, assessed by transthoracic echocardiography [36–39]

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 ≥45°
Posterior leaflet tethering distance ≥40 mm
Mitral annulus diameter ≥37 mm[a]
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)

[a]Assessed by transoesophageal echocardiography.
LV: left ventricle; MR: mitral regurgitation.

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].

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

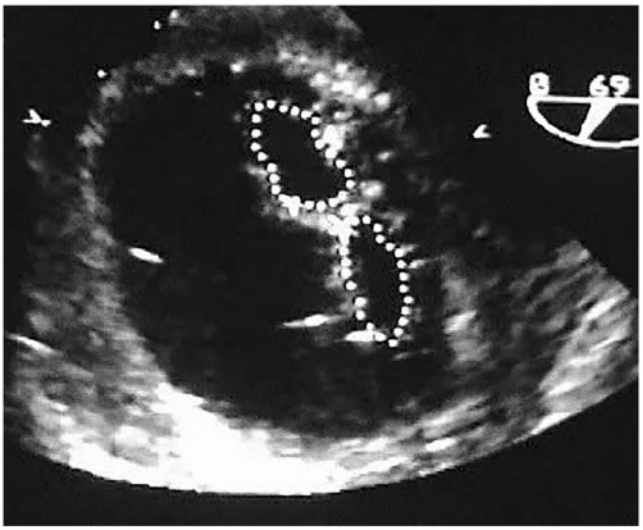

Figure 3: Echocardiographic image of the edge-to-edge procedure.

central jet (between A2 and P2), a central edge-to-edge repair is performed leading to a double-orifice MV configuration (Fig. 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].

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 (Fig. 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.

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

Satoru Wakasa, Sapporo, Japan

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 (Fig. 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 (Fig. 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 -0.2 mm 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.

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].

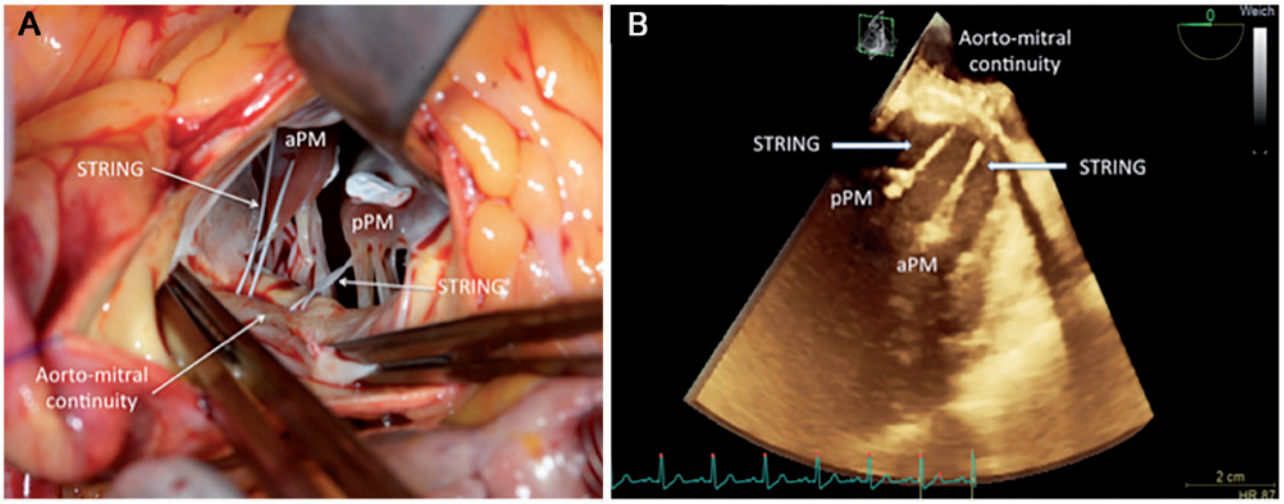

Figure 4: Intraoperative and echocardiographic image of the RING + STRING procedure. (**A**): intraoperative view via horizontal aortotomy: 2 polytetrafluoroethylene (PTFE) sutures ('STRING') anchored in heads of both papillary muscles (aPM: anterior papillary muscle; pPM: posterior papillary muscle) and exteriorized through the aorto-mitral continuity. (**B**): 3-dimensional-transesophageal echocardiography: 2 PTFE sutures ('STRING') anchored in heads of both papillary muscles fixed at the aorto-mitral continuity.

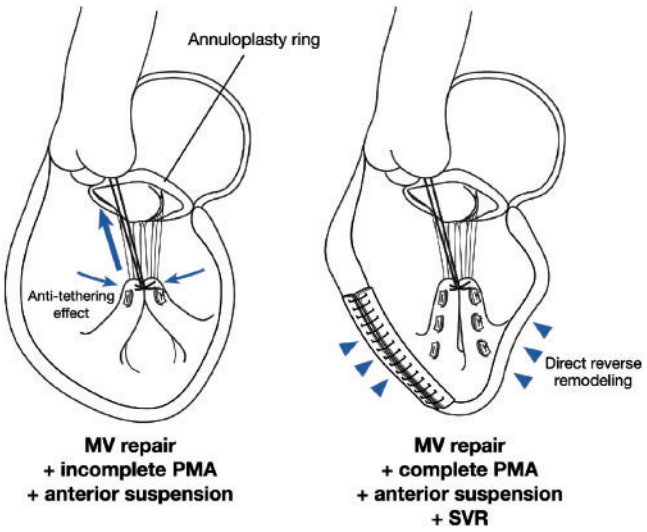

Figure 5: Schematic image of papillary muscle approximation and concomitant procedures. MV: mitral valve; PM: papillary muscle; PMA: papillary muscle approximation; SVR: surgical ventricular reconstruction.

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 end point 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 -6.5 ml/m^2). 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 and 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 end point 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

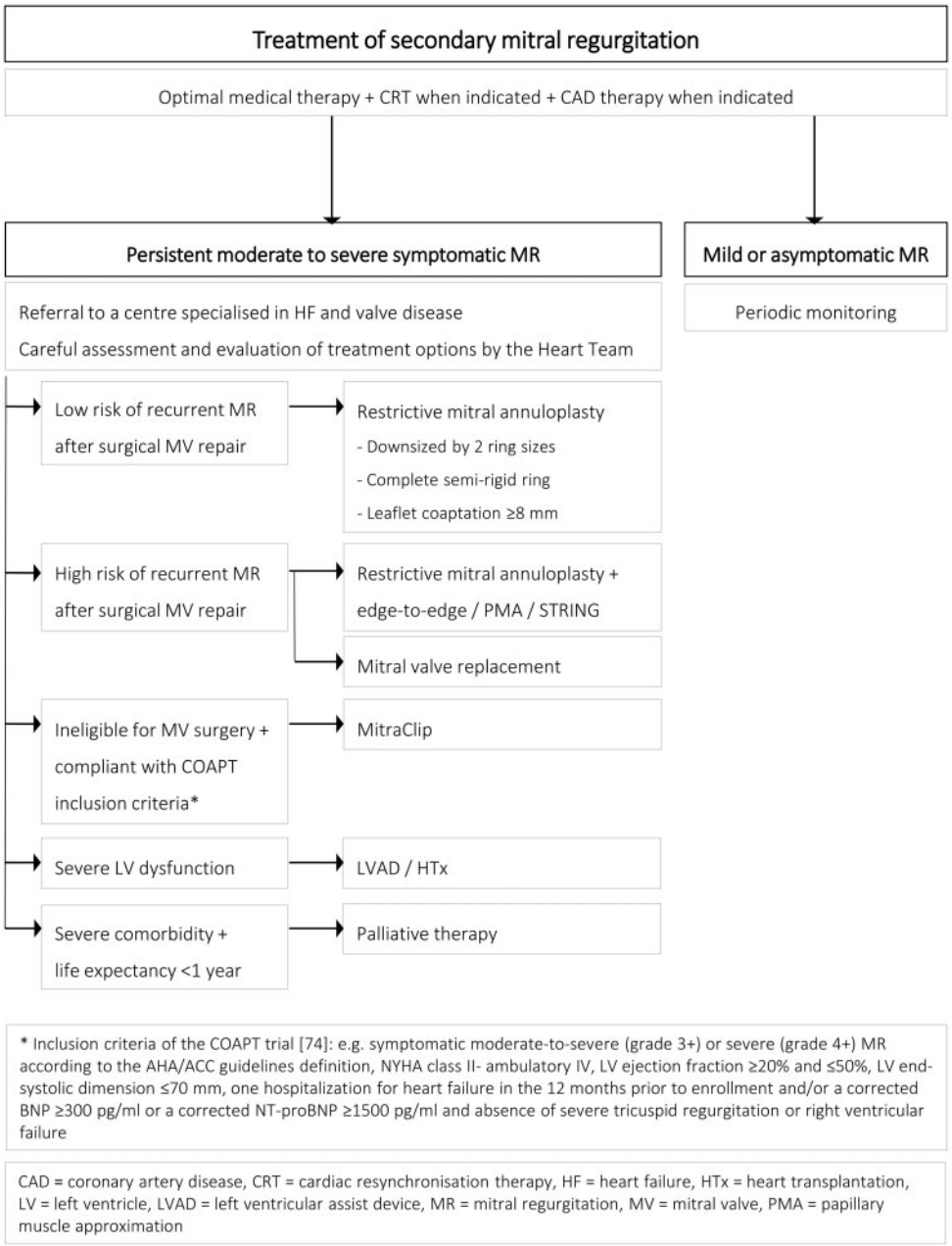

Figure 6: Flowchart regarding the treatment of secondary mitral regurgitation.

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.

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 Fig. 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 Fig. 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 10 mm, 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.

Conflict of interest: Alec Vahanian discloses that he receives speakers' honoraria from Abbott and is a consultant to Cardiovalve.

REFERENCES

[1] Levine RA, Hung J, Otsuji Y, Messas E, Liel-Cohen N, Nathan N. Mechanistic insights into functional mitral regurgitation. Curr Cardiol Rep 2002;4:125–9.
[2] Rossi A, Dini FL, Faggiano P, Agricola E, Cicoira M, Frattini S *et al*. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. Heart 2011;97:1675–80.
[3] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA *et al*. AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:e57–185.
[4] Trichon BH, Felker GM, Shaw LK, Cabell CH, O'Connor CM. Relation of frequency and severity of mitral regurgitation to survival among patients with left ventricular systolic dysfunction and heart failure. Am J Cardiol 2003;91:538–43.
[5] Falk V, Baumgartner H, Bax J, De Bonis M, Hamm C, Holm R *et al*. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur J Cardiothorac Surg 2017;52:616–64.
[6] Sousa-Uva M, Neumann FJ, Ahlsson A, Alfonso F, Banning AP, Benedetto U *et al*. 2018 ESC/EACTS guidelines on myocardial revascularization. Eur J Cardiothorac Surg 2019;55:4–90.
[7] Hillis LD, Smith PK, Anderson JL, Bittl JA, Bridges CR, Byrne JG *et al*. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation 2011;124:e652–735.
[8] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ *et al*. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J 2016;37:2129–200.
[9] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA *et al*. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252–89.

[10] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH *et al*. ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation 2013;128: e240–327.

[11] Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM *et al*. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. J Am Coll Cardiol 2017;70:776–803.

[12] American Association for Thoracic Surgery Ischemic Mitral Regurgitation Consensus Guidelines Writing Committee; Kron IL, Acker MA, Adams DH, Ailawadi G, Bolling SF *et al*. 2015 The American Association for Thoracic Surgery Consensus Guidelines: ischemic mitral valve regurgitation. J Thorac Cardiov Sur 2016;151:940–56.

[13] Kron IL, LaPar DJ, Acker MA, Adams DH, Ailawadi G, Bolling SF *et al*. 2016 update to The American Association for Thoracic Surgery (AATS) consensus guidelines: ischemic mitral valve regurgitation. J Thorac Cardiov Sur 2017;153:e97–114.

[14] Bolling SF, Deeb GM, Brunsting LA, Bach DS. Early outcome of mitral valve reconstruction in patients with end-stage cardiomyopathy. J Thorac Cardiovasc Surg 1995;109:676–82.

[15] Bach DS, Bolling SF. Early improvement in congestive heart failure after correction of secondary mitral regurgitation in end-stage cardiomyopathy. Am Heart J 1995;129:1165–70.

[16] Tibayan FA, Rodriguez F, Langer F, Liang D, Daughters GT, Ingels NB Jr *et al*. Undersized mitral annuloplasty alters left ventricular shape during acute ischemic mitral regurgitation. Circulation 2004;110:II-98–102.

[17] Aklog L, Filsoufi F, Flores KQ, Chen RH, Cohn LH, Nathan NS *et al*. Does coronary artery bypass grafting alone correct moderate ischemic mitral regurgitation? Circulation 2001;104:I68–75.

[18] Chan KM, Punjabi PP, Flather M, Wage R, Symmonds K, Roussin I *et al*. Coronary artery bypass surgery with or without mitral valve annuloplasty in moderate functional ischemic mitral regurgitation: final results of the randomized ischemic mitral evaluation (RIME) trial. Circulation 2012;126:2502–10.

[19] Smith PK, Puskas JD, Ascheim DD, Voisine P, Gelijns AC, Moskowitz AJ *et al*. Surgical treatment of moderate ischemic mitral regurgitation. N Engl J Med 2014;371:2178–88.

[20] Michler RE, Smith PK, Parides MK, Ailawadi G, Thourani V, Moskowitz AJ *et al*. Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. N Engl J Med 2016;374:1932–41.

[21] Braun J, van de Veire NR, Klautz RJ, Versteegh MI, Holman ER, Westenberg JJ *et al*. Restrictive mitral annuloplasty cures ischemic mitral regurgitation and heart failure. Ann Thorac Surg 2008;85:430–6; discussion 36–7.

[22] Geidel S, Lass M, Schneider C, Groth G, Boczor S, Kuck KH *et al*. Downsizing of the mitral valve and coronary revascularization in severe ischemic mitral regurgitation results in reverse left ventricular and left atrial remodeling. Eur J Cardiothorac Surg 2005;27:1011–6.

[23] Grossi EA, Woo YJ, Patel N, Goldberg JD, Schwartz CF, Subramanian VA *et al*. Outcomes of coronary artery bypass grafting and reduction annuloplasty for functional ischemic mitral regurgitation: a prospective multicenter study (randomized evaluation of a surgical treatment for off-pump repair of the mitral valve). J Thorac Cardiovasc Surg 2011;141: 91–7.

[24] Gelsomino S, Lorusso R, De Cicco G, Capecchi I, Rostagno C, Caciolli S *et al*. Five-year echocardiographic results of combined undersized mitral ring annuloplasty and coronary artery bypass grafting for chronic ischaemic mitral regurgitation. Eur Heart J 2007;29:231–40.

[25] Crabtree TD, Bailey MS, Moon MR, Munfakh N, Pasque MK, Lawton JS *et al*. Recurrent mitral regurgitation and risk factors for early and late mortality after mitral valve repair for functional ischemic mitral regurgitation. Ann Thorac Surg 2008;85:1537–42.

[26] Onorati F, Rubino AS, Marturano D, Pasceri E, Santarpino G, Zinzi S *et al*. Midterm clinical and echocardiographic results and predictors of mitral regurgitation recurrence following restrictive annuloplasty for ischemic cardiomyopathy. J Thorac Cardiovasc Surg 2009;138:654–62.

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

[28] Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P *et al*. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med 2014;370:23–32.

[29] Goldstein D, Moskowitz AJ, Gelijns AC, Ailawadi G, Parides MK, Perrault LP *et al*. Two-year outcomes of surgical treatment of severe ischemic mitral regurgitation. N Engl J Med 2016;374:344–53.

[30] Westenberg JJ, Braun J, Van de Veire NR, Klautz RJ, Versteegh MI, Roes SD *et al*. Magnetic resonance imaging assessment of reverse left ventricular remodeling late after restrictive mitral annuloplasty in early stages of dilated cardiomyopathy. J Thorac Cardiovasc Surg 2008;135: 1247–52.

[31] Braun J, Ciarka A, Versteegh MI, Delgado V, Boersma E, Verwey HF *et al*. Cardiac support device, restrictive mitral valve annuloplasty, and optimized medical treatment: a multimodality approach to nonischemic cardiomyopathy. J Thorac Cardiovasc Surg 2011;142:e93–100.

[32] De Bonis M, Taramasso M, Verzini A, Ferrara D, Lapenna E, Calabrese MC *et al*. Long-term results of mitral repair for functional mitral regurgitation in idiopathic dilated cardiomyopathy. Eur J Cardiothorac Surg 2012;42:640–6.

[33] Petrus AHJ, Tops LF, Timmer E, Versteegh MIM, Dekkers OM, Klautz RJM *et al*. Prognostic value of left ventricular reverse remodelling and recurrent mitral regurgitation after personalized surgical treatment of patients with non-ischaemic cardiomyopathy and functional mitral regurgitation. Interact CardioVasc Thorac Surg 2018;27:657–63.

[34] Acker MA, Bolling S, Shemin R, Kirklin J, Oh JK, Mann DL *et al*. Mitral valve surgery in heart failure: insights from the acorn clinical trial. J Thorac Cardiovasc Surg 2006;132:568–77.e1–4.

[35] Acker MA, Jessup M, Bolling SF, Oh J, Starling RC, Mann DL *et al*. Mitral valve repair in heart failure: five-year follow-up from the mitral valve replacement stratum of the Acorn randomized trial. J Thorac Cardiovasc Surg 2011;142:569–74, 74 e1.

[36] Ciarka A, Braun J, Delgado V, Versteegh M, Boersma E, Klautz R *et al*. Predictors of mitral regurgitation recurrence in patients with heart failure undergoing mitral valve annuloplasty. Am J Cardiol 2010;106: 395–401.

[37] Kron IL, Hung J, Overbey JR, Bouchard D, Gelijns AC, Moskowitz AJ *et al*. Predicting recurrent mitral regurgitation after mitral valve repair for severe ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2015;149: 752–61 e1.

[38] Magne J, Senechal M, Dumesnil JG, Pibarot P. Ischemic mitral regurgitation: a complex multifaceted disease. Cardiology 2009;112:244–59.

[39] Lancellotti P, Marwick T, Pierard LA. How to manage ischaemic mitral regurgitation. Heart 2008;94:1497–502.

[40] Bertrand PB, Verbrugge FH, Verhaert D, Smeets CJ, Grieten L, Mullens W *et al*. Mitral valve area during exercise after restrictive mitral valve annuloplasty: importance of diastolic anterior leaflet tethering. J Am Coll Cardiol 2015;65:452–61.

[41] Umana JP, Salehizadeh B, DeRose JJ Jr, Nahar T, Lotvin A, Homma S *et al*. "Bow-tie" mitral valve repair: an adjuvant technique for ischemic mitral regurgitation. Ann Thorac Surg 1998;66:1640–6.

[42] Kinnaird TD, Munt BI, Ignaszewski AP, Abel JG, Thompson RC. Edge-to-edge repair for functional mitral regurgitation: an echocardiographic study of the hemodynamic consequences. J Heart Valve Dis 2003;12: 280–6.

[43] Petrus AHJ, Tops L, Holman ER, Marsan NA, Bax J, Schalij MJ *et al*. Exercise haemodynamics after restrictive mitral annuloplasty for functional mitral regurgitation. Eur Heart J Cardiovasc Imaging 2019.

[44] Glasson JRK, Daughters GT, Bolger AF, Karlsson MO, Foppiano LE, Hayase M *et al*. Early systolic mitral leaflet "loitering" during acute ischemic mitral regurgitation. J Thorac Cardiovasc Surg 1998;116: 193–205.

[45] Bhudia SK, McCarthy PM, Smedira NG, Lam BK, Rajeswaran J, Blackstone EH. Edge-to-edge (Alfieri) mitral repair: results in diverse clinical settings. Ann Thorac Surg 2004;77:1598–606.

[46] De Bonis M, Lapenna E, La Canna G, Ficarra E, Pagliaro M, Torracca L *et al*. Mitral valve repair for functional mitral regurgitation in end-stage dilated cardiomyopathy: role of the "edge-to-edge" technique. Circulation 2005;112:I402–8.

[47] Frater RW. The effects on cordal and leaflet stiffness of severe apical, posterior, and outward papillary displacement in advanced ventricular mechanism heart failure and mitral insufficiency. J Heart Valve Dis 2011; 20:608–18.

[48] Athanasopoulos LV, Casula RP, Punjabi PP, Abdullahi YS, Athanasiou T. A technical review of subvalvular techniques for repair of ischaemic

mitral regurgitation and their associated echocardiographic and survival outcomes. Interact CardioVasc Thorac Surg 2017;25:975–82.
[49] De Bonis M, Lapenna E, Barili F, Nisi T, Calabrese M, Pappalardo F *et al*. Long-term results of mitral repair in patients with severe left ventricular dysfunction and secondary mitral regurgitation: does the technique matter? Eur J Cardiothorac Surg 2016;50:882–9.
[50] Calafiore AM, Gallina S, Di Mauro M, Gaeta F, Iaco AL, D'Alessandro S *et al*. Mitral valve procedure in dilated cardiomyopathy: repair or replacement? Ann Thorac Surg 2001;71:1146–52; discussion 52–3.
[51] Langer F, Kunihara T, Hell K, Schramm R, Schmidt KI, Aicher D *et al*. RING+STRING: successful repair technique for ischemic mitral regurgitation with severe leaflet tethering. Circulation 2009;120:S85–91.
[52] Langer F, Schafers HJ. RING plus STRING: papillary muscle repositioning as an adjunctive repair technique for ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2007;133:247–9.
[53] Shingu Y, Yamada S, Ooka T, Tachibana T, Kubota S, Tsutsui H *et al*. Papillary muscle suspension concomitant with approximation for functional mitral regurgitation. Circ J 2009;73:2061–7.
[54] Wakasa S, Shingu Y, Ooka T, Katoh H, Tachibana T, Matsui Y. Surgical strategy for ischemic mitral regurgitation adopting subvalvular and ventricular procedures. Ann Thorac Cardiovasc Surg 2015;21:370–7.
[55] Wakasa S, Kubota S, Shingu Y, Ooka T, Tachibana T, Matsui Y. The extent of papillary muscle approximation affects mortality and durability of mitral valve repair for ischemic mitral regurgitation. J Cardiothorac Surg 2014;9:98.
[56] Fattouch K, Lancellotti P, Castrovinci S, Murana G, Sampognaro R, Corrado E *et al*. Papillary muscle relocation in conjunction with valve annuloplasty improve repair results in severe ischemic mitral regurgitation. J Thorac Cardiovasc Surg 2012;143:1352–5.
[57] Fattouch K, Castrovinci S, Murana G, Dioguardi P, Guccione F, Nasso G *et al*. Papillary muscle relocation and mitral annuloplasty in ischemic mitral valve regurgitation: midterm results. J Thorac Cardiovasc Surg 2014; 148:1947–50.
[58] Roshanali F, Vedadian A, Shoar S, Naderan M, Mandegar MH. Efficacy of papillary muscle approximation in preventing functional mitral regurgitation recurrence in high-risk patients with ischaemic cardiomyopathy and mitral regurgitation. Acta Cardiol 2013;68:271–8.
[59] Nappi F, Lusini M, Spadaccio C, Nenna A, Covino E, Acar C *et al*. Papillary muscle approximation versus restrictive annuloplasty alone for severe ischemic mitral regurgitation. J Am Coll Cardiol 2016;67:2334–46.
[60] Misumi Y, Masai T, Toda K, Nakamura T, Miyagawa S, Yoshikawa Y *et al*. Restrictive mitral annuloplasty with or without papillary muscle approximation for functional mitral regurgitation. J Heart Valve Dis 2017;26: 447–55.
[61] Yun KL, Sintek CF, Miller DC, Pfeffer TA, Kochamba GS, Khonsari S *et al*. Randomized trial comparing partial versus complete chordal-sparing mitral valve replacement: effects on left ventricular volume and function. J Thorac Cardiovasc Surg 2002;123:707–14.
[62] Gillinov AM, Wierup PN, Blackstone EH, Bishay ES, Cosgrove DM, White J *et al*. Is repair preferable to replacement for ischemic mitral regurgitation? J Thorac Cardiovasc Surg 2001;122:1125–41.
[63] Grossi EA, Goldberg JD, LaPietra A, Ye X, Zakow P, Sussman M *et al*. Ischemic mitral valve reconstruction and replacement: comparison of long-term survival and complications. J Thorac Cardiovasc Surg 2001; 122:1107–24.
[64] Lorusso R, Gelsomino S, Vizzardi E, D'Aloia A, De Cicco G, Luca F *et al*. Mitral valve repair or replacement for ischemic mitral regurgitation? The Italian Study on the Treatment of Ischemic Mitral Regurgitation (ISTIMIR). J Thorac Cardiovasc Surg 2013;145:128–39.
[65] De Bonis M, Lapenna E, Maisano F, Barili F, La Canna G, Buzzatti N *et al*. Long-term results (</=18 years) of the edge-to-edge mitral valve repair without annuloplasty in degenerative mitral regurgitation: implications for the percutaneous approach. Circulation 2014;130:S19–24.
[66] Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS *et al*. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364:1395–406.
[67] Maisano F, Franzen O, Baldus S, Schafer U, Hausleiter J, Butter C *et al*. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. J Am Coll Cardiol 2013;62:1052–61.
[68] Puls M, Lubos E, Boekstegers P, von Bardeleben RS, Ouarrak T, Butter C *et al*. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. Eur Heart J 2016;37: 703–12.
[69] Swaans MJ, Bakker AL, Alipour A, Post MC, Kelder JC, de Kroon TL *et al*. Survival of transcatheter mitral valve repair compared with surgical and conservative treatment in high-surgical-risk patients. JACC Cardiovasc Interv 2014;7:875–81.
[70] Nickenig G, Estevez-Loureiro R, Franzen O, Tamburino C, Vanderheyden M, Luscher TF *et al*. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. J Am Coll Cardiol 2014;64:875–84.
[71] Velazquez EJ, Samad Z, Al-Khalidi HR, Sangli C, Grayburn PA, Massaro JM *et al*. The MitraClip and survival in patients with mitral regurgitation at high risk for surgery: a propensity-matched comparison. Am Heart J 2015;170:1050–9.e3.
[72] Giannini C, Fiorelli F, De Carlo M, Guarracino F, Faggioni M, Giordano P *et al*. Comparison of percutaneous mitral valve repair versus conservative treatment in severe functional mitral regurgitation. Am J Cardiol 2016;117:271–7.
[73] Mendirichaga R, Singh V, Blumer V, Rivera M, Rodriguez AP, Cohen MG *et al*. Transcatheter mitral valve repair with MitraClip for symptomatic functional mitral valve regurgitation. Am J Cardiol 2017;120: 708–15.
[74] Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N *et al*. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018;379:2297–306.
[75] Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM *et al*. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379:2307–18.
[76] Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. JACC Cardiovasc Imaging 2019;12:353–62.
[77] Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D *et al*. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241–51.
[78] de By T, Mohacsi P, Gahl B, Zittermann A, Krabatsch T, Gustafsson F *et al*. The European Registry for Patients with Mechanical Circulatory Support (EUROMACS) of the European Association for Cardio-Thoracic Surgery (EACTS): second report. Eur J Cardiothorac Surg 2018;53: 309–16.
[79] Fang JC. Rise of the machines-left ventricular assist devices as permanent therapy for advanced heart failure. N Engl J Med 2009;361: 2282–5.
[80] Petrus AHJ, Dekkers OM, Tops L, Timmer E, Klautz RJM, Braun J. Impact of recurrent mitral regurgitation after mitral valve repair for functional mitral regurgitation: long-term analysis of competing outcomes. Eur Heart J 2019; doi: 10.1093/eurheartj/ehz306.
[81] Sandoval E, Singh SK, Carillo JA, Baldwin ACW, Ono M, Anand J *et al*. Impact of concomitant mitral valve repair for severe mitral regurgitation at the time of continuous-flow left ventricular assist device insertion. Interact CardioVasc Thorac Surg 2017;25:620–3.