

# Mitral valve interventions in heart failure

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## Abstract

Secondary mitral regurgitation (MR) results from left ventricular dilatation and dysfunction. Quantification of secondary MR is challenging because of the underlying myocardial disease. Clinical and echocardiographic evaluation requires a multi-parametric approach. Severe secondary MR occurs in up to one-fourth of patients with heart failure with reduced ejection fraction, which is associated with a mortality rate of 40% to 50% in 3 years. Percutaneous edge-to-edge mitral valve repair (MitraClip) has emerged as an alternative to surgical valve repair to improve symptoms, functional capacity, heart failure hospitalizations, and cardiac haemodynamics. Further new transcatheter strategies addressing MR are evolving. The Carillon, Cardioband, and Mitralign devices were designed to reduce the annulus dilatation, which is a frequent and important determinant of secondary MR. Several transcatheter mitral valve replacement systems (Tendyne, CardiAQ-Edwards, Neovasc, Tiara, Intrepid, Caisson, HighLife, MV Valve System, and NCSI NaviGate Mitral) are emerging because valve replacement might be more durable compared with valve repair. In small studies, these interventional therapies demonstrated feasibility and efficiency to reduce MR and to improve heart failure symptoms. However, neither transcatheter nor surgical mitral valve repair or replacement has been proven to impact on the prognosis of heart failure patients with severe MR, which remains high with a mortality rate of 14–20% at 1 year. To date, the primary indication for treatment of secondary severe MR is the amelioration of symptoms, reinforcing the value of a Heart Team discussion. Randomized studies to investigate the treatment effect and long-term outcome for any transcatheter or surgical mitral valve intervention compared with optimized medical treatment are urgently needed and underway.

**Keywords** Heart failure; Secondary mitral regurgitation; Hemodynamic; Transcatheter mitral valve repair; Surgical mitral valve repair

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## Pathophysiology of secondary mitral regurgitation

Secondary (syn.: functional) mitral regurgitation (MR) results from left ventricular (LV) dilatation and dysfunction or mitral annulus dilatation, while the mitral valve (MV) is structurally intact (Figure 1).<sup>1,2</sup> Mitral annulus dilatation can occur due to LV or left atrial (LA) dilatation, e.g. in atrial fibrillation.<sup>3–5</sup> In contrast, primary MR is caused by structural disease of the mitral leaflets or the subvalvular apparatus.

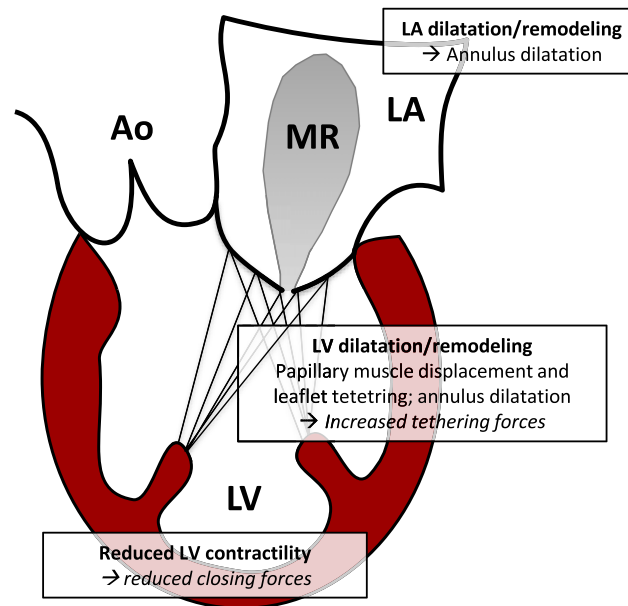
Left ventricular dilatation causes papillary muscle apical and lateral displacement. The consequence is a tethering of the mitral leaflets that can be visualized as the ‘tenting’ sign in echocardiography (Figure 2A), leading to incomplete valve closure and MR (Figure 2B). LV dysfunction with impaired

contractility results in reduced closing forces on the MV. The imbalance between tethering forces and closing forces leads to MV insufficiency.<sup>1,6</sup> Mitral annulus dilatation due to LA dilatation in atrial fibrillation is characterized by a pronounced LA enlargement in comparison with the LV without a ‘tenting’ sign.<sup>5</sup>

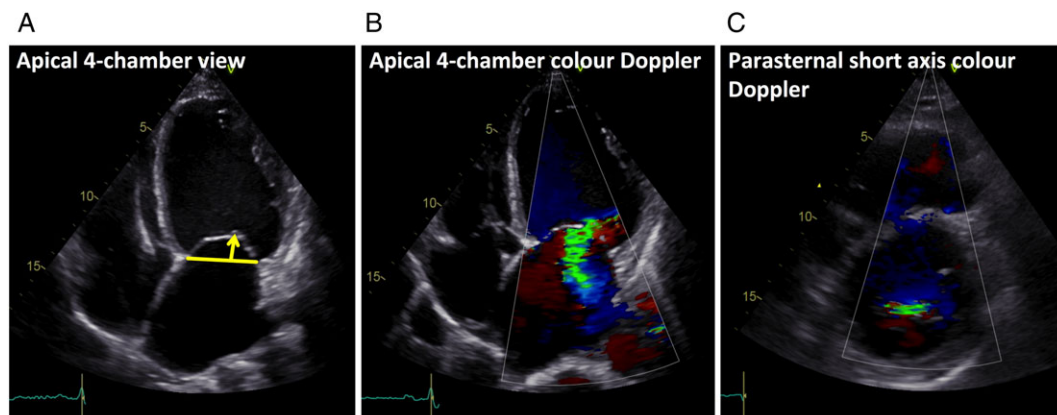
In the literature, ischaemic and non-ischaemic MR has been described. Ischaemic MR does not encompass a specific entity but denotes the occurrence of MR in the presence of significant coronary artery disease, resulting either from regional wall motion abnormality with papillary muscle dysfunction or from ischaemic cardiomyopathy with global LV dysfunction.<sup>7</sup> Non-ischaemic MR occurs in dilated cardiomyopathy.

In MR, the total stroke volume consists of the forward and the regurgitant stroke volumes.<sup>8</sup> With increasing severity of

**Figure 1** Pathophysiology of secondary mitral regurgitation (MR). Scheme of a dilated left ventricle (LV), leading to papillary muscle displacement and increased tethering forces on the mitral leaflets. Closing forces are reduced because of impaired LV contractility. Annulus dilatation occurs frequently, either due to LV or left atrial (LA) dilatation, or both. The imbalance between closing and tethering forces causes secondary MR. Ao, aorta.



**Figure 2** Echocardiography of secondary mitral regurgitation (MR). (A) Echocardiographic four-chamber view demonstrates the mechanism of secondary MR. Mitral valve leaflet tethering can be visualized as the ‘tenting’ sign, i.e. apical displaced leaflet coaptation. The yellow line simulates the virtual mitral annulus, the yellow arrow the tenting high. (B) Apical four-chamber colour Doppler visualizes the central regurgitant flow of secondary MR. However, colour Doppler evaluation is not sufficient to quantify MR. (C) Parasternal short axis colour Doppler view of the mitral valve demonstrates a typical elliptical orifice area of MR along the entire leaflet coaptation line.



secondary MR, the volume load on the LV increases and aggravates LV dilatation and eccentric LV hypertrophy. With increasing severity, regurgitant volume becomes substantial and may exceed forward stroke volume, leading to reduced forward cardiac output and increased LA pressures and pulmonary congestion.<sup>8</sup> Symptoms such as reduced exercise tolerance, exercise dyspnoea, tachypnoea, lower extremity oedema, and acute kidney failure may occur. These signs and symptoms are not specific for secondary MR but reflect symptomatic heart failure.<sup>1,8</sup>

## Diagnosis and definition of severe secondary mitral regurgitation

Echocardiography is the primary method to diagnose and quantify MR.<sup>3</sup> Transthoracic echocardiography usually allows to visualize MR, to identify the mechanism (*Figure 2*), and to assess MR severity by qualitative, semi-quantitative, and quantitative parameters.<sup>9</sup> Transoesophageal echocardiography may be indicated in case of insufficient transthoracic

ultrasound windows and for detailed visualization of the MV anatomy and pathology prior to MV intervention.<sup>4,9</sup> Cardiac magnetic resonance may be useful for additional assessment of the severity and the mechanism of MR in selected patients and to obtain additional information about myocardial remodelling and viability.<sup>4,10</sup>

The quantification of MR may be challenging because secondary MR is dynamic in nature, depends on loading conditions, LV function, and size.<sup>11</sup> Therefore, it requires a systematic approach.<sup>4</sup> The colour flow area of the regurgitant jet is not recommended to quantify MR severity.<sup>9</sup> Semi-quantitative parameters are helpful but not sufficient for the assessment of MR severity. A robust parameter is the ratio of transmitral and LV outflow tract velocity time integrals because it is independent of jet geometry.<sup>9</sup> From a haemodynamic point of view, the best quantitative parameter may be the regurgitant fraction, calculated either by echocardiography or by magnetic resonance tomography. The effective regurgitant orifice area (EROA) and regurgitation volume, derived from the proximal isovelocity surface area method, has been extensively studied. In secondary MR, an EROA > 20 mm<sup>2</sup> and regurgitation volume > 30 mL are associated with an impaired prognosis independent of LV function.<sup>12–14</sup> This applies for both ischaemic and non-ischaemic cardiomyopathy.<sup>12</sup> Therefore, ‘severe’ secondary MR is defined in the 2017 European Society of Cardiology (ESC) valvular heart disease guideline as EROA > 20 mm<sup>2</sup> and regurgitation volume > 30 mL.<sup>3</sup> The 2017 American Society of Echocardiography guidelines define ‘severe’ secondary MR similar to severe primary MR, i.e. EROA > 40 mm<sup>2</sup>, with high specificity. However, an EROA > 30 mm<sup>2</sup> could also indicate severe MR if additional parameters suggest severe MR, for instance, systolic pulmonary flow reversal.<sup>4</sup> The uncertainty about the definition of ‘severe’ secondary MR arises from the fact that any degree of secondary MR affects outcome, even mild and moderate MR,<sup>12–14</sup> and that a prognostic impact of MR correction does not yet exist.<sup>4</sup> Furthermore, the shape of the regurgitation orifice area in secondary MR is rather semilunar than round as in primary MR (*Figure 2C*), leading to underestimation of MR severity by EROA calculation, which has been validated for primary MR.<sup>4,9</sup> An alternative and direct method to assess EROA is to measure the vena contracta area,<sup>4</sup> either from perpendicular biplane views or from a 3D multiplanar reconstruction. It can identify severe secondary MR in cases when the proximal isovelocity surface area method might underestimate EROA and MR severity because of its geometric assumptions.<sup>4</sup> A clear characterization of the degree of secondary MR under stable conditions, particularly with regard to intravascular volume status, and under optimal medical treatment is a prerequisite for the subsequent management of MR. In addition to the mechanism and severity of MR, LV dimensions and function, the size of the LA, pulmonary vein flow using pulsed-wave Doppler, right ventricular function, and pulmonary pressures,

preferably derived from right heart catheterization or from tricuspid regurgitation continuous-wave Doppler signal, complete the haemodynamic assessment and should be reported.

## Left ventricular function and secondary mitral regurgitation

Because the prognostic impact of MV interventions for secondary MR is unknown, it remains unclear if MR is a marker or mediator of prognosis, i.e. if MR indicates advanced stage of heart failure or increases itself the risk for adverse outcome. Kamperidis *et al.* demonstrated with speckle-tracking echocardiography in patients matched for left ventricular ejection fraction (LVEF) but various degrees of secondary MR that those with severe MR had impaired global longitudinal strain, indicating a more deteriorated LV function than LVEF would suggest.<sup>15</sup> LVEF is an imperfect parameter of LV systolic function in MR because of its load dependency.<sup>16</sup> Because a load-independent parameter of LV function is not yet available for clinical routine, forward ejection fraction (calculated as forward stroke volume divided by LV end-diastolic volume) or global longitudinal strain seem to be superior to LVEF to assess LV systolic function in MR.<sup>15,17</sup>

## Transcatheter mitral valve interventions

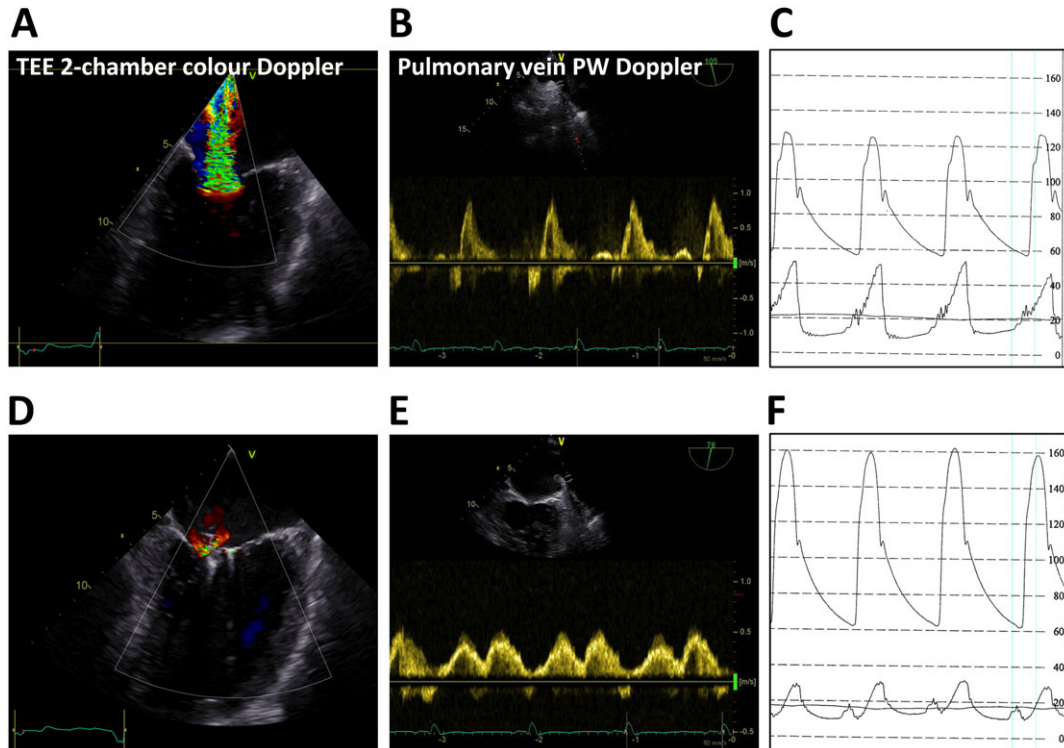
### MitraClip

The MitraClip device (Abbott Vascular, Santa Rosa, CA, USA) is the most widely used technique of transcatheter mitral valve repair (TMVR) with more than 50 000 performed procedures worldwide (ESC Congress 2017, pers. comm.). The principle of MitraClip is based on Alfieri’s edge-to-edge repair, where the anterior and the posterior leaflets are grasped and attached at the location of the regurgitation jet, thus creating a double orifice MV.<sup>18–20</sup> Several clips can be implanted until the regurgitation is sufficiently reduced, but MV orifice area during diastole has to be monitored carefully during the procedure because elevated mitral gradients after TMVR are associated with adverse outcome.<sup>21,22</sup> The edge-to-edge repair technique is a symptomatic therapy because the mechanism, either leaflet tethering or annulus dilatation, is not targeted.

Transcatheter mitral valve repair with MitraClip implantation can immediately improve cardiac haemodynamics (*Figure 3*).<sup>17,23</sup> The pressure–volume relationship in patients with secondary MR undergoing TMVR is displayed in *Figure 4*, indicating reduced volume load with maintained LV contractility despite a drop in LVEF.<sup>17</sup>

The EVEREST (Endovascular Valve Edge-to-Edge Repair Study) trial<sup>19</sup> compared surgical MV repair with the MitraClip

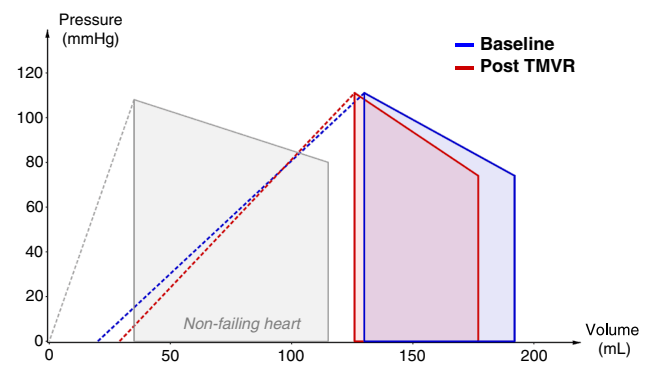
**Figure 3** Haemodynamic changes during percutaneous edge-to-edge repair. (A) Transoesophageal echocardiography (TEE) two-chamber colour Doppler view visualizes severe mitral regurgitation at baseline before transcatheter mitral valve repair (TMVR). (B) Pulsed-wave (PW) Doppler shows blunted systolic antegrade pulmonary vein flow with late-systole flow reversal at baseline. (C) Left atrial (bottom) and peripheral arterial (top) pressure tracings before TMVR. Left atrial pressure is elevated with a prominent v-wave. (D) Two-chamber colour Doppler view shows minimal residual mitral regurgitation after implantation of two MitraClips. (E) PW Doppler demonstrates similar systolic and diastolic antegrade flow in the pulmonary veins after TMVR. (F) Left atrial pressure (bottom) is reduced after successful TMVR despite higher arterial blood pressure (top). The latter might result from increased forward stroke volume but is also affected by the rate of vasopressor administration due to general anaesthesia during TMVR.



device, but only one-third of the patients ( $n = 279$ ) suffered from secondary MR.<sup>19</sup> Overall mortality at 12 months was similar (6%), but the surgical group experienced higher peri-operative morbidity. Major adverse events occurred in 15% vs. 48% ( $P < 0.01$ ) at 30 days, driven by an increased amount of blood transfusion in the surgical group, whereas the TMVR group underwent more often recurrent MV interventions (20% vs. 2%,  $P < 0.001$ ). In the subgroup of patients with secondary MR, the primary efficacy outcome (a composite of freedom from death, surgery for MV dysfunction, and MR  $\leq$  moderate at 12 months) was similar between surgery and TMVR at 1 and 4 years.<sup>19,24</sup> Beyond 1 year, the rates of recurrent MR requiring MV surgery increased only slightly.<sup>24</sup> The EVEREST trial remains the only prospective randomized trial using MitraClip to date. In a study of 120 propensity-matched patients with secondary MR, TMVR was associated with better survival and reduced heart failure re-hospitalizations compared with optimal medical therapy.<sup>25</sup>

Until now, MitraClip is not licenced to treat secondary MR in the USA. Safety and efficacy of TMVR have been confirmed

**Figure 4** Pressure–volume relationship before and after transcatheter mitral valve repair. Schematic pressure–volume relationship derived from non-invasive single-beat analysis in patients with secondary mitral regurgitation before (blue) and after (red) transcatheter mitral valve repair (TMVR) with MitraClip implantation. The dotted lines represent the end-systolic pressure–volume relationship whose slope, the end-systolic elastance, is a marker of left ventricular contractility. The grey lines represent a normal, non-failing heart. Modified according to Lavall *et al.*<sup>17</sup>





in three European registries including a total of >1900 patients,<sup>26–28</sup> whereby >70% of patients suffered from secondary MR. Overall procedural success rate was >91%, with 30 day mortality <5%.<sup>26</sup> The 1 year follow-up demonstrated a mortality rate of 15% to 20% and a re-hospitalization rate of 63%, of which 20% were because of cardiac decompensation.<sup>26</sup> Less than 10% of patients underwent additional MV procedures (surgical or interventional). Further observational studies determined that TMVR is a safe and efficacious procedure in advanced heart failure (LVEF < 25%, New York Heart Association class III/IV) with regard to functional improvement.<sup>29</sup> TMVR seems to be feasible in non-responders to cardiac resynchronization therapy.<sup>30</sup>

## Carillon

The Carillon Mitral Contour System (Cardiac Dimension Inc., Kirkland, WA, USA) is a fixed-length double anchor implant that serves as an indirect annuloplasty system. Implanted in the coronary sinus around the mitral annulus, reduction of MR results from septal–lateral compression of the posterior mitral annulus,<sup>18</sup> thus approaching the mitral leaflets. This technique targets mitral annulus dilatation, similar to surgical annuloplasty. It does not improve tethering of the leaflets. Stretching of the annulus and valvular structures is also an important contributor of recurrent MR after edge-to-edge MV repair.<sup>31</sup> Because leaflet morphology is unaffected by the device, subsequent MV interventions are possible.

In the Carillon Mitral AMADEUS (Annuloplasty Device European Union Study)<sup>32</sup> including 48 patients with dilated cardiomyopathy, LVEF < 40%, and moderate-to-severe secondary MR, the device was successfully implanted in 30 patients. Access issues, insufficient MR reduction and compromise of coronary artery blood flow were reasons in the remaining patients to remove the device before final deposition. The major adverse event rate was 13% at 30 days. The TITAN (Transcatheter Implantation of Carillon Mitral Annuloplasty Device) trial<sup>33</sup> included 83 patients with successful implantation of the device in 66 patients. The 30 day major adverse event rate was 1.9%. After 12 months, there was sustained MR reduction and functional capacity. A second-generation device to avoid previously observed anchor fractures was safe and similarly effective in 36 patients (TITAN II trial).<sup>34</sup> The effects on clinical outcomes are unknown.

## Cardioband

The Cardioband technique (Edwards Lifesciences; Irvine, USA) is derived from the concept of surgical MV restrictive annuloplasty. The Cardioband is a direct transcatheter annuloplasty system, which is anchored into the annulus

tissue at several points along the posterior MV annulus under 3D echocardiographic guidance.<sup>18,35</sup> After complete implantation, the band is contracted by external rotation on the delivery catheter, thereby narrowing the septal–lateral dimension of the MV annulus until MR is sufficiently reduced on transoesophageal echocardiography. This system targets annulus dilatation. A first-in-man study of 31 high-risk patients with secondary MR showed feasibility and safety without procedural death, a high rate of technical success, and sustained reduction of MR ( $\leq$  moderate MR) in 88% of patients at 30 days.<sup>35</sup> Cardioband implantation is (still) time-consuming; the mean implantation time was  $2:45 \pm 0:44$  min.

## Mitralign

Mitralign is a direct annuloplasty system that uses radiofrequency energy to penetrate sutures for two pledgets into the mitral annulus tissue posterior and anterior to the commissure. By cinching the sutures, the mitral annulus becomes reduced.<sup>18</sup> In the Mitralign Percutaneous Annuloplasty First-in-Man Study,<sup>36</sup> the device was successfully implanted in 50 out of 71 patients with secondary MR. The 30 day mortality was 4.4%. Echocardiography demonstrated reduction of MR grade in 50% of patients 6 months after implantation, associated with reverse LV remodelling and improved functional status.

## Transcatheter mitral valve replacement

Concerns about the durability of any TMVR repair technique yielded the concept of transcatheter MV replacement. The implantation of a prosthesis into the MV is challenging because of the oval and saddle-shaped MV geometry, the non-rigid nature of the mitral annulus, the need to anchor the prosthesis, the large variation in mitral annular sizes, and the risk of LV outflow tract obstruction. There are currently eight biological, self-expanding prostheses that are under clinical development. The implantation is executed mostly through a transapical access.<sup>37</sup> Observational studies for each prosthesis consist of 5–50 high-risk patients with predominantly secondary MR and varying follow-up times up to 20 months. Feasibility was demonstrated by successful device implantation rate of 76–93%, conversion to open heart surgery 0–15%, procedural mortality 0–30%, and 30 day mortality 3–53%.<sup>37,38</sup> At follow-up, MR reduction was sustained (no patients with more than moderate MR at follow-up in all reports), and symptom status improved. A recent review summarizes the current state of transcatheter MV replacement.<sup>37</sup> No transcatheter MV prosthesis is currently approved for clinical use. Further studies are expected in the next years.

Transcatheter MV replacement has been performed in failed mitral bioprosthetic valves (valve-in-valve) and failed ring annuloplasty (valve-in-ring) in patients at high risk for re-operation. A recent multicentre registry of 248 patients determined feasibility using transcatheter balloon-expandable aortic valves through a transseptal or transapical access.<sup>39</sup> Mean LVEF in this study was  $52.5\% \pm 13.9\%$ . Technical success was 92.3% at the end of the procedure and 30 day mortality 6.5%. Post-procedural morbidity as well as 1 year mortality was higher in patients with valve-in-ring compared with valve-in-valve procedures (28.7% vs. 12.6%).<sup>39</sup>

## Surgical solutions

Because the underlying LV myocardial dysfunction in secondary MR cannot be corrected, surgical approaches are restricted to reduce heart failure morbidity. Secondary MR surgery should aim to alter LV geometry, i.e. reducing mitral annulus and LV dimensions in order to reduce tethering forces. Complete restrictive ring annuloplasty with implantation of an undersized complete MV ring to improve leaflet co-adaptation is the most widely applied technique.<sup>1–3,7</sup> However, it addresses only one determinant of secondary MR, i.e. annulus dilatation. Restrictive annuloplasty is associated with high rates of MR recurrence because it can increase posterior MV leaflet tethering when there is a mismatch between ring size and LV dimension.<sup>40</sup> Additional subvalvular procedures, such as secondary chordal cutting<sup>41</sup> and papillary muscle repositioning with a trans-ventricular suture ('string' technique),<sup>42</sup> have been proposed to overcome this issue.<sup>2</sup> Reports on subvalvular repair techniques are limited by their small sample size and single centre, retrospective designs.<sup>43</sup> Papillary muscle approximation in addition to complete surgical myocardial revascularization and undersized restrictive MV annuloplasty reduced LV dimensions and MR recurrence at 5 years in a randomized trial, but overall mortality and quality of life did not differ.<sup>44</sup>

The impact of surgical MV repair on mortality in secondary MR is unclear. A subgroup analysis of the prospective STICH (Surgical Treatment for Ischemic Heart Failure) trial showed that surgical MV repair combined with coronary artery bypass grafting (CABG) in patients with LVEF < 35% was associated with reduced mortality compared with CABG alone (hazard ratio 0.41,  $P < 0.006$ ).<sup>14</sup> Of note, the decision to treat the MV in this trial was left to the surgeon. In a prospective trial in 301 patients with moderate MR (defined as EROA 20–39 mm<sup>2</sup>) undergoing CABG randomized to either CABG or CABG with surgical MV repair,<sup>45</sup> there were neither differences in LV remodelling (the primary endpoint) nor in mortality after 1 year. However, patients in the MV repair group had longer hospital stay and more neurologic events but lower rates of recurrent moderate or severe MR at follow-up. Two other prospective randomized trials showed beneficial effects

of concomitant MV repair with regard to LV reverse remodelling and functional capacity compared with those treated with CABG alone, with no differences in mortality.<sup>46,47</sup> In patients with secondary MR and dilated cardiomyopathy, the existing small studies do not allow to draw definite conclusions regarding the impact of MV surgery on survival.<sup>3</sup>

Recurrent MR after MV repair is an important issue occurring in up to 25% of patients after 1 year.<sup>1</sup> Bioprosthetic surgical MV replacement with preservation of the subvalvular apparatus was similarly effective as MV repair in secondary MR regarding death, ventricular remodelling, and serious adverse events. However, recurrent MR occurred more frequently in the repair group (58.8% vs. 3.8%,  $P < 0.001$ ), thus resulting in more re-hospitalizations (48.3% vs. 42.2%,  $P = 0.01$ ) and adverse events due to heart failure (24.0% vs. 15.2%,  $P = 0.05$ ).<sup>48</sup>

## Guideline recommendations

Optimal medical therapy, i.e. up-titration of angiotensin-converting enzyme inhibitor, beta-blocker, and MR antagonist as well as diuretics according to volume status, is the first-line treatment for secondary MR.<sup>3,49</sup> Cardiac resynchronization therapy is indicated in left bundle branch block with a QRS width > 130 ms because in responders, LV reverse remodelling and restoration of synchronous papillary muscle contraction increase MV closing forces, thus reducing MR.<sup>3,49</sup>

Surgical MV repair is recommended in patients with severe secondary MR undergoing CABG (level of recommendation, I). MV replacement instead of MV repair should be considered if morphological risk factors on echocardiography for MR recurrence are present.<sup>3,9</sup> In those patients with LVEF < 30%, MV surgery should be considered if there are options for revascularization and evidence of myocardial viability (IIa). In patients without indication for revascularization and LVEF > 30%, either surgery or transcatheter edge-to-edge repair may be considered, depending on the surgical risk and the valve morphology (IIb). In patients with an LVEF < 30% who remain symptomatic despite optimal heart failure therapy, the Heart Team should discuss therapeutic options including LV assist device implantation, heart transplantation, MV surgery, and transcatheter edge-to-edge repair on an individual basis (IIb). Overall, the evidence for these recommendations is low (level of evidence C).<sup>3</sup>

## Perspectives

There are several ongoing clinical trials that randomize patients with secondary MR and symptomatic heart failure to either TMVR (using different devices) or optimal medical therapy (Table 1). In 2018, the results of the COAPT trial

Table 1 Ongoing randomized clinical trials of transcatheter MV repair in secondary MR

Study acronym	ClinicalTrials.gov identifier	Device	Control group	Key inclusion criteria	Primary outcome measures	Duration	Patients scheduled
COAPT	NCT01626079	MitraClip	Standard hospital clinical practice	Symptomatic functional MR ( $\geq 3+$ ), optimal HF therapy, NYHA II–IV, LVEF 20–50%, $> 1$ HF hospitalization $< 12$ months or elevated BNP/NT-proBNP	(i) Safety: Device detachment or embolization, endocarditis requiring surgery, mitral stenosis requiring surgery, LVAD implant, heart transplant, and any device-related complications requiring non-elective cardiovascular surgery (ii) Effectiveness: Survival and recurrent HF hospitalizations All-cause mortality, unplanned hospitalizations for HF	12 months	610
MITRA-FR	NCT01920698	MitraClip	GDMT	Severe MR (RV $> 30$ mL or EROA $> 20$ mm <sup>2</sup> ), NYHA $\geq$ II, LVEF 15–40%, optimal HF therapy, $> 1$ HF hospitalization $< 12$ months Clinically significant MR ( $\geq 3+$ ), optimal HF therapy, NYHA II–IV, LVEF 15–45%, $> 1$ HF hospitalization $< 12$ months or elevated BNP/NT-proBNP	Cardiovascular death and composite rate of recurrent HF hospitalizations and cardiovascular death	12 months	288
RESHAPE-HF2	NCT02444338	MitraClip	Optimal standard of care therapy	Clinically significant MR ( $\geq 3+$ ), optimal HF therapy, NYHA II–IV, LVEF 15–45%, $> 1$ HF hospitalization $< 12$ months or elevated BNP/NT-proBNP	Cardiovascular death and composite rate of recurrent HF hospitalizations and cardiovascular death	$\geq 24$ months	420
MATTERHORN	NCT02371512	MitraClip		Clinically significant MR, LVEF 20–45%, optimal HF treatment, NYHA III–IV	Composite of death, re-hospitalization for HF, re-intervention (repeat operation or repeat intervention), assist device implantation and stroke (whatever is first)	12 months	210
MITRA-CRT	NCT02592889	MitraClip	Optimized GDMT	MR $\geq 2+$ , previous CRT implantation, adequate CRT therapy without clinical response to CRT (NYHA III or NYHA II with a hospital admission for HF $< 12$ months), LVEF 15–40%	(i) Safety: Number of participants without adverse events related with the therapy (stroke, device embolization, emergent surgery/pericardiocentesis or procedural-related mortality) (ii) Effectiveness: Improvement $> 10\%$ in 6MWT, no readmissions for HF, heart transplantation, or mortality Change in regurgitant volume	12 months	30
REDUCE FMR	NCT02325830	Carillon	Optimized GDMT	MR $\geq 2+$ , NYHA II–IV, LVEF $< 50\%$ , 6MWT 150–450 m, stable HF medication for at least 3 months		12 months	180
ACTIVE	NCT03016975	Cardioband	GDMT	Clinically significant MR, NYHA II–IV, previous HF hospitalization $< 12$ months or elevated BNP	Prevalence of MR $\leq 2+$ , time to cardiovascular death, number of HF hospitalizations, improvement in 6MWT distance and KCCQ	12 months	375

6MWT, six min walk test; ACTIVE, Annular Reduction for Transcatheter Treatment of Insufficient Mitral Valve trial; COAPT, Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; CRT, cardiac resynchronization therapy; EROA, effective regurgitant orifice area; GDMT, guideline-directed medical therapy; HF, heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MATTERHORN, Multicenter, Randomized, Controlled Study to Assess Mitral Valve Reconstruction for advanced Insufficiency of Functional or isChemic Origen; MITRA-CRT, MitraClip in Non-Responders to Cardiac Resynchronization Therapy; MITRA-FR, Multicenter Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation; MR, mitral regurgitation; MV, mitral valve; NT-proBNP, N terminal pro brain natriuretic peptide; NYHA, New York Heart Association functional class; REDUCE FMR, Safety and Efficacy of the Carillon Mitral Contour System in Reducing Functional Mitral Regurgitation Associated with Heart Failure; RESHAPE-HF2, Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation; RV, regurgitation volume.

are awaited at the Transcatheter Cardiovascular Therapeutics congress and those of the MITRA-FR trial at the ESC congress.

In the rapidly evolving field of MV interventions, there are many unresolved issues:

- Prognostic impact: Most importantly, adequately powered, randomized controlled trials to evaluate the impact on long-term prognosis of any MV intervention, i.e. transcatheter or surgical, compared with optimal medical therapy in patients with chronic heart failure and secondary MR are urgently needed.
- Endpoints in trials: Relevant endpoints include mortality and heart failure hospitalizations. Exercise capacity, i.e. 6 min walk test and/or spiroergometry, quality of life, and symptom status should be assessed in a controlled study designs.
- Timing of MV intervention: Because there are disparities in MR quantification between European and American guidelines, studies should concisely describe their method of quantification. Previous studies included mostly patients with 'moderate-to-severe' MR. There are no data if an earlier intervention in patients 'at risk', for instance, with mild or moderate MR, would impact the clinical course of chronic heart failure. On the other side, patients with 'severe' MR are at highest risk for decompensation, i.e. MV intervention could have the greatest impact in these patients.
- Target of intervention: Should TMVR aim to reduce or to eliminate MR? Despite the evidence that procedural failure of TMVR is a strong predictor for death,<sup>26</sup> there are no data how aggressively MR needs to be treated during the intervention. This applies particularly for the edge-to-

edge repair where several clips can be implanted if needed.

- Choice of device: The available devices address different mechanisms of MR, thus an individual therapy based on the underlying mechanism of MR may become applicable. For instance, failing annuloplasty could be followed by edge-to-edge repair. However, these pathophysiological considerations require prospective data to support this strategy.

## Conclusions

Secondary MR remains a diagnostic and therapeutic challenge. Indications for interventions are symptomatic heart failure despite optimal medical and device therapy. Surgical MV repair is indicated in severe secondary MR and options for coronary revascularization. TMVR is emerging with many new devices. Transcatheter edge-to-edge repair may be considered for patients at high risk for surgery according to the current guidelines. However, the prognostic impact of any surgical or transcatheter MV intervention is unproven, reinforcing the need for randomized controlled clinical studies.

## Conflict of interest

M.A.B. is a consultant for Edwards Lifesciences, CryoLife, and Medtronic. D.L., A.H., S.H.S., M.B., and U.L. declared no conflicts of interest.

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