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CURRENT OPINION

# Surgical and interventional management of mitral valve regurgitation: a position statement from the European Society of Cardiology Working Groups on Cardiovascular Surgery and Valvular Heart Disease

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## Executive summary

- Surgical and interventional treatment for mitral regurgitation (MR) requires a multidisciplinary approach. Experienced operators in high volume centers with a dedicated Heart Team obtain best outcomes.
- Surgical repair is the reference standard treatment in primary MR. Timely surgery is associated with excellent outcome and restoration of normal life expectancy. Percutaneous procedures should be reserved for high-risk or inoperable symptomatic patients.
- The choice of treatment in secondary MR is more controversial:
  - Surgical correction can improve symptoms and quality of life, and reverse left ventricular (LV) remodelling in selected patients. However, a clear prognostic benefit in comparison with optimal medical therapy has not been demonstrated. Undersized annuloplasty might offer a satisfactory result if performed before the onset of severe LV dilatation and in the absence of echocardiographic predictors of post-operative residual or recurrent MR. Otherwise, mitral valve (MV) replacement with preservation of the sub-valvular apparatus is preferable.
  - Percutaneous edge-to-edge (EE) repair for secondary MR is a low-risk option to reduce symptoms and induce reverse LV remodelling but is commonly associated with residual and recurrent MR. The procedure should be reserved for patients who have significant symptoms despite optimal heart failure therapy (including cardiac resynchronisation where appropriate), are judged to be at excessive risk for MV surgery by a Heart Team, fulfil the echocardiographic criteria of eligibility, and do not have existing comorbidities to preclude the benefits of correction or reduction of MR.
- Ongoing trials in patients with isolated secondary MR will define whether percutaneous EE repair has a significant role in the management of heart failure.

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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- Randomized studies are needed to clarify whether correction of MR in high-risk patients provides clinical and prognostic benefit in comparison with optimal medical therapy.

# Introduction

Mitral regurgitation (MR) has a prevalence of 2% in the general population and is even more common in the elderly.[1] Organic (or primary) MR arises as a result of pathology affecting one or more components of the mitral valve (MV) apparatus, whereas functional (or secondary) MR is a consequence of annular dilatation and geometrical distortion of the sub-valvular apparatus secondary to left ventricular (LV) remodelling and dyssynchrony, most usually associated with cardiomyopathy or coronary artery disease.

Primary MR is usually a consequence of degenerative disease, which may remain asymptomatic for many years—intervention has generally been withheld until the onset of symptoms or evidence of haemodynamic decompensation. However, treatment algorithms have been redefined in recent years as a result of the excellent outcomes of surgical repair. International guidelines now recommend risk stratification and earlier intervention when the probability of durable repair is high and when surgery can be undertaken by experienced teams with high repair rates and low operative mortality and morbidity.[2]

Secondary MR has worse prognosis and treatment options are complex, including optimized medical therapy, biventricular pacing, valve surgery (with or without revascularization), long-term LV assist devices or cardiac transplantation. Surgery is challenging with inferior outcomes than in primary MR and the indications and choice of technique are not supported by robust evidence.[2]

In recent years, a variety of approaches to percutaneous treatment of primary and secondary MR has emerged. The most widely adopted has been the edge-to-edge (EE) procedure with promising results in large registries and small randomized trials. Meanwhile, numerous alternative technologies (including percutaneous MV replacement) are in development.

Herein, a Task Force of the European Society of Cardiology (ESC) Working Groups on Cardiovascular Surgery and Valvular Heart Disease outline the indications and limitations of surgical and percutaneous treatment of MR, and propose recommendations for case selection, team working and outcome monitoring.

# The Heart Team

A multidisciplinary Heart Team (interventional cardiologists, cardiac surgeons, anaesthetists, imaging, and heart failure specialists) should evaluate the pros and cons of surgical, percutaneous and conservative approaches in all high-risk patients with MR, assessing the risk–benefit ratio of each option whilst incorporating relevant comorbidities and individualized life expectancy. The possible futility of intervention in very high-risk subjects must also be considered—some will not benefit from surgical or percutaneous intervention and conservative management (and possible palliative care) is more appropriate.

Risk assessment is fundamental to decision-making, particularly when considering a procedure other than the reference standard.

**Table 1 Echocardiographic criteria for the definition of severe mitral regurgitation**

| | |
|---|---|
| **Qualitative** | |
| Mitral valve morphology | Flail leaflet/ ruptured papillary muscle |
| Colour flow regurgitant jet | Very large central or eccentric jet adhering, swirling and reaching the posterior wall of the left atrium |
| Continuous wave signal of regurgitant jet | Dense/triangular |
| Flow convergence zone | Large[a] |
| **Semi-quantitative** | |
| Vena contracta width (mm) | ≥7 (>8 for biplane)[b] |
| Pulmonary vein flow | Systolic flow reversal |
| Inflow | E-wave dominant ≥1.5 m/s[c] |
| TVI mitral/TVI aortic | ≥1.4 |
| **Quantitative** | |
| EROA ($mm^2$) | ≥40 (primary)<br>≥20 (secondary) |
| Regurgitant volume (mL/beat) | ≥60 (primary)<br>≥30 (secondary) |
| Cardiac chamber enlargement | Left ventricle, left atrium |

TVI, time-velocity integral; EROA, effective regurgitant orifice area.
[a]Nyquist limit 50–60 cm/s.
[b]Average between apical four- and two-chamber views.
[c]In the absence of mitral stenosis or other causes of elevated left atrial pressure.

Percutaneous intervention in MR should currently be reserved for high-risk or inoperable patients. While most procedural risk scores discriminate between high and low risk, they were not developed in large cohorts with valvular heart disease and are poorly calibrated in high-risk subjects.[3] Definitions of 'high surgical risk' and the 'inoperable patient' remain elusive and significantly influenced by surgeon and centre experience.[4,5] Established risk scores (e.g. STS, Euroscore) should be utilized in conjunction with other factors (e.g. frailty, porcelain aorta) as recommended by the VARC-2 consensus document.[6]

A tailored approach for individual patients remains appropriate in the absence of guidelines for the conduct of Heart Team activity and an evidence-base to demonstrate its effectiveness.[3] Research to confirm the intuitive benefits of the Heart Team approach is required, potentially by the ESC or European Union using centralized audit resources.

# Imaging assessment

Detailed (usually transoesophageal) echocardiography (TEE) is essential to quantitate MR (*Table 1*, *Figure 1*), define anatomical suitability for surgical or percutaneous MV repair and demonstrate the presence of LV/left atrial thrombi or active endocarditis which might contraindicate intervention or suggest an alternative approach.

In patients with primary MR suitable for surgery, all scallops of the posterior and anterior leaflets should be carefully assessed with

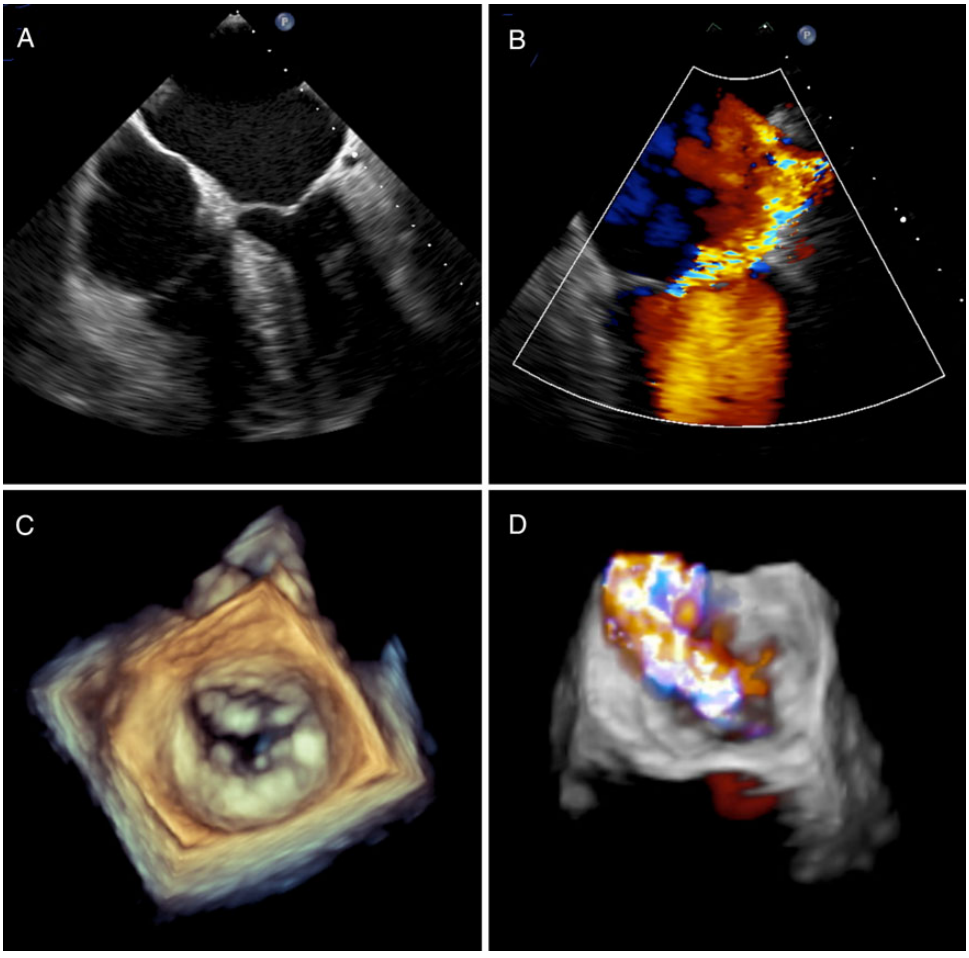


**Figure 1** Three-dimensional transoesophageal echocardiographic evaluation of the mitral valve. (*A*) 0° plane illustrating left left atrial dilatation and leaflet configuration. (*B*) 60° plane demonstrating an eccentric anteriorly directed jet of moderate–severe mitral regurgitation. (*C*) Three-dimensional surgical view from the left atrium demonstrating mitral valve orifice in mid-diastole. (*D*) Three-dimensional view with colour flow Doppler confirming eccentric anteriorly directed jet of moderate–severe mitral regurgitation. Images courtesy of Dr Ronak Rajani, St Thomas' Hospital, London, UK.

comprehensive description of the lesion(s), their location and the presence of annular calcification.

When surgery is considered in secondary MR, echocardiographic LV parameters are mandatory (volume, ejection fraction, and sphericity index) accompanied by assessment of geometric MV distortion (tenting area, coaptation depth, leaflet angles, and inter-papillary muscle distance). Numerous predictors of recurrent MR after undersized annuloplasty have been identified[2] (*Table 2*, *Figures 2* and *3*) and their presence should lead to consideration of MV replacement as a more durable solution.

Transoesophageal echocardiography is also essential to confirm anatomical eligibility for percutaneous EE repair. No specific guidelines are currently available and the EVEREST II trial anatomical inclusion criteria are the principal reference (*Table 3*). Percutaneous treatment outwith these criteria (including pronounced flail gap or width, commissural MR, advanced LV remodelling, anatomic cleft, and asymmetric tethering) is now common, although certain anatomical conditions predict failure or suboptimal outcome (*Table 4*).

**Table 2 Echocardiographic predictors of repair failure or recurrent mitral regurgitation after undersized annuloplasty in secondary mitral regurgitation**

| |
|---|
| Coaptation depth >1 cm |
| Systolic tenting area >2.5 $cm^2$ |
| Posterior mitral leaflet angle >45° |
| Distal anterior mitral leaflet angle >25° |
| LV end-diastolic diameter >65 mm |
| LV end-systolic diameter >51 mm |
| End-systolic inter-papillary muscle distance >20 mm |
| Systolic sphericity index >0.7 |

LV, left ventricular.

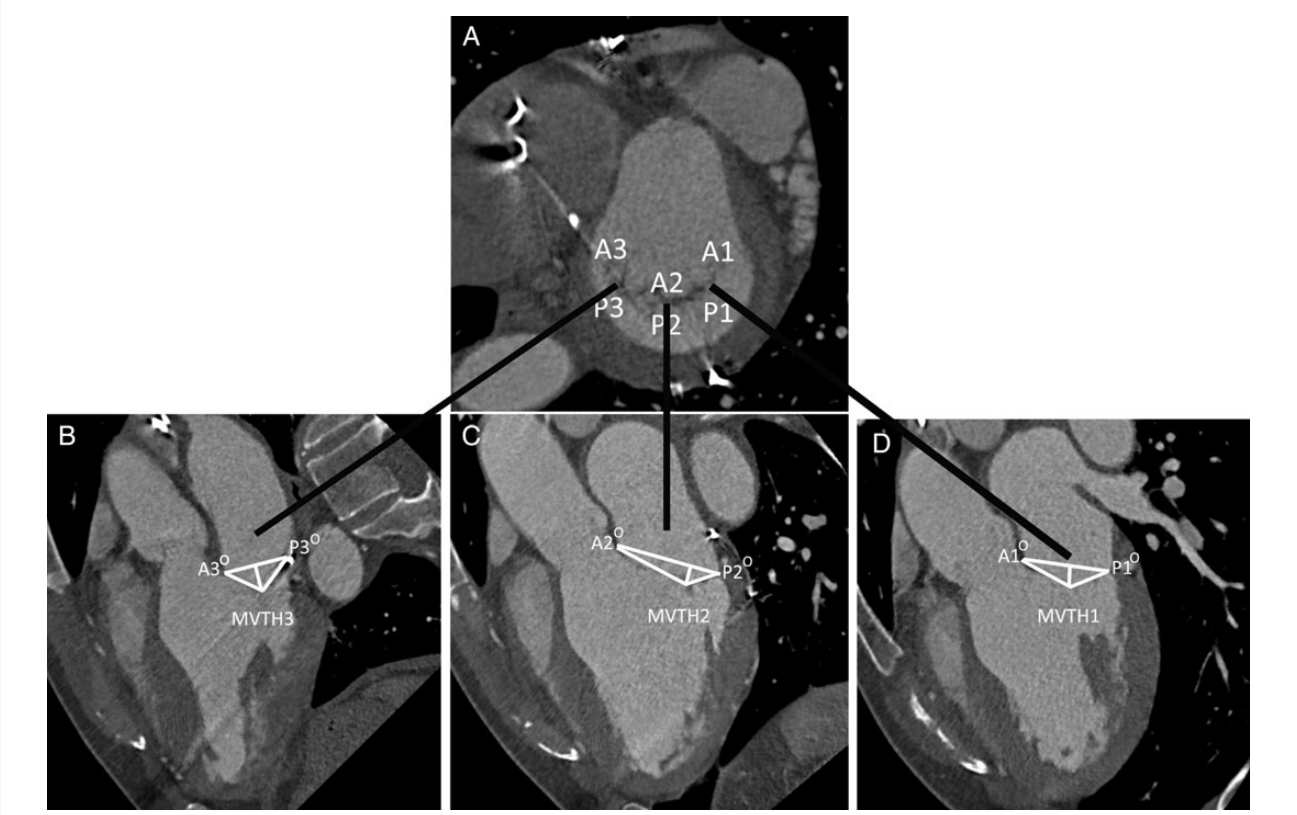


**Figure 2** Contrast-enhanced ECG-gated cardiac computed tomographic evaluation of the mitral valve. (*A*) En face view illustrating segmental anatomy of anterior (A1–A3) and posterior (P1–P3) valve leaflets. (*B–D*) Corresponding multiplanar images of individual scallops, their relation to the left ventricle and angulation relative to the mitral valve plane. MVTH, mitral valve tenting height. Image courtesy of Dr Ronak Rajani, St Thomas' Hospital, London, UK.

# Treatment recommendations

## Primary mitral regurgitation

### Medical therapy

There is no evidence-based medical therapy for patients with primary MR and minimal or no symptoms. Whilst β-blockers and angiotensin converting enzyme (ACE) inhibitors may palliate symptoms once heart failure has developed, they should not be used to postpone the need for intervention.[2]

### Surgery

Mitral valve repair is the preferred surgical treatment for severe degenerative MR with significant advantages over MV replacement.[2,7,8] The main goals—restitution of physiological leaflet motion, achievement of adequate leaflet coaptation and annular stabilisation with maintenance of an adequate mitral orifice[2]—can be achieved using a variety of isolated or combined techniques (leaflet resection, implantation of artificial chordae, chordal transposition/transfer, edge-to-edge technique, annuloplasty using a prosthetic ring or band) according to the type and location of the mitral lesion(s). Nowadays, >95% of degenerative MV lesions can be successfully repaired in expert centres.[9–11] Although the risk of repair failure increases in patients with anterior or bileaflet prolapse,[12] advanced myxomatous disease, annular calcification, or failure to undertake ring annuloplasty,[13] freedom from reoperation is >90% at 10 years and >80% at 20 years.[12–14]

Surgical outcomes depend on pre-operative status, mechanism of MR, technique of repair, and experience of the centre and surgeon. Centres with large experience in MV repair achieve hospital mortality <1%, very low rates of major adverse events and good long-term results[13–17] and patients should be referred to experienced centres to maximize the likelihood of a durable repair (particularly if a policy of 'early repair' is adopted).[18,19] Long-term survival and quality of life after timely MV repair mirror the age-matched general population. In contrast, late survival is reduced if MV repair is carried out in patients with congestive heart failure, reduced LV ejection fraction, pulmonary hypertension, or atrial fibrillation.[2,13,20]

### Percutaneous intervention

Several new transcatheter mitral devices are currently under investigation, although the MitraClip® System (Abbott Vascular, CA, USA), approved for use in high risk or inoperable patients with severe MR and suitable anatomic criteria[21] is the only one widely available, with >30 000 implantations performed worldwide.

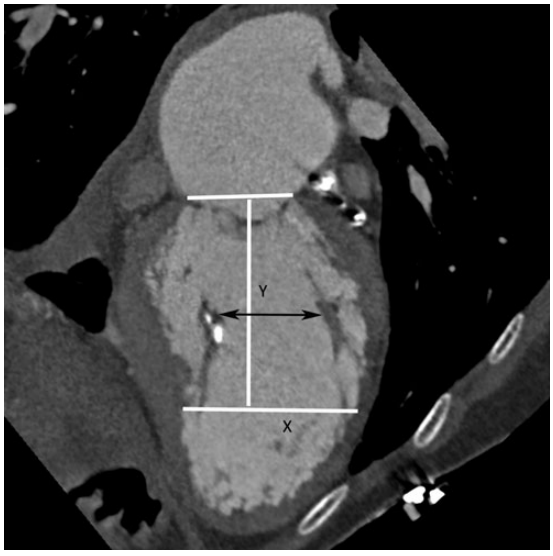


**Figure 3** Use of contrast-enhanced ECG-gated cardiac computed tomography in reconstructed end-systolic phase to facilitate mitral valve assessment. White lines indicate planes used to derive sphericity index (X/Y), black arrowed line = inter-papillary muscle distance. Image courtesy of Dr Ronak Rajani, St Thomas' Hospital, London, UK.

**Table 3 Key anatomic eligibility criteria for percutaneous edge-to-edge repair (EVEREST II)**

| |
|---|
| Moderate-to-severe MR (Grade 3/4 or more) |
| Pathology in A2–P2 zone |
| Coaptation length ≥2 mm |
| Coaptation depth <11 mm |
| Flail gap <10 mm |
| Flail width <15 mm |
| Mitral valve orifice area >4 $cm^2$ |
| Mobile leaflet length >1 cm |

**Table 4 Unfavourable anatomical conditions for percutaneous edge-to-edge repair**

| |
|---|
| Commissural lesions |
| Short posterior leaflet |
| Severe asymmetric tethering |
| Calcification in the grasping area |
| Severe annular calcification |
| Cleft |
| Severe annular dilatation |
| Severe left ventricular remodelling |
| Large (>50%) inter-commissural extension of regurgitant jet |
| Severe myxomatous degeneration with multi-scallop prolapse |

Percutaneous EE repair with this device is safe in degenerative MR with low rates of procedural and 30-day mortality,[22–24] complications (stroke, bleeding, tamponade, or resuscitation)[23–26] and short mean hospital stay.[23,27] One-year survival is 80%[24] mirroring the advanced age and multiple comorbidities of the populations studied. Post-procedural mitral stenosis is very rare and rates of clip detachment <2%.[28] Acute procedural success rate (final MR grade ≤2) is ~80–85% and maintained at 1- and 4-year follow-up.[22,24,29]

*Comparisons of surgery and percutaneous intervention in primary mitral regurgitation*

In the EVEREST II study,[22] 279 patients with Grades 3–4 MR were randomized 2 : 1 to undergo percutaneous EE repair or surgery (repair or replacement). Most had degenerative MR, relatively low-risk profile, moderate LV dysfunction, and strict inclusion criteria regarding LV size–function and MV anatomy. Percutaneous repair was associated with a higher rate of MR requiring repeat surgery (20.4 vs. 2.2% at 1 year; 24.8 vs. 5.5% at 4 years, both $P < 0.001$)[22,29] and reduced efficacy as defined by freedom from death, surgery for MV dysfunction or MR Grades 3–4 [55 vs. 73% ($P = 0.007$) at 1 year; 40 vs. 53% ($P = 0.07$) at 4-years]. Reported improvements in safety with the percutaneous technique were driven by the higher need for blood transfusion in the surgical arm.

It should be noted that EVEREST II patients were significantly different from those currently treated in Europe who mainly have secondary MR, severe LV dysfunction/remodelling, congestive heart failure, multiple comorbidities, and higher surgical risk. Moreover, the outcome data refer to the early stage of procedural experience and high volume centres are experiencing rapidly improving outcomes.

**Summary statements: primary mitral regurgitation**

- Surgery remains the first option in primary MR with very low operative mortality and established efficacy and durability in high volume centres.
- Percutaneous EE repair is an alternative in symptomatic inoperable and high-risk patients. Early mortality following percutaneous treatment in this high-risk subgroup has been high (up to 9%)[4,24,30] and >50% of patients have been left with residual or recurrent ≥2/4 MR at 1 year.[5,24]
- Properly designed randomized studies are needed to establish the best therapeutic option in this high-risk subset.

## Secondary mitral regurgitation

### Medical therapy

Medical therapy (ACE inhibitors, β-blockers, and aldosterone antagonists) is mandatory in secondary MR.[31] Diuretics may be required for fluid overload and vasodilators have a role in acute haemodynamic decompensation. Cardiac resynchronisation therapy should be considered in appropriate candidates.[31]

### Surgery

The best surgical treatment for secondary MR remains controversial.[32–34] Mitral repair performed with an undersized rigid complete ring to restore leaflet coaptation and valve competence is the

reference standard[35] and can be performed with acceptable peri-operative risk in carefully selected patients with secondary MR and poor LV function.[36] More advanced leaflet tethering predicts repair failure and recurrent MR[37,38] and concomitant techniques to improve durability (secondary chordal resection, suturing of the posteromedial papillary muscle to the aorto-mitral continuity, infarct plication, papillary muscle imbrication, and posterior LV restoration) have been described in small, non-randomized, and observational studies.[39–41] Restrictive annuloplasty was recently compared with chordal-sparing MV replacement in a randomized study of patients with secondary MR of ischaemic origin and demonstrated no advantage with regard to LV end-systolic volume index or 1-year mortality.[34] However, the trial was underpowered for mortality at 1 year and included patients with pre-operative predictors of repair failure. Further studies are required to determine whether selected patients with secondary MR benefit from surgical repair.

Moreover, no study has convincingly demonstrated a survival benefit compared with medical therapy[42] which argues against surgical intervention in asymptomatic patients and poses a complex surgical decision in high-risk cases. Recurrent MR is the main disadvantage[37,38] which may underlie the lack of observed survival benefit—several predictors have been identified and should be considered during patient selection (*Table 2*).[2,43,44]

### Percutaneous intervention

Secondary MR is currently the most common indication for percutaneous EE repair, accounting for 65–75% of patients.[23,25,27,45] The ACCESS-EU registry[23] enrolled 393 patients with secondary MR, severe LV dysfunction, and congestive heart failure—mortality was 3% at 30 days and 17% at 1 year with significant complications (stroke, resuscitation, and tamponade) in 1–2% of cases. Efficacy was similar to previous findings in degenerative MR with residual MR Grades 3–4 in 8 and 22% at discharge and 12-month follow-up, respectively. The majority (69%) were in NYHA class I/II at 12 months with demonstrable reverse LV and left atrial remodelling but residual MR Grade 2+ in almost 50%.[46,47] Similar results have been reported in other series.[30,48,49]

#### *Comparisons of surgery and percutaneous intervention in secondary mitral regurgitation*

Direct comparisons between percutaneous EE repair and surgery in secondary MR are difficult since patients treated with either strategy are significantly different. One small non-randomized series reported higher efficacy of surgery compared with percutaneous intervention (freedom from MR $\geq$3+ at 1 year 94 vs. 79%, $P = 0.01$).[46] In contrast, *post hoc* analysis of the EVEREST II trial demonstrated equivalence of the two strategies in this setting.[22,29] However, in the absence of a medical therapy control group, it is not possible to establish whether either treatment has positive impact on survival—ongoing randomized studies will address this question.

Surgery following failed percutaneous EE repair can be challenging as a consequence of clip-induced scarring and fibrosis (*Figure 4*).[50,51] Whilst this may be acceptable in high-risk patients with secondary MR, this is not the case in low-risk primary MR patients—percutaneous techniques are not appropriate in this population.

**Figure 4** Excised mitral valve (ventricular view) after implantation of two edge-to-edge clips.

**Summary statements: secondary mitral regurgitation**

- Medical therapy is paramount in secondary MR.
- The role of surgery is controversial, particularly when concomitant revascularization is not an option,[2] owing to significant operative mortality, high rates of recurrent MR, and absence of proven survival benefit.[42,52]
- Percutaneous EE repair is a lower risk option to reduce symptoms and induce reverse LV remodelling but commonly associated with residual and recurrent MR. Thus, it should only be considered in addition to optimal medical therapy (including cardiac resynchronization where appropriate) in patients who are symptomatic, fulfil anatomical criteria, and judged high-risk or inoperable by the Heart Team.

## Recommendations for outcome assessment

Head-to-head comparison of surgical and percutaneous interventions is not possible since they are used as complementary rather than alternative techniques in different populations. Ongoing randomized studies will require careful design and interpretation to enable future evidence-based decision-making:

- Endpoints should be rigorously pre-defined with adjustment for cross-over.
- Outcome definitions and nomenclature should adhere to international recommendations (including those designed for percutaneous valve interventions).[6,53,54]
- Specific echocardiographic criteria should be defined and validated.
- Safety and efficacy should be evaluated jointly by cardiologists and cardiac surgeons.
  - Safety has a major role in driving the choice between surgical and percutaneous approaches—clinically relevant endpoints should be used to compare strategies.
  - Patient-reported outcome measures relating to quality of life should be incorporated alongside conventional clinical endpoints and assessed routinely.

- The components of each endpoint should be related and of similar clinical importance.
- Procedure-specific complications should not be used when their clinical implications are unclear. For example, the EVEREST II trial suggested superiority of percutaneous EE repair since these patients received fewer blood transfusions than surgical controls.[22] Although blood transfusion is a marker of adverse clinical outcome, use of conglomerate endpoints which measure different but unrelated aspects of the same disease process should be avoided.
- Efficacy should be measured at pre-defined long-term follow-up—most recurrent MR arises during the first post-operative year[55,56] and early outcomes should be interpreted with caution.
- The goal of MV repair should be defined to achieve consistent outcome reporting. For example, residual Grade 2 MR is unsatisfactory following surgical repair,[55] but often classified as procedural success following percutaneous intervention (despite negative prognostic impact).[47,55]
- Minor changes of regurgitant volume or LV ejection function should not be used to argue the superiority of a particular approach—there are no data to demonstrate their impact on clinical outcome.[22,57]

# Future perspectives

Percutaneous interventions offer potential for beating-heart MV repair and replacement under physiological conditions without need for cardiopulmonary bypass. Beyond percutaneous EE repair, transcatheter chordal replacement, and indirect annuloplasty (using coronary sinus devices, radiofrequency-mediated annular remodelling, and cinching devices) are in various stages of development.[58,59] These technologies have no surgical equivalent and their efficacy needs to be proven. Conversely, percutaneous direct annuloplasty reproduces surgical techniques and can be achieved with annular plication[60] or commissure-to-commissure implant.[61]

Techniques for percutaneous MV replacement are progressing[62] and need to encompass large device delivery, anchoring without impinging the LV outflow tract or other adjacent structures, avoidance of paravalvular regurgitation, and maintained durability.

Three-dimensional echocardiography, fusion imaging, and computer modelling will guide device selection, procedural efficacy, and safety. Education of mitral intervention specialists will be vital to ensure appropriate patient selection, procedural skills, and perioperative management. Further evolution of percutaneous technologies and advanced imaging will require regulatory approval and appropriate reimbursement.

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