Management of secondary mitral regurgitation: from drugs to devices

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ABSTRACT
Severe secondary mitral regurgitation carries a poor prognosis with one in five patients dying within 12 months of diagnosis. Fortunately, there are now a number of safe and effective therapies available to improve outcomes. Here, we summarise the most up-to-date treatments. Optimal guideline-directed medical therapy is the mainstay therapy and has been shown to reduce the severity of mitral regurgitation in 40–45% of patients. Rapid medication titration protocols reduce heart failure hospitalisation and facilitate earlier referral for device therapy. The pursuit of sinus rhythm in patients with atrial fibrillation has been shown to significantly reduce mitral regurgitation severity, as has the use of cardiac resynchronisation devices in patients who meet guideline-directed criteria. Finally, we highlight the key role of mitral valve intervention, particularly transcatheter edge-to-edge repair (TEER) for management of moderate-severe mitral regurgitation in carefully selected patients with poor left ventricular systolic function, with a number needed to treat of 3.1 to reduce heart failure hospitalisation and 5.9 to reduce all-cause death. To slow the rapid accumulation of morbidity and mortality, we advocate a proactive approach with accelerated medical optimisation, followed by management of atrial fibrillation and cardiac resynchronisation therapy if indicated, then, rapid referral to the Heart Team for consideration of mitral valve intervention in patients with ongoing symptoms and at least moderate-severe mitral regurgitation. Mitral TEER has been shown to be ‘reasonably cost-effective’ (but not cost-saving) in the UK in selected patients, although TEER remains underused with only 6.5 procedures per million population (pmp) compared with Germany (77 pmp), Switzerland (44 pmp) and the USA (32 pmp).

INTRODUCTION
Mitral regurgitation (MR) is described as ‘secondary’ or ‘functional’ when the aetiology of the valve dysfunction is related to changes in the left atrium (LA), left ventricle (LV) or mitral valve annulus. MR is described as ‘primary’ or ‘degenerative’ when the valve dysfunction is due to defects in the valve leaflets or subvalvular apparatus. Secondary MR (sMR) is a common consequence of LA and LV remodeling and is an important finding in patients because it is strongly correlated with adverse outcomes. The presence of severe MR is associated with worsening heart failure symptoms, impaired quality of life, increased heart failure hospitalisation (HFFH) and higher risk of mortality, compared with patients with little or no MR.1

The maturation of the field of transcatheter mitral intervention into a safe and efficacious form of treatment has come hand in hand with a revolution in the way we think about the mitral valve. This has led to a reassessment of our understanding of MR: the way we quantify it, the imaging modalities we use and the types of patients who might benefit from intervention. Over the last few years, there has been an expansion in the definition of sMR to include subtypes such as atrial sMR (AsMR), ventricular sMR (VsMR) and mixed sMR,2 although the precise definition of each of these subtypes has not yet reached consensus. The role of atrial fibrillation (AF) in sMR is also increasingly recognised to be important not only in the prognosis of those with sMR, but also their treatment response.3 The mainstay of treatment remains optimal medical therapy, as this can improve MR, and may even resolve it altogether in some patients. The importance of addressing ventricular dyssynchrony in patients with bundle-branch block by cardiac resynchronisation device therapy (CRT) is also increasingly recognised and now included in guideline management of sMR.4 Transcatheter mitral intervention, predominantly transcatheter edge-to-edge repair (TEER), has expanded treatment options for this group of patients. As a result of these changes, our approach to the management of sMR is increasingly nuanced, and a ‘one-size-fits-all’ approach cannot be adopted. Here, the role of the multidisciplinary Heart Team in directing patients towards optimal therapy is crucial. The Heart Team should include at minimum a structural interventional cardiologist, a cardiothoracic surgeon with experience in mitral valve surgery, an echocardiologist and a heart failure specialist; other useful specialties to include are electrophysiology/device experts, cardiac anaesthetists, intensive care physicians and aged-care physicians.

In this review, we present a practical approach to the treatment of sMR, based on currently available evidence. We advocate an accelerated approach to treatment optimisation to reduce symptoms, HFFH and death.

MEDICAL MANAGEMENT OF SMR
sMR and heart failure with reduced ejection fraction: VsMR
Optimised guideline-directed medical therapy (GDMT) for patients with VsMR is important as many patients will have a significant reduction in the severity of their MR following treatment.5 In
recent years, there have been advances in GDMT for the management of heart failure with reduced ejection fraction (HFrEF), both in terms of the availability of additional medication and in optimising their delivery.

First, we have seen the introduction of two new medication classes: angiotensin receptor nephrilisin inhibitors (ARNIs) and sodium-glucose cotransporter-2 (SGLT2) inhibitors. These both now carry class I indications to reduce HFH and death in patients with chronic HFrEF. The availability of four main classes of medication in the armamentarium of GDMT has increased the complexity of delivering this, and has focused research interest on simple mechanisms to safely and effectively initiate these four classes rapidly. Several authors have proposed rapid optimisation protocols designed to rapidly establish patients onto these ‘four pillars’ of heart failure therapy (beta-blocker (BB), ACE inhibitor/angiotensin II receptor blocker/ARNI, SGLT2 inhibitor, mineralocorticoid receptor antagonist (MRA)). The STRONG-HF trial showed that a rapid uptitration strategy, alongside intensive medical and nursing support, was associated with a 34% decrease in HFH or death, demonstrating that this strategy is effective. It showed there is some evidence for specific reduction of MR with medical therapy. A small trial using triple heart failure therapy, but not SGLT2 inhibitors, showed that sMR was reduced by at least one grade in 40% of patients. This was also investigated in the larger PROVE-HF Study. In 794 patients, ARNI, alongside BB and MRA, showed a major improvement in MR with triple therapy. The prevalence of 3–4+ MR decreased by 45% over 6 months.

AF in VsMR

The management of AF is an important part of the optimisation of patients with VsMR. Heart failure guidelines support the pursuit of rhythm control in HFrEF with direct current (DC) cardioversion, AF ablation (class IIA indication) or medical therapy with amiodarone (class IIB) in symptomatic patients. This may well have the additional benefit of reducing the severity of sMR as well, although this has not been tested in a randomised fashion.

The long-term prognosis of patients with moderate or severe sMR and HFrEF who do not improve over 6–12 months of treatment with optimal medical therapy alone is poor. In the COAPT trial, which enrolled patients with severe sMR and ongoing symptoms despite optimal medical therapy, the all-cause mortality in the control group (GDMT) was 46.1%. Other trials have demonstrated similar outcomes. Agricola et al reported an all-cause mortality over 4 years of 50–51% in patients with moderate or severe sMR and HFrEF despite optimal medical therapy, compared with 36% for those with mild MR. For this reason, it is crucial that patients who do not fully respond to medical therapy are referred early for consideration of other therapies including mitral valve intervention.

AsMR and the role of AF

Changes in atrial size and dilatation of the mitral annulus are increasingly recognised as mechanisms involved in sMR. Both AF and heart failure with preserved ejection fraction (HFpEF) appear to be associated with the evolution of AsMR. The exact prevalence of AsMR is unclear because of varied definitions within published literature. One retrospective observational cohort study of the community in Olmsted County, USA reported that isolated atrial dilatation was responsible for 27% of moderate or severe MR, compared with 38% due to ventricular remodelling and 32% due to primary valve dysfunction. Gertz et al reported a prevalence of 7% for AsMR in patients referred for first AF ablation. The ATTEND registry observed that 18% of patients with decompensated HFrEF had moderate-to-severe AsMR and that this was associated with increased rates of death and HFH, compared with those with mild or no MR.

To unify our approach and understanding, Farhan et al. have proposed defining AsMR based on the following echocardiographic features: (1) MR with structurally normal mitral valve leaflets without mitral annular calcification; (2) LA enlargement (indexed LA volume of >34 mL/m²); (3) secondary AF and/or elevated mean LA pressure caused by LV diastolic dysfunction; (4) normal indexed LV end-diastolic volume for age and sex; (5) an ejection fraction of ≥60% (by biplane) without regional wall motion abnormalities; (6) increased mitral annular area as measured by three-dimensional echo.

AF plays an important role in both the development of AsMR and its prognosis following treatment. This is demonstrated by studies showing that restoration of sinus rhythm following catheter ablation for AF correlated with reductions in LA area and severity of sMR. In 2011, Gertz et al observed that patients with moderate or severe MR, who underwent catheter ablation resulting in restoration of sinus rhythm, were much less likely at 12-month follow-up to have significant MR compared with those who remained in AF (24% vs 82%, p=0.005). As a result, some groups have supported a more aggressive approach to treating symptomatic AsMR with AF, including: standard heart failure therapies to reduce LA pressure; aggressive pursuit of rhythm control with a combination of medical therapy, cardioversion and catheter ablation to promote positive LA and mitral annular remodelling; and finally, surgical management if necessary. However, randomised data for this approach are lacking and decision-making should be guided by the Heart Team. It is worth noting that following recent positive
trials in HFpEF with SGLT2 inhibitors, it is likely that new guidelines will recommend these drugs as part of management of HFpEF, which would include patients with AsMR.

**DEVICE-BASED MANAGEMENT OF SMR**

**Cardiac resynchronisation device therapy**

CRT has been shown in multiple trials to result in a significant decrease in ventricular volumes and MR, and an increase in ejection fraction. For example, in the MIRACLE trial, MR was shown to decrease very significantly (−2.1 cm² vs 0.1 cm² jet area). The effects of CRT on MR are likely to be multifactorial. CRT improves atrioventricular synchrony, and is thus likely to reduce the time available for MR. Mechanistic studies have shown immediate changes in effective mitral regurgitant orifice area in a majority of patients, perhaps by altering the transmural pressure gradient.

So-called physiological pacing, such as left bundle branch pacing, is a topic of intense interest, although currently still practised only by a minority of operators around the world. Early studies suggest that left bundle branch pacing is probably at least as effective as conventional CRT in terms of reducing functional MR, for example, in 38 patients with significant functional MR, 82% had a significant reduction in functional MR with left bundle branch pacing.

With both medical therapy and cardiac resynchronisation therapy, the concept of ‘responders’ and ‘non-responders’ to therapy has been discussed. While most patients will improve, some will continue to deteriorate despite optimal medical therapy and cardiac resynchronisation therapy, and targeting this group for additional treatments is important as without this, their outcomes are very poor.

**Surgical management of sMR**

In primary MR (pMR), there is significant evidence for isolated mitral valve surgery; however, trials in sMR primarily studied patients undergoing concomitant coronary artery bypass grafting (CABG). In this population with at least moderate MR, observational prospective randomised controlled trial (RCT) data support the addition of mitral valve repair to CABG by demonstrating improvement in reverse remodelling, symptom status and functional capacity. There was no improvement in mortality with the addition of mitral valve repair to CABG. Based on these data, international guidelines recommend surgical mitral intervention in patients with severe sMR undergoing CABG or other cardiac surgery (2021 European Society of Cardiology/European Association for Cardio-Thoracic Surgery class I/level B; 2020 American College of Cardiology/American Heart Association class 2a/level B). Surgical intervention is supported in patients with severe sMR who remain symptomatic despite GDMT±CRT if this is supported by the Heart Team (class I).

**Mitral TEER**

**Patient selection**

Mitral TEER (m-TEER) has been shown to be a safe and effective treatment for VsMR. There are two major randomised trials that have examined the benefits of m-TEER in patients with sMR and HFrEF: the MITRA-FR trial and the COAPT trial, both published in 2018. While superficially similar, these trials had a number of significant differences which have been extensively discussed and are summarised in table 1 (adapted from Praz et al)

Both trials demonstrated the significant morbidity and mortality observed in patients with sMR and HFrEF treated with GDMT alone; approximately 20% annualised death rate and 50% annualised HFH rate. Only the COAPT trial demonstrated a benefit of m-TEER in selected patients, with a reduction in HFH over 24 months from 67.9% (GDMT alone) to 35.8% in patients treated with m-TEER (HR 0.53; 95% CI 0.40 to 0.70; p<0.001, absolute risk reduction (ARR) 32%). There was also a reduction in all-cause death observed over 24 months from 46.1% to 29.1% in patients treated with m-TEER (HR 0.62; 95% CI 0.46 to 0.82; p<0.001, ARR 17%). Furthermore, these results appear to be durable over 3-year and 5-year follow-up with a number needed to treat of 3.1 and 5.9 for HFH and death, respectively.

Guidelines have upgraded the role of m-TEER in the management of VsMR (class IIa/level B). m-TEER can be recommended in patients fulfilling the COAPT trial inclusion criteria (refer to table 1) who are not eligible for surgery. In patients with sMR who do not fulfil the COAPT criteria, m-TEER may still be considered for symptomatic benefit if the Heart Team is supportive (class IIIb/level C). Despite these guideline-directed recommendations, there is considerable discrepancy between European countries in the uptake of this intervention. For example, in the UK, TEER (for all indications) is performed at a rate of 6.5 procedures per million population (pmp) compared with Germany, Switzerland and the USA, which performed 77 pmp, 44 pmp and 32 pmp TEER in 2019, respectively. Discrepancies may relate to funding models; however, in the UK, modelling of the cost of TEER in patients from the COAPT trial showed an increase in life expectancy by 1.57 years and quality-adjusted life expectancy by 1.12 quality-adjusted life-years (QALYs), and was demonstrated to be a reasonably cost-effective (but not cost-saving) therapy with an incremental cost-effectiveness ratio of £23 270 per QALY gained (after discounting).

**When to refer**

A recent paper by the EuroSMR investigators has explored the idea of progressive stages of VsMR, and whether these categories may be used to improve patient selection and better predict outcomes after intervention. The concept of staging valve disease was originally put forward by Genereux et al for aortic stenosis. Stolz et al have built on this
concept for MR. They identified patients from EuroSMR registry, which from 2008 to 2019 included patients from 11 cardiac centres across Europe treated with TEER using the MitraClip device (Abbott). They divided patients into the following groups: stage (1) LV involvement (LV end-diastolic volume ≥159 mL and/or LV ejection fraction <50%); stage (2) LA involvement (history of AF and/or indexed LA volume >34 mL/m²); stage (3) right ventricular pressure/volume overload (tricuspid regurgitation ≥3+ and/or systolic pulmonary artery pressure >65 mm Hg); and stage (4) biventricular failure (right ventricular pulmonary arterial coupling <0.274 mm/mm Hg). Ten per cent of patients were in stage 1, 46% stage 2, 15% stage 3 and 29% were in stage 4, respectively. Patients in stages 1 and 2 appeared to have similar outcomes with a combined survival rate of 73.1% over a 2-year period, compared with 62.9% for stage 3 and 48.9% for stage 4, respectively (HR 1.47, CI 1.26 to 1.67, p<0.001). There were no significant differences between the groups in terms of patient demographics to explain this difference in survival. None of the patients in stage 1 had AF, compared with 74% of stage 2, 65% of stage 3 and 65% of stage 4; however, as previously stated, stage 1 and 2 patients had essentially the same outcomes post-TEER.

### Table 1 Comparison of the COAPT and MITRA-FR trials

<table>
<thead>
<tr>
<th></th>
<th>COAPT</th>
<th>MITRA-FR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients screened</td>
<td>1576</td>
<td>452</td>
</tr>
<tr>
<td>Number of patients enrolled (ITT)</td>
<td>614</td>
<td>304</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>72±12</td>
<td>70±10</td>
</tr>
<tr>
<td>Mean LVEF (%)</td>
<td>31±10</td>
<td>33±7</td>
</tr>
<tr>
<td>Inclusion/exclusion criteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVEF</td>
<td>20–50%</td>
<td>15–40%</td>
</tr>
<tr>
<td>Regurgitant volume</td>
<td>No restriction</td>
<td>&gt;30 mL</td>
</tr>
<tr>
<td>EROA</td>
<td>No restriction</td>
<td>&gt;20 mm²</td>
</tr>
<tr>
<td>NYHA class</td>
<td>II–IV</td>
<td>II–IV</td>
</tr>
<tr>
<td>MR severity</td>
<td>Moderate-severe</td>
<td>Severe</td>
</tr>
<tr>
<td>MR anatomical restrictions</td>
<td>Inclusion: ‘the primary regurgitant jet is non-commissural, and in the opinion of the MitraClip implanting investigator can be successfully be treated by the MitraClip (if a secondary jet exists, it must be considered clinically insignificant)’</td>
<td>No specific restriction although 24 patients excluded from enrolment due to annular or valvular calcification</td>
</tr>
<tr>
<td>LVEDd ≤70 mm</td>
<td></td>
<td>No exclusion</td>
</tr>
<tr>
<td>Evidence of right-sided heart failure with moderate or severe right ventricular dysfunction</td>
<td>Excluded</td>
<td>No exclusion</td>
</tr>
<tr>
<td>Severe COPD on home oxygen or requiring chronic steroid use</td>
<td>Excluded</td>
<td>No exclusion</td>
</tr>
<tr>
<td>Pulmonary artery pressure &gt;70 mm Hg</td>
<td>Excluded</td>
<td>No exclusion</td>
</tr>
<tr>
<td>Baseline medical therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>91%</td>
<td>88%</td>
</tr>
<tr>
<td>ACEi/ARB/ARNI</td>
<td>72% (4.3% ARNI)</td>
<td>83% (10% ARNI)</td>
</tr>
<tr>
<td>MRA</td>
<td>51%</td>
<td>57%</td>
</tr>
<tr>
<td>Procedural outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Residual MR ≤2+</td>
<td>93%*</td>
<td>92%†</td>
</tr>
<tr>
<td>% of intention to treat population that had TEER procedure attempted</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>Procedural success rate</td>
<td>99%</td>
<td>96%</td>
</tr>
<tr>
<td>Procedure-related complications (%)‡</td>
<td>8.5</td>
<td>14.6</td>
</tr>
</tbody>
</table>

*Thirty days post-procedure.
†At time of discharge, however, 19% of intervention group did not have imaging available at discharge.
‡MITRA-FR definition of prespecified serious adverse events: device implant failure, transfusion or vascular complication requiring surgery, ASD, cardiogenic shock, cardiac embolism/mitrode, tamponade and urgent cardiac surgery.

ACEi, ACE inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor neprylisin inhibitor; ASD, atrial septal defect; COPD, chronic obstructive pulmonary disease; EROA, effective regurgitant orifice area; ITT, intention to treat; LVEDd, left ventricular end-diastolic dimension (mm); LVEF, left ventricular ejection fraction; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; TEER, transcatheter edge-to-edge repair.

These data support the idea that early intervention with m-TEER for patients in VsMR stages 1 and 2, before they progress to stage 3 or 4, is important for improving survival, and delays in referral should be avoided. However, more data are needed. Additionally, despite poorer outcomes in patients in stages 3 and 4, it is important to note that regardless of stage, all groups had a significant improvement in symptoms (table 2). Therefore, we should not interpret these data as a reason to deny patients a low-risk intervention that can significantly improve
their symptoms and quality of life, simply because they may experience a smaller mortality benefit.

**Practicalities of the m-TEER procedure**
The m-TEER procedure is performed under general anaesthetic with transoesophageal echo guidance and fluoroscopy. The TEER device is delivered via the right femoral vein, through a transseptal puncture into the LA and mitral valve. If a single device is insufficient to reduce the MR severity to mild, then a second or third device may be implanted provided that this does not result in mitral stenosis. If the TEER device does not improve the MR severity, it may be removed at the time of the procedure. Prophylactic broad-spectrum intravenous antibiotics are given at induction of anaesthesia. Intravenous heparin is given to maintain an activated clotting time of >300 s. Post-procedure patients are required to be on at least one antiplatelet agent, or if taking anticoagulation for AF or another indication, then anticoagulation alone is sufficient. Most patients will be able to be transferred to a cardiology ward following their procedure and discharged the day after their procedure.

**Device choice for m-TEER**
There are currently two device systems available in the UK and Europe for m-TEER: the PASCAL system (Edwards Lifesciences) and the MitraClip system (Abbott). Their features are summarised in [table 3](#). A recent systematic review by Srinivasan et al.16 has demonstrated the PASCAL device to be both safe and effective in both standard and challenging anatomy (pMR and sMR). Based on their review of 13 articles from 2016 to August 2022, which included randomised data, prospective and retrospective cohorts, they found that in high-risk patients (mean logistic EuroSCORE 16.39%), with severe symptomatic MR (84% NYHA III–IV, both pMR and sMR were included), there was a high technical success rate (95.7%) and a high procedural success rate (95.2%) with 94.7% of patients left with ≤2+ MR at discharge. Additionally, 76.8% of patients reported a symptomatic benefit with a reduction of ≤2 NYHA classes at 30 days. The composite major adverse event rate (defined and derived from the 13 studies evaluated) was low at 4%; however, the CLASP Study15 reported a composite major adverse event in sMR alone of 10.6% (n=85). None of the trials assessed had exclusion criteria based on valve anatomy.

The MitraClip device is well studied and has also been shown to be a safe and effective treatment for sMR. The COAPT trial represents robust evidence for this device in selected anatomy (patients were excluded based on ‘leaflet anatomy which may preclude MitraClip implantation, proper MitraClip positioning on the leaflets or sufficient reduction in mitral regurgitation by the MitraClip’) demonstrating procedural success in 98%, device-related complications rate of 3.4% at 12 months, ≤2+ MR at discharge of 95%, 30-day stroke rate in the device group was 0.7% and no patients needed bail-out mitral valve surgery. The MITRA-FR trial25 also demonstrated the MitraClip to be safe with no peri-procedural deaths, stroke and tamponade rate of 1–2%, and 4% major bleeding rate, despite being an overall neutral trial. Common complications are summarised in [table 4](#).

There is a prospective, multicentre RCT underway to assess the performance of the PASCAL device in sMR in comparison with MitraClip (CLASP IIIF, ClinicalTrials.gov ID: NCT03706833) with results expected in early 2024.

**Other transcatheter mitral interventions**
While m-TEER is currently the mainstay of transcatheter mitral intervention for sMR, several other technologies have received CE mark approval and have been trialled in patients. The Tendyne (Abbott) valve is a transcatheter mitral valve replacement implanted via the transapical approach, through a left anterolateral thoracotomy. Two-year outcomes of 100 patients in

### Table 2 NYHA functional class before and after TEER according to stage

<table>
<thead>
<tr>
<th>NYHA class ≥II</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-TEER %</td>
<td>19.8</td>
<td>14.1</td>
<td>12.4</td>
<td>11.4</td>
</tr>
<tr>
<td>Post-TEER %</td>
<td>78.1</td>
<td>65.7</td>
<td>64.6</td>
<td>64.5</td>
</tr>
</tbody>
</table>

NYHA, New York Heart Association; TEER, transcatheter edge-to-edge repair.

### Table 3 Comparison of TEER device features

<table>
<thead>
<tr>
<th></th>
<th>PASCAL</th>
<th>MitraClip</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devices available</td>
<td>P10; ACE</td>
<td>NT, NTW, XT, XTW</td>
</tr>
<tr>
<td>Device material</td>
<td>Nitinol</td>
<td>Cobalt-chromium</td>
</tr>
<tr>
<td>Closing mechanism</td>
<td>Passive</td>
<td>Active</td>
</tr>
<tr>
<td>Independent grasping</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Retention elements</td>
<td>3 hooks at tip of clasps</td>
<td>Two rows of 4 (NT) or 6 (XT) hooks along length of clasps</td>
</tr>
<tr>
<td>Central spacer for sMR</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Device elongation</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Left atrial pressure monitoring</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>sMR, secondary mitral regurgitation.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 4  Common complications following a TEER procedure for secondary mitral regurgitation

<table>
<thead>
<tr>
<th></th>
<th>COAPT (MitraClip) N=293</th>
<th>MITRA-FR (MitraClip) N=144</th>
<th>CLASP Study (Pascal) N=85</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single leaflet detachment</td>
<td>0.7%*</td>
<td>Not reported</td>
<td>1%</td>
</tr>
<tr>
<td>Device embolisation</td>
<td>0.3%</td>
<td>Not reported</td>
<td>0%</td>
</tr>
<tr>
<td>Endocarditis requiring surgery</td>
<td>0%</td>
<td>0%</td>
<td>Not reported</td>
</tr>
<tr>
<td>Mitral stenosis requiring surgery</td>
<td>0%</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>30-day death rate</td>
<td>2.3%</td>
<td>3.3%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Repeat valve intervention to 30 days</td>
<td>1%</td>
<td>Not reported</td>
<td>1.2%</td>
</tr>
<tr>
<td>Stroke to 30 days</td>
<td>0.7%</td>
<td>1.4%</td>
<td>1.2%</td>
</tr>
<tr>
<td>MI to 30 days</td>
<td>1%</td>
<td>Not reported</td>
<td>0%</td>
</tr>
<tr>
<td>Tamponade</td>
<td>0.6%</td>
<td>1.4%</td>
<td>Not separately reported</td>
</tr>
</tbody>
</table>

*Up to 12 months.
MI, myocardial infarction.

non-randomised prospective study (including 89% of patients with sMR or mixed MR) reported a 96% technical success rate, reduction in annualised HFH rates and improvement in NYHA class. No surviving patients had greater than mild residual MR at 2-year follow-up. Thirty-nine percent of patients died within the follow-up period. The benefits of the procedure were offset by a significant incidence of life-threatening or fatal bleeding events and stroke post-intervention. Furthermore, few patients with sMR will be found to be suitable for Tendyne due to strict anatomical selection criteria. There are little published data about screening failure rates for Tendyne; however, one small study suggested that 60–82.5% of screened patients are excluded. The SUMMIT prospective trial is currently enrolling patients with severe symptomatic MR to be randomly assigned to m-TEER or Tendyne mitral valve replacement. The Carillon Mitral Contour System (Cardiac Dimension) performs an indirect reductive annuloplasty. Improvements in NYHA class, 6-minute walking distance, MR grade and LV volumes have been demonstrated with a sham-controlled randomised study of 120 patients with sMR. The EMPOWER trial is currently enrolling patients with at least mild sMR to be randomised 1:1 to device treatment using Carillon or to GDMT with the intention of enrolling 300 participants. The Cardioband system (Edwards Lifesciences) is a transcatheter annular reduction system. In a multicentre, safety and efficacy trial of 62 patients, 95% of patients had moderate or less MR at 1 year with associated improvement in symptom and functional status. The ACTIVE multicentre randomised trial is enrolling patients with...
significant sMR, randomised 2:1 to receive Cardioband or GDMT.

SUMMARY AND RECOMMENDATIONS
The evolution of device therapies for the mitral valve has led to a renaissance in our understanding of this complex valve system. With it comes the opportunity to improve outcomes for our patients in a variety of ways, and with each of these strategies, the benefits appear to be additive. In figure 1, we outline an accelerated treatment pathway guided by the Heart Team, designed to rapidly optimise patients with sMR and direct “non-responders” towards device therapy to minimise the early accumulation of morbidity and mortality in these patients.

From the time of diagnosis, we recommend commencement and rapid uptitration of GDMT over a period of 6 weeks–3 months according to published protocols. This should include one of each of the four classes of heart failure therapies. During this time, consideration should be given to the management of AF if present, either with medical therapy, DC cardioversion and/or catheter ablation. After 3–6 months of stable therapy, the patient can be reassessed for ongoing symptoms and MR severity. If the patient continues to have symptoms ≥NYHA class II and MR severity ≥moderate-severe, then they should be referred to the Heart Team for consideration of mitral valve intervention according to what is most suitable for and available to that patient. If the patient meets criteria for CRT, then this should be undertaken prior to any mitral valve intervention being performed.

Patients who fulfil the COAPT criteria should be referred for m-TEER. Patients who do not fulfil these criteria, such as patients with AsMR, could still be considered for m-TEER if the Heart Team feel it is appropriate. This will be the majority of patients. Patients who are felt to be unsuitable for m-TEER or in whom m-TEER was unsuccessful, other transcatheter therapies should be considered, if available. Patients who require CABG or other cardiothoracic surgery should have mitral valve intervention at the same time.

Based on the data presented above, if we take this approach, we will significantly reduce mortality and morbidity in this important patient group.

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Contributors All authors have made a substantial contribution to this paper including inception, writing and editing.
Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.
Competing interests SD has received honoraria from Abbott Cardiovascular and Edwards Lifesciences.
Patient consent for publication Not required.
Ethics approval Not applicable.
Provenance and peer review Commissioned; internally peer reviewed.
Author note References which include a * are considered to be key references.
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Key messages
What is already known on this subject?
⇒ Severe mitral regurgitation in the presence of left ventricular systolic dysfunction has a poor prognosis with an approximately 20% annualised death rate and 50% annualised heart failure hospitalisation rate when treated with medical therapy alone (in a pre-angiotensin receptor neprilysin inhibitor and sodium-glucose cotransporter-2 era).
⇒ Atrial secondary mitral regurgitation is common and often coexists with atrial fibrillation and heart failure with preserved ejection fraction (HFrEF).
⇒ In some patients with atrial fibrillation, the aggressive pursuit of sinus rhythm will significantly improve the severity of their mitral regurgitation.
⇒ In patients with a guideline-directed indication, cardiac resynchronisation therapy may significantly improve their mitral regurgitation.
⇒ In patients who meet the COAPT trial criteria, mitral transcatheter edge-to-edge repair (TEER) is a low-risk treatment that can improve quality of life, reduce heart failure hospitalisation and prolong life with a number needed to treat of 3.1 for heart failure hospitalisation and 5.9 for all-cause mortality.
⇒ Mitral TEER carries a class IIA recommendation for patients meeting the COAPT criteria and class IIb in patients who do not meet the COAPT criteria but are approved by the Heart Team.
⇒ Mitral TEER for patients meeting the COAPT criteria has been shown to be reasonably cost-effective in the UK.

New concepts:
⇒ New drug classes in the management of heart failure with reduced ejection fraction have increased the complexity of delivering guideline-directed medical therapy (GDMT) and could lead to delays in optimising medical therapy. Adopting accelerated uptitration protocols has been shown to reduce heart failure hospitalisation and death and may allow expedious referral for device therapy.
⇒ Patients who continue to be symptomatic with at least moderate-severe mitral regurgitation despite GDMT, management of atrial fibrillation (if indicated) and cardiac resynchronisation device therapy (if indicated) should be referred without delay to the Heart Team for discussion about suitability for mitral valve intervention.
⇒ In general, mitral TEER is the preferred intervention for patients meeting the COAPT criteria. Patients who are unsuitable for TEER, or in whom TEER was unsuccessful, could be considered for other transcatheter mitral interventions (if available); however, further data are needed.

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Management of secondary mitral regurgitation - from drugs to devices: MCQ:

1) Which of the following best describes patients with mitral regurgitation who meet the ‘COAPT criteria’
   a) Symptomatic moderate-severe/severe mitral regurgitation, LVEDd >70mm, LVEF 20-50%, without moderate or severe right ventricular dysfunction, despite optimal medical therapy
   b) Asymptomatic moderate-severe/severe mitral regurgitation, LVEDd >70mm, LVEF 20-50%, without moderate or severe right ventricular dysfunction
   c) Symptomatic moderate-severe/severe mitral regurgitation, LVEDd ≤70mm, LVEF 20-50%, without moderate or severe right ventricular dysfunction, despite optimal medical therapy
   d) Symptomatic severe mitral regurgitation, LVEDd ≤70mm, LVEF 20-50%, without moderate or severe right ventricular dysfunction, despite optimal medical therapy
   e) Asymptomatic severe mitral regurgitation, LVEDd ≤70mm, LVEF 20-50%, without moderate or severe right ventricular dysfunction

2) Which of the following mechanisms are not thought to contribute to secondary mitral regurgitation
   a) Mitral annular dilatation
   b) Left atrial dilatation
   c) Atrial fibrillation
   d) Ventricular dyssynchrony
   e) Mitral annular calcification

3) Which statement best describes the role of surgery in the management of severe secondary mitral regurgitation?
   a) Surgical mitral intervention is recommended in patients with severe secondary mitral regurgitation undergoing CABG or other cardiac surgery
   b) There is a limited role for surgical mitral intervention in severe secondary mitral regurgitation
   c) Surgical intervention is supported in patients with severe secondary mitral regurgitation who remain symptomatic despite optimal medical therapy (+/- cardiac resynchronisation device therapy if indicated) if this is supported by the Heart Team
   d) A) and C)
   e) None of the above

4) In patients with symptomatic severe secondary mitral regurgitation, the likelihood of procedural success from transcatheter edge-to-edge repair (TEER) is:
   a) > 95%
   b) 92-95%
   c) > 90%
   d) 88-92%
   e) 85%

5) Transcatheter edge-to-edge repair (TEER) is performed via:
   a) A central sternotomy
   b) A puncture in the femoral artery
   c) A puncture in the femoral vein
   d) A lateral thoracotomy
   e) A transapical incision
6) Regarding the benefits of transcatheter edge-to-edge repair (TEER) in severe secondary mitral regurgitation; which statement is FALSE?

a) In patients who meet the COAPT criteria, the number needed to treat to prevent 1 heart failure hospitalisation is 3.1, and to prevent 1 fatality is 5.9

b) In patients who meet the COAPT criteria, mitral TEER has been shown to be cost effective in the UK

c) In patients who do not fulfill the COAPT criteria, TEER may still be considered for symptomatic benefit if the Heart Team is supportive

d) In intermediate and high surgical risk patients, mitral TEER is a low-risk procedure with 30 day mortality rate of 2-3%

e) Referring suitable TEER candidates early for mitral valve intervention is unlikely to result in better outcomes