

Moderate Secondary Mitral Regurgitation: Not Clearly Benign, Not Clearly Actionable

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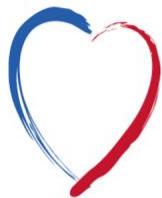
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Take Home Messages

- Moderate secondary mitral regurgitation (SMR) is common in heart failure (HF) and associated with adverse outcomes, but its prognostic impact remains uncertain in heart failure with preserved ejection fraction, in part due to inconsistent grading
- Guideline-directed medical therapy (GDMT) remains the mainstay of management as with HF without valve disease
- Recent data suggest symptomatic improvement and reduction in HF hospitalisations with mitral transcatheter edge-to-edge repair (M-TEER) but are yet to demonstrate definitive mortality benefit in moderate SMR
- Future trials should focus on multi-parametric echocardiographic criteria and optimised GDMT before randomisation to clarify whether moderate SMR is a useful treatment target

Secondary mitral regurgitation (SMR) is defined as MR in the absence of significant abnormalities of the valve leaflets or apparatus. It can be classified by underlying pathophysiology: ventricular SMR, related to left ventricular (LV) disease and heart failure with reduced ejection fraction (HFrEF), and atrial SMR, resulting from left atrial (LA) dilatation and mitral annular enlargement, typically seen in heart failure with preserved ejection fraction (HFpEF) and atrial fibrillation (AF) (1). SMR is also classified by severity and is highly prevalent across the heart failure spectrum (2). Severe SMR is associated with excess mortality in all heart failure types (3) and moderate SMR is increasingly recognised as a risk factor for adverse outcomes. However, it is uncertain whether the adverse effects are due to comorbidities, inconsistent grading, or progression towards more severe disease. Riccardi et al explored the prevalence and prognostic meaning of moderate SMR and evaluated the strength of evidence supporting medical and interventional approaches (4).

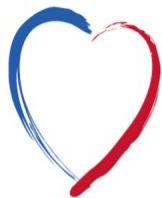


Grading of SMR

Grading thresholds of SMR differ among societies. According to the European Association of Cardiovascular Imaging, moderate SMR in echocardiography is defined by an effective regurgitant orifice area (EROA) of 0.20-0.29 cm², regurgitant volume (RVol) 30-44 mL, and regurgitant fraction (RFrac) 30-39%. Inconsistencies in trial inclusion criteria have likely contributed to variable outcomes. For instance, the COAPT trial enrolled patients with heart failure and moderate-to-severe or severe SMR who remained symptomatic despite maximally tolerated GDMT. Patients had a relatively large mean EROA of 0.41 cm² with relatively mild LV systolic dysfunction, showing lower HF hospitalisations and all-cause mortality with mitral transcatheter edge-to-edge repair (M-TEER) versus medical therapy (5). Conversely, MITRA-FR enrolled patients with symptomatic heart failure and severe SMR; there is smaller mean EROA (0.31 cm²) but more severe LV dilatation and no M-TEER benefit was found (6).

Prognostic impact of moderate SMR

While severe SMR is established as a predictor of mortality and HF hospitalisation (7,8), the impact of moderate SMR is less clear. Evidence suggests its prognostic significance may differ by ejection fraction. In HFrEF, De la Espriella et al. found that moderate SMR was associated with an increase in all-cause mortality or readmission by 50% within 90 days after adjusting for variables including age, gender, and previous acute HF hospitalisation (9). Among heart failure with mildly reduced ejection fraction (HFmrEF) patients, Abel et al. reported a 38% increase in all-cause mortality associated with moderate SMR (4). The JASPER registry is a Japanese observational prospective registration of hospitalised HFpEF patients. In those with LVEF >50%, moderate MR independently predicted all-cause mortality (HR 2.26, p=0.041). A possible explanation might be that high left atrial (LA) pressure and mitral annular dilatation increases LA pushing forces on the mitral leaflets, which reduces coaptation area (10). Overall, moderate SMR appears linked to higher mortality and HF hospitalisation. However, its impact in HFpEF remains uncertain, as those with HFpEF tend to have better outcomes than those with HFrEF; extended follow-up is needed to clarify this relationship (4).



Management

Management of moderate SMR focuses on GDMT for concurrent HF. Angiotensin receptor/neprilysin inhibitor (ARNI) improves SMR by reducing preload and afterload through its natriuretic effect, promoting LV reverse remodelling and better coaptation of the mitral valve leaflets, and inhibiting tissue growth factor beta-mediated leaflet thickening. The PRIME trial randomly assigned patients with heart failure and chronic SMR to either sacubitril/valsartan or valsartan; it found that sacubitril/valsartan reduced EROA by 30% versus 9% with valsartan alone (11).

Cardiac resynchronisation therapy (CRT) has been shown to be associated with significant reductions in SMR severity. The possible mechanisms include LV reverse remodelling, treating mechanical dyssynchrony, and reduction in leaflet coaptation (12).

Surgical treatment of moderate SMR has not demonstrated clinical benefit. Trials have shown no improvement in HF hospitalisations, with increased operation time and neurological sequelae (13). Likewise, in patients undergoing aortic valve replacement, correction of moderate SMR did not improve outcomes (14). This likely reflects the underlying mechanism of SMR – ventricular or atrial remodelling – rather than intrinsic valve disease (4). M-TEER is a less invasive alternative; the MATTERHORN trial enrolled patients with heart failure and SMR with EROA ≥ 0.2 cm². It demonstrated its non-inferiority to surgery for death, HF hospitalisation, stroke, reintervention and implantation of assist device (15).

Future direction

Current European and American guidelines restrict M-TEER to patients with severe SMR who remain symptomatic despite GDMT (16,17). Further randomised controlled trials are required to determine whether M-TEER benefits patients with moderate SMR. However, such studies face certain challenges: a) defining inclusion criteria is complex given the dynamic nature of SMR; a multi-parametric approach including stress echocardiography should be used; b) core echo lab adjudication is essential for accurate grading; c) since GDMT can improve SMR, there needs to be a period of GDMT before randomisation. Trial endpoints should include not only clinical



outcomes but also quality of life and exercise capacity. Future research should evaluate cost-effectiveness and health resource use (4).

Conclusion

Moderate SMR is common among patients with HF across the ejection fraction spectrum. While severe SMR worsens outcomes, moderate SMR is also associated with increased mortality and hospitalisation, particularly in HFrEF. Its prognostic role in HFpEF remains uncertain. A multi-parametric approach assessing EROA, RVol and RFrac may refine patient selection for future trials. Though recent data hint at potential benefit of M-TEER, moderate SMR currently serves as a marker of disease burden rather than a therapeutic target. Future trials should determine whether M-TEER can improve symptoms and outcomes in patients with moderate SMR who remain symptomatic despite GDMT.

Disclosures

None.

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