

Mitral and Tricuspid Regurgitation: Timing Intervention in Heart Failure

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The management of functional mitral regurgitation (FMR) and functional tricuspid regurgitation (FTR) in patients with heart failure (HF) presents a persistent clinical dilemma. While severe regurgitation is associated with adverse outcomes, the optimal timing for intervention, particularly in asymptomatic or mildly symptomatic patients, remains undefined. This article reviews the current understanding of when intervention may be most beneficial, considering the progressive nature of these valvular pathologies in the context of myocardial dysfunction.

KEY TAKEAWAYS

- **The Pivot:** The debate centers on whether early intervention in moderate FMR/FTR improves long-term outcomes beyond guideline-directed medical therapy (GDMT).
- **The Data:** Current evidence suggests that while intervention can reduce regurgitation severity, a clear mortality benefit in asymptomatic or mildly symptomatic patients with moderate disease is not consistently demonstrated.
- **The Action:** Clinicians should continue to prioritize comprehensive GDMT and consider valvular intervention primarily in symptomatic patients with severe regurgitation or those with progressive ventricular dysfunction despite optimal medical management.

Functional mitral regurgitation (FMR) and functional tricuspid regurgitation (FTR) are common complications of left ventricular (LV) and right ventricular (RV) dysfunction, respectively, frequently observed in patients with heart failure (HF). FMR results from geometric changes in the LV, leading to incomplete coaptation of anatomically normal mitral valve leaflets. Similarly, FTR often develops secondary to RV dilation and dysfunction, causing annular dilatation and leaflet tethering. Both conditions contribute to volume overload, further exacerbating ventricular remodeling and HF symptoms. The presence of moderate to severe FMR or FTR is independently associated with increased morbidity and mortality in HF patients. However, the exact point at which surgical or transcatheter intervention provides a benefit beyond optimized guideline-directed medical therapy (GDMT) is a subject of ongoing investigation.

Current guidelines generally recommend intervention for severe, symptomatic FMR or FTR that persists despite optimal GDMT. The challenge lies in identifying patients who might benefit from earlier intervention, before the development of irreversible ventricular damage or severe symptoms. The concept of a 'tipping point' implies a stage where the natural history of the disease shifts, and intervention becomes more effective than continued medical management alone. This point is difficult to define due to the heterogeneity of HF etiologies, patient comorbidities, and the progressive nature of ventricular remodeling.

Intervention Strategies and Outcomes

For FMR, both surgical mitral valve repair or replacement and transcatheter mitral valve repair (TMVr), primarily using edge-to-edge repair devices, are available. Surgical repair is typically considered in patients undergoing concomitant coronary artery bypass grafting (CABG) or those with severe symptoms and suitable anatomy. TMVr offers a less invasive option for high-surgical-risk patients. Studies evaluating TMVr in symptomatic HF patients with severe FMR have demonstrated significant reductions in mitral regurgitation severity, improvements in functional status, and reductions in HF hospitalizations. However, a consistent mortality benefit has not been universally observed across all trials, particularly in those with less severe baseline regurgitation or more advanced LV dysfunction. The COAPT trial, for example, showed a reduction in HF hospitalizations and mortality with TMVr in symptomatic HF patients with severe FMR and suitable anatomy, emphasizing patient selection. Conversely, the MITRA-FR trial, which enrolled a similar population but with different inclusion criteria for LV size and MR severity, did not demonstrate a significant difference in mortality or HF hospitalizations.

For FTR, surgical repair or replacement has historically been reserved for patients undergoing left-sided valve surgery or those with severe, symptomatic FTR and progressive RV dysfunction. Transcatheter tricuspid valve intervention (TTVI) is an emerging field, with various devices under investigation, including leaflet coaptation devices, annuloplasty rings, and valve replacement systems. Early data from registries and small trials suggest that TTVI can reduce TR severity and improve symptoms in carefully selected patients. However, the long-term efficacy and impact on mortality and HF hospitalizations are still being evaluated. The complexity of tricuspid valve anatomy and the often-advanced stage of RV dysfunction at presentation pose significant challenges for effective intervention.

The 'tipping point' for intervention in FMR and FTR likely involves a confluence of factors, including the severity of regurgitation, the degree of ventricular remodeling and dysfunction, the presence and severity of symptoms, and the patient's overall clinical status and comorbidities. Early intervention in asymptomatic or mildly symptomatic patients with moderate FMR or FTR, before significant ventricular dilation or irreversible myocardial damage occurs, remains an area of active research. The challenge is to identify biomarkers or imaging parameters that can predict which patients

will progress rapidly and benefit most from early intervention versus those who can be managed effectively with GDMT alone. The risk-benefit profile of intervention must be carefully weighed against the potential for complications, especially in a population often characterized by advanced age and multiple comorbidities.

CLINICAL IMPLICATIONS

The ongoing discussion regarding the optimal timing for intervention in functional mitral and tricuspid regurgitation highlights a persistent gap in our evidence base. While devices like the MitraClip have demonstrated efficacy in reducing mitral regurgitation and improving quality of life in selected patients, the broader question of when to intervene in less severe disease, or in asymptomatic individuals, remains largely unanswered. Clinicians are left to balance the known risks of surgery or transcatheter procedures against the potential for progressive ventricular dysfunction if intervention is delayed. This often leads to a reactive approach, where intervention is considered only after significant symptoms or advanced disease manifest, potentially missing a window where myocardial recovery might be more robust.

From an industry perspective, the pursuit of a 'tipping point' is critical for expanding market access for transcatheter devices. Demonstrating a clear mortality benefit or preventing irreversible cardiac remodeling in earlier stages of disease would significantly broaden the eligible patient population beyond the current high-risk, symptomatic cohort. This necessitates more robust, adequately powered trials focusing on earlier intervention, perhaps in patients with moderate regurgitation and early signs of ventricular dysfunction, rather than waiting for severe disease. The development of more precise diagnostic tools, such as advanced imaging or novel biomarkers, that can identify patients at high risk of progression would also be invaluable, guiding both clinical decision-making and device development.

For patients, the current uncertainty translates into varying approaches to care, depending on the clinician and institution. While guideline-directed medical therapy is paramount, the lack of definitive guidance on early intervention means some patients may experience avoidable progression of their heart failure. A clearer understanding of the 'tipping point' would empower patients and their physicians to make more informed decisions, potentially leading to interventions that preserve cardiac function and improve long-term outcomes, rather than simply mitigating symptoms in advanced disease. This underscores the need for continued research to refine patient selection and timing for these complex interventions.

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