Heart Valve Society
Mitral Tricuspid Valve
Database

**Project Application**

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**Title of the project application:** Clinical and echocardiographic results of mitral valve repair for secondary mitral valve regurgitation

**Introduction**

Surgical treatment of ventricular functional mitral valve disease remains challenging and the results of valve repair highly unpredictable. The primary problem of ventricular functional mitral valve disease lies in the functionally impaired and geometrically remodeled left ventricle (1). This in turn leads to papillary muscle displacement and leaflet tethering in combination with mitral annular dilation. Owing to the imbalance between closing and tethering forces, this can result in mitral valve insufficiency with poor patient prognosis (2).

The interventional management of ventricular functional mitral regurgitation is complex. The mainstay of heart failure treatment presents optimal guideline-directed medical therapy combined with cardiac resynchronization therapy, when indicated. Interventional therapy, particularly stand-alone intervention performed in patients not undergoing coronary artery bypass surgery for coronary artery disease, is generally reserved for patients who fail to respond to optimal non-interventional therapy measurements and in whom severe regurgitation and heart failure symptoms remain coexisting (3). The optimal patient selection, treatment modality and surgical/interventional treatment options all remain unclear to date.

It is clear that while the focus is often set on the mitral valve, the primary treatment goal is the induction of left ventricular reverse remodeling, a marker of improved prognosis in heart failure patients (4, 5). Specialized centers have reported good surgical results with undersized annuloplasty in carefully selected patients, but the results have not been widely reproduced (6). Owing to the unsatisfactory results of surgical treatment in these patients, sub-annular repair techniques, including approximation of papillary muscles and relocation of papillary muscles, have been introduced, specifically targeting the left ventricle and aiming to restore normal ventricular geometry (7-10). Encouraging results have been reported but to what extent these techniques have been adopted in surgical valve centers remains unknown. A randomized controlled trial, comparing mitral valve repair to replacement in patients with ventricular functional mitral valve disease, failed to demonstrate superiority of valve repair in this setting (11). The drawbacks of the trial have been widely discussed and the optimal surgical treatment strategy remains elusive to date.
Recently, the rapid development of transcatheter techniques of mitral valve repair resulted in the development of new promising treatment options for patients suffering from ventricular functional

mitral valve disease. The MitraClip system remains the most studied and used transcatheter treatment option. The results of randomized trials on the effectivity of this transcatheter therapy, when compared to optimal medical therapy, have been controversial and demonstrated conflicting results, with the COAPT trial demonstrating very good results of the transcatheter therapy and the MITRA-FR failing to do so (12, 13). Recently, transcatheter valve repair therapies have been compared to surgical repair in a non-randomized setting. While, as expected, the risk of surgery is greater, resulting in poorer results in the (very) early period after surgery, reports showing improved late and cumulative clinical and echocardiographic results have been published recently (14). It is unclear if transcatheter therapy provides an equivalent treatment option to surgical interventions, especially to the techniques of valve repair combined with sub-annular repair techniques.

With all the controversies in patient and treatment selection in ventricular functional mitral valve disease, new, multi-center studies are needed in order to gain insight into the current state of treatment of ventricular functional mitral valve disease and provide evidence-based recommendations on patient management.

## Aim of the project

- Provide an overview of the current state of surgical and transcatheter treatment in ventricular functional mitral valve disease,
- To compare the clinical and echocardiographic results of surgical and transcatheter treatment in ventricular functional mitral valve disease at 1-year after intervention in a real-world setting,
- To assess the potential for left ventricular reverse remodeling of various surgical and transcatheter treatment options,
- To compare the effect of various surgical repair techniques on diastolic mitral valve performance at 1-year after surgery.

## Included patients

Inclusion criteria:

- Secondary mitral valve disease of ischemic or non-ischemic origin with restrictive systolic leaflet motion (Carpentier IIIb type). Ventricular functional mitral regurgitation will be defined as mitral valve regurgitation caused by ventricular remodeling caused by primary ventricular disease (ischemic or nonischemic dilatative cardiomyopathy) with leaflet tethering height ≥10 mm, left ventricular end-diastolic diameter ≥55 mm and left ventricular ejection fraction ≤50%.
- Any type of surgical (mitral valve repair, regardless of the type of technique used, or replacement) or trans-catheter (edge-to-edge repair, trans-catheter annuloplasty or valve replacement) mitral valve intervention,
- The patients should be on stable guideline-directed medical therapy at maximum tolerated doses and receive cardiac resynchronization therapy, if indicated, prior to intervention.

Exclusion criteria:

- Previous cardiac surgery,
- Any other type of mitral valve disease, including atrial functional mitral regurgitation, primary or mixed mitral valve disease,
- Patients undergoing left ventricular aneurysmectomy and reconstruction surgery.

## Duration project

□ Retrospective **X** Prospective

Inclusion period _01-10-2024_ - _30-09-2025_

Follow-up period _01-10-2024_ - _30-09-2026_ (Can be the same as inclusion period)

**Primary outcomes**

The primary outcome will be left ventricular reverse remodeling, defined as ≥15% reduction in indexed left ventricular end systolic volume, at 1 year after intervention.

**Secondary outcomes**

Secondary outcomes will be:

- Overall survival at 1 year after intervention,
- Freedom from hospitalization for heart failure at 1 year after surgery,
- Freedom from recurrent mitral valve regurgitation (defined as ≥grade 2+ mitral regurgitation after an initial successful mitral valve repair, the latter defined as ≤grade 1+ regurgitation on predischarge echocardiography),
- Left ventricular strain at 1 year after intervention,
- Diastolic mitral valve gradient and mitral valve area at 1 year after intervention,
- Functional status (6-minutes walking test),
- Health-related quality of life (EQ-5D-5L)
- Blood NT-pro-BNP levels.

**Collection of data outside standard of care**

All clinical and echocardiographic data will be collected at regular visits at the outpatient clinic, which presents the standard of care. Data on patient survival and cause of death will be obtained from municipal registries.

Additional echocardiographic parameters of specific interest to this project can be obtained from standard echocardiographic imaging performed during regular follow-up. This includes left ventricular strain measurements.

**Variables entered**

All fields in the database will be entered.

Additional data to be collected: history of hospitalization for heart failure, use of preoperative diuretics (none, oral, i.v.), cardiac resynchronization therapy.

**Data analysis plan**

Continuous data will be presented as means ± standard deviation for normally distributed and median with interquartile range for skewed data, and compared using Student t-test or U-test of Wilcoxon-

Mann-Whitney, respectively. Categorical data will be presented as counts and percentages compared using the chi-squared test or Fisher's exact test, as appropriate.

The Kaplan-Meier method will be used to estimate cumulative survival rates and inter-group comparisons will be made using the log-rank test. To adjust for potential confounders, Cox-proportional regression analyses, inverse probability of treatment weighting analyses and propensity score matching will be performed. Univariable and multivariable linear regression models will be built to explore the factors associated with left ventricular end-diastolic volume and left ventricular strain at follow-up. The proportional hazards assumption will be tested by visual inspection of the Kaplan-Meier curves and assessing the Schoenfeld's residuals. A predesigned landmark survival analysis, with the landmark set at 30 days, will be considered. The propensity scores will be constructed using a "nonparsimonious" multivariable logistic regression model with the treatment variable (surgical mitral valve intervention vs. transcatheter valve intervention) as the dependent variable. Matching will be done in a 1:1 ratio using nearest neighbor matching with a caliper width equal to a 0.20 standard deviation of the propensity score. The balance of propensity score matching and inverse probability treatment weighting will be assessed using (weighted) standardized mean difference.

To compensate for the competing risk of death, cumulative incidence function for hospitalization for heart failure, with death as competing risk, will be computed.

All tests will be 2-tailed and a P-value of <0.05 will be considered statistically significant. Statistical analysis will performed using IBM Statistics for Windows, version 29.0 (IBM Corp. IBM SPSS Statistics for Windows, Armonk, NY, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

Based on the prospective study design and the fact that all clinical and echocardiographic data can be obtained from standard clinical follow-up data, the amount of missing data is expected to be low and not significant.

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