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Leiden

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## **Advanced echocardiography in characterization and management of patients with secondary mitral regurgitation**

Namazi, F.

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# Chapter seven

*Summary, conclusions and future  
perspectives*

*Samenvatting, conclusie en  
toekomstperspectieven*





## Summary

In this thesis the role of advanced echocardiography was evaluated in the risk stratification and management of patients with secondary mitral regurgitation (MR).

The general introduction (**Chapter 1**) provided insights in the role of multimodality imaging in the evaluation of patients with mitral regurgitation referred for transcatheter interventions. An important part of patient selection for transcatheter MV therapies is MR quantification and an accurate assessment of the mitral valve anatomy. These parts cannot be visualized during transcatheter intervention and therefore interventionalist need visualization of the MV apparatus. Three-dimensional imaging techniques, i.e. transesophageal echocardiography, computed tomography, and cardiovascular magnetic resonance, are key in the evaluation of anatomical assessment of the MV apparatus and the suitability of the patient for transcatheter intervention. Fusion imaging is being implemented in catheterization laboratories to precisely guide the procedure and to maximize safety and optimal results.

### Part I: epidemiology in secondary mitral regurgitation

In this first part epidemiological characteristics of patients with secondary MR is evaluated. Secondary MR is more prevalent in men than women, but little is known about its association with prognosis. In **Chapter 2** the sex distribution of secondary MR and the prognostic differences between sexes has been evaluated. We demonstrated that secondary MR was more frequently seen in men and associated with a worse prognosis. Also ischemic heart failure was more significantly common in men, whereas non-ischemic heart failure was more prevalent in women. The underlying ischemic etiology of secondary MR is known to respond less well to heart failure therapies and may further progress over time, leading to worse outcome.

### Part II: Echocardiography and prognosis in secondary mitral regurgitation

In this second part we focused on the role of echocardiography in defining predictors of outcome in patients with secondary mitral regurgitation. Left ventricular (LV) systolic function may be overestimated in patients with secondary MR when using LV ejection fraction (LVEF). LV global longitudinal strain (LVGLS) derived from speckle tracking echocardiography has shown it is more sensitive to detect LV systolic dysfunction. **Chapter 3** evaluates the incremental prognostic value of LVGLS. Patients with more impaired LV systolic function according to a LVGLS value of less than 7% showed significantly higher mortality rates. LVGLS also demonstrated to be of incremental prognostic value over LVEF. The results of the current study suggest that LV GLS

might be a better prognostic marker than LVEF and therefore could aid further risk stratification of patients with secondary MR.

Quantification of secondary MR remains challenging and its severity can be over- or underestimated. **Chapter 4** evaluates the ratio of mitral regurgitant volume (RVol) and LV end-diastolic volume (LVEDV) and its association with prognosis. Patients with a RVol/EDV ratio  $<20\%$ , defining a smaller RVol/larger EDV (i.e. more LV remodeling), had significantly higher mortality rates when compared to their counterparts. When considering patients receiving medical therapy only, patients with RVol/EDV ratio  $\geq 20\%$  tended to have higher mortality rates than those with RVol/EDV ratio  $<20\%$ . Higher RVol/EDV ratio was independently associated with all-cause mortality. These results reflect the importance to take the relative severity of both MR and LV volume into account. RVol/EDV ratio may further improve risk stratification of patients with secondary MR and identify those who may benefit from transcatheter and surgical therapies to reduce severe secondary MR.

**Chapter 5** examines the impact of MV geometry on outcomes after transcatheter edge-to-edge mitral valve repair with the MitraClip device (Abbott Vascular, Santa Clara, CA) compared to patients treated with guideline-directed medical therapy (GDMT). This present echocardiographic core laboratory study from the multicenter COAPT trial demonstrated that amongst many geometrical characteristics of the MV, a large anteroposterior mitral annular diameter and greater effective regurgitant orifice area (EROA) were the strongest echocardiographic predictors of HFH and death in patients treated with GDMT alone and with the MitraClip. A large anteroposterior mitral annular diameter was associated with increased risk of the composite outcome of all-cause death or HFH and HFH alone. Greater EROA was an independent predictor of mortality. Treatment with the MitraClip plus GDMT compared with GDMT alone reduced death and HFH consistently in patients with and without these extremes.

The chronic volume overload in patients with secondary MR eventually leads to pulmonary hypertension and right ventricular (RV) dysfunction with an increased risk of morbidity and mortality. In **Chapter 6** we evaluated the ratio between tricuspid annular plane systolic excursion (TAPSE) and pulmonary arterial systolic pressure (PASP) as a non-invasively measure of RV to pulmonary artery (RV-PA) coupling (the relationship between RV contractility and afterload). A TAPSE/PASP ratio  $<0.35$ , defined as an impaired RV-PA coupling, was associated with an excess mortality. Patients with a TAPSE/PASP  $\geq 0.35$  showed significantly better survival rates. TAPSE/PASP ratio also remained independently associated with all-cause mortality and showed to have an

incremental prognostic value over TAPSE. By taking into account TAPSE/PASP ratio (as a measure for RV-PA coupling), it may improve further risk stratification of patients with secondary MR.

## Conclusions and future perspectives

Secondary MR is a result of changes in the LV geometry and MV annular dilation and has an increasing incidence. Severe secondary MR is known to be associated with a worse prognosis, whilst the effect of reducing MR on prognosis has still been unclear. The question remains what influences the prognosis of these patients: is it the LV or the valve (i.e. the MR)? Characterization and risk-stratification of patients with secondary MR therefore remains challenging. Until recently the decision to intervene for secondary MR was based also on the LVEF. However, LVEF is subject to many limitations. The conflicting results of two major trials evaluating transcatheter mitral valve repair therapy using the MitraClip device (Abbott Vascular, Menlo, CA) demonstrated differences in LV volumes, but had similarities in LVEF suggesting that LVEF is not the best parameter to assess LV systolic function in patients with secondary MR. Advanced echocardiography, such as speckle tracking echocardiography, from which LVGLS could be derived has shown to be of much more diagnostic and prognostic value in various valvular heart disease and is currently being implemented more in valvular heart disease guidelines. This supports the fact that LVGLS can detect LV dysfunction in an earlier stage and therefore guide physicians to refer patients for intervention before it is too late. Also the mitral valve geometry has an important role in the technical feasibility of intervention, but also could elaborate on which specific transcatheter intervention is more appropriate according to their targets (i.e. leaflets, annulus or sub apparatus). Additionally, multimodality imaging remains key in characterization and quantification of secondary MR and may help further risk-stratification.