Reverse Remodeling in the Perspective of Decision-Making for
Mitral Valve Repair with the MitraClip

Running title: Rosenhek; Reverse Remodeling after MitraClip Therapy

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Degenerative and functional mitral regurgitation (MR) constitute two separate disease entities: while the pathophysiological problem is directly addressed by a successful intervention on the valve in the first case, the underlying ventricular disease persists in the latter.

Indications for surgery in mitral regurgitation are well defined for degenerative MR, where the relief of the valve lesion leads to a relief on the left ventricular volume overload. The timing of surgery is based on symptoms, left ventricular size and function, atrial fibrillation and pulmonary hypertension\textsuperscript{1,2}. When following these criteria, surgery is associated with symptomatic improvement and also with a survival benefit. Nevertheless, up to 50\% of patients, in particular when they are elderly or present with comorbidities or reduced ventricular function are denied surgery despite having a clear indication for intervention\textsuperscript{3}.

Criteria for surgical intervention are less well defined in functional mitral regurgitation, where the valve is structurally normal and regurgitation is caused by an imbalance between closing and tethering forces related to a ventricular pathology\textsuperscript{4}, which is not entirely corrected by the relief of MR. From the surgical experience it is known that a valve intervention leads to an initial reduction of MR, although the recurrence rate is high and a survival benefit has not been demonstrated so far\textsuperscript{5}. Furthermore the surgical risk is frequently non-negligible and as a result indications for surgery are not strong unless there is an indication for coronary artery bypass surgery\textsuperscript{1,2}. On a general basis, the first approach in these patients is the initiation of a heart failure therapy including cardiac resynchronization therapy, which has a proven survival benefit.

Nevertheless, a percutaneous approach for the therapy of MR is an attractive concept for the management of inoperable and selected high-risk patients. The percutaneous MitraClip system has been adapted from the surgical edge-to-edge technique proposed by Alfieri\textsuperscript{6}. When introducing a novel technique into clinical practice, several important questions need to be
addressed regarding the safety of implantation, the efficacy in reducing MR, the effect on symptomatic improvement, the effect on left ventricular remodeling and last but not least the effect on overall survival. Obviously these question need to be answered for degenerative and for functional MR.

The EVEREST I study was performed to demonstrate the feasibility, safety and efficacy of the procedure\(^7\). In a systematic review it has been shown that the MitraClip can be safely and effectively implanted in high-risk surgical patients\(^8\). While in the EVEREST II trial (randomizing patients to MitraClip or surgical therapy), the majority of patients had degenerative mitral regurgitation, data from postapproval studies such as ACCESS-EU\(^9\) trial and the TRAMI registry\(^10\) indicate that the larger part of patients being treated in clinical practice have functional MR. These studies have confirmed an efficacious reduction in MR severity and symptomatic improvement for the majority of the patients.

The present paper by Grayburn et al.\(^11\) has the merits to demonstrate the effect of the reduction of MR on reverse left ventricular and left atrial remodeling after MitraClip implantation in 801 patients with severe MR derived from the EVEREST II, the EVEREST II high risk study and the continued access EVEREST II (REALISM) study, as well as in 80 surgically treated patients. The study has the merits to separately assess the entities of degenerative and of functional MR.

In patients with degenerative MR a reduction of the left ventricular end-diastolic volume (LVEDV) from 140±40 to 120±35 ml was observed, while the end-systolic volume (LVESV) remained rather stable with 53±21 and 50±20 ml at baseline and at 12 months, respectively. These findings are explained by an effective reduction of volume overload.

In patients with functional MR, a reduction in LVEDV from 166±52 to 151±49 ml and of
the LVESV from 96±41 to 87±41 ml was observed. Furthermore, significant residual MR (3-4+) was associated with significantly less ventricular remodeling both in degenerative and in functional MR as compared to lesser residual MR. Finally, reverse left atrial remodeling was also related to the magnitude MR reduction observed with the intervention. Thus, the greater the reduction of MR, the more reverse remodeling can be expected.

The documented reverse remodeling in this large series is another important piece of information supporting the concept of percutaneous correction of MR. These data may also be seen in the context with the findings of the MitraSwiss registry that included 100 patients in which the magnitude of residual MR after a MitraClip intervention was predictive of 1-year survival12.

It needs to be noted that the inclusion criteria for the EVEREST II trial, required an ejection fraction > 25 % and a left ventricular end-systolic diameter < 55 mm for inclusion13 and in the EVEREST II high-risk trial, patients with an ejection fraction < 20% or a left ventricular end-systolic diameter > 60 mm14 were excluded. Indeed, the average ejection fraction at baseline in the present analysis was 44±11% for patients with functional MR and 62±8% for those with degenerative MR. The endsystolic diameters at baseline were 46±7 mm and 34±7 mm for patients with functional and degenerative MR, respectively. It is thus not proven that a similar extent of reverse remodeling can be expected in patients with very poor ventricular function and excessive left ventricular dilation. The potential futility of an intervention needs to be considered in such cases.

From the currently available data, it is justified to consider a MitraClip implantation in inoperable or high-risk patients with degenerative MR, when their valve anatomy is suitable1. In secondary MR the MitraClip procedure should be considered in inoperable or high-risk patients.
after the optimization of medical therapy and having considered cardiac resynchronization therapy. While there is increasing evidence, that in functional MR the procedure leads to reduction of MR, symptomatic improvement and reverse ventricular remodeling, the important question, regarding a potential survival benefit remains unanswered yet. A sufficiently powered randomized study comparing the survival of patients with functional MR receiving optimal medical therapy to those undergoing a MitraClip implantation is eagerly awaited. In the meantime a careful risk-assessment and individualized decision-making is required. The impact on reverse remodeling is one additional element to consider in the decision process.

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