What to do with functional mitral regurgitation: what do we really know and how can we find out?

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Managing heart failure patients with left ventricular dysfunction-associated mitral regurgitation (functional mitral regurgitation or FMR) is challenging and requires a multidisciplinary approach. Optimal medical therapy (OMT) with vigilant outpatient surveillance, cardiac resynchronization therapy (CRT) and myocardial revascularization can all have positive impacts on quality of life, and perhaps even survival. Since as many as 30% of individuals with heart failure have moderate–severe mitral regurgitation (MR), it is mechanistically appealing to postulate that correcting MR, whether by surgery or transcatheter MitraClip therapy, should benefit these patients. However, data supporting FMR correction are largely observational. The current American College of Cardiology/American Heart Association (ACC/AHA) guidelines give mitral valve repair in patients with symptomatic severe left ventricular dysfunction a Class IIa (level of evidence C) recommendation [1]. The European Society of Cardiology (ESC) guidelines also cite limited data (level of evidence C) supporting mitral valve correction and give primarily Class IIa/b recommendations for the surgical correction of MR in the setting of left ventricle (LV) dysfunction with or without coronary artery disease and planned CABG [2]. MitraClip therapy, by virtue of its percutaneous delivery, may offer improved safety when compared with surgical mitral valve repair in patients with predominantly degenerative MR, but at the expense of far less effective MR reduction [3]. It is felt, however, that MitraClip therapy may be ideally suited for the treatment of higher- or extreme-surgical-risk FMR patients in whom other treatment options are limited. What then, does the accompanying report add to our understanding of applying surgery or MitraClip to patients with FMR? And how does it help us answer the question of what to do with FMR?

In this issue of the journal, Taramasso et al. [4] retrospectively describe the clinical characteristics, in-hospital and intermediate to long-term follow-up of two groups of patients undergoing correction of FMR. The first group consists of 91 patients undergoing surgical correction of FMR over the last 10 years, the second group comprises 52 patients undergoing MitraClip implantation during the last 3 years of the surgical experience. All patients had either moderate–severe or severe MR, were symptomatic despite medical therapy (the nature of which is not specified) and had ischaemic or idiopathic dilated cardiomyopathy (a very heterogenous group, in terms of outcome behaviour and competing risks). The decision to perform surgical correction vs MitraClip therapy was based on a ‘multimodality decision-making process’, which included the logistic EuroSCORE, as well as other less-quantifiable factors such as liver cirrhosis, neurological impairment and frailty. Patients had pre- and post-procedure echocardiography (non-core lab adjudicated) and were followed clinically for a variable amount of time (median 18 months for surgery and 8.5 months for MitraClip).

Based on the selection process for surgery vs MitraClip therapy as described by the authors, it is not surprising that two highly divergent groups emerge. While the surgery and MitraClip cohorts are both interesting in and of themselves, the vastly different clinical characteristics of the two groups make any comparison statistically and logically difficult. The surgical group underwent multiple concomitant procedures aside from differing techniques of mitral correction at the time of surgery [coronary artery bypass surgery (CABG) 35%, tricuspid valve repair 25% and atrial fibrillation ablation 26% of the time]. The MitraClip group was older, had over two-fold higher logistic EuroSCOREs and had more chronic kidney disease, chronic obstructive pulmonary disease, prior CABG, cerebrovascular accidents and diabetes mellitus. In the MitraClip group, baseline ejection fraction (EF) was worse (28 vs 32% in the surgical group), left ventricular size was greater left ventricular end diastolic diameter (LVEDD) 70 vs 66 mm in the surgical group), mitral annular dimensions were worse and tricuspid regurgitation (TR) grade was higher. Baseline New York Heart Association (NYHA) class was not different at baseline between the two groups. It is also interesting to note that the patients in both groups had relatively advanced disease, with clinical features that have been associated with poorer FMR surgical outcomes, such as LV end-diastolic diameter ≥65 mm and mitral valve (MV) coaptation depth ≥11 mm.

The outcomes for both groups were described. For the surgical group, in-hospital mortality was 6.6% (with all patients discharged to a rehabilitation facility), median postoperative length of stay was 11 days, 17% had major infection/sepsis, no patient had pre-discharge MR grade ≥3+ and 1-year freedom from MR.


...was excellent at 94% with 89% surviving. For the MitraClip group, in-hospital mortality was 0% (with 61% of patients discharged to home), median postoperative length of stay was 5 days, 4% had major infection/sepsis, 9.6% of patients had pre-discharge MR grade ≥3+ and 1-year freedom from MR ≥3+ was 79% with 88% surviving. In terms of functional status at 1-year follow-up, 89% of the patients in the surgery group were NYHA Class I/II (22% NYHA Class I). In the MitraClip group at 1 year, 84% of the patients were NYHA Class I/II (48% NYHA Class I).

The MitraClip cohort of this report is extremely important in that there are few reports of MR correction with MitraClip in subjects with solely functional MR at high-surgical risk. Franzen et al. reported 6-month follow-up on a series of 50 subjects with purely FMR with left ventricular ejection fraction (LVEF) ≤25%, MR ≥3+ and in NYHA functional Class III or IV. MR ≤2+ was present in 92% at discharge, and 30-day and 6-month mortalities were 6 and 19%, respectively. There were improvements in functional class, but only mildly favorable LV remodelling at 6 months [5]. Auricchio et al. described 51 symptomatic non-responders to CRT with FMR grade ≥2+. They reported that MitraClip treatment was feasible in all patients, with two peri-procedural deaths, additional 30-day mortality of 4.2% and a median 14-month follow-up mortality of 18%. Overall, subjects undergoing MitraClip therapy had improvements in MR grade, functional class, LV size and EF [6]. Although other reported series utilizing MitraClip therapy are interspersed with FMR subjects (ranging 58–90% when compared with degenerative MR), there remain few data reports focused on MitraClip outcomes in FMR patients [7–8].

The surgical outcomes in the report by Taramasso are notable for a relatively low mortality rate despite the predicted high-surgical risk and very effective MR reduction. We are still left with the question of whether or not any intervention to correct FMR in high-surgical-risk patients has a meaningful survival impact when compared with OMT, CRT or revascularization therapy alone. The sole published randomized prospective FMR trial by Fattouch et al. [9] describes 102 patients with moderate chronic ischaemic MR (mean MR grade 2+ and LVEF 43%) and moderately dilated left ventricles (mean LVEDD 59 mm) that were randomized to CABB plus mitral valve repair (n = 48) or CABB alone (n = 54). Postoperative and follow-up MR grade, NYHA class and LV remodelling were improved in the MV repair group. That trial was not powered for mortality analysis, and in-hospital and 5-year survivals were not statistically different between the groups. However, given the improvements seen with MR correction in patients with only moderate MR and moderate LV dysfunction, it is tempting to hypothesize even greater clinical benefits in patients with more advanced degrees of LV dysfunction and MR severity. Reinforcing this, Deja et al. published the results of mitral surgery for all patients with FMR and an EF of <35% from the STICH trial. This report of 1212 patients showed not only a quality of life improvement, but hinted at a survival benefit from the addition of mitral valve repair to CABG in these high-risk patients [10]. Finally, Chan et al. have reported preliminary results from a randomized, prospective survival trial of CABB with or without mitral valve repair for FMR. Already at 1-year follow-up, FMR patients who had the addition of mitral valve repair had lower left ventricular end systolic volume (LVEDV), brain natriuretic peptide (BNP) and MR grade, as well as better sphericity indices and exercise performance [11].

However, actually answering the question of ‘what to do with FMR’ has been difficult to achieve. The randomized National Heart, Lung and Blood Institute (NHLBI) SMMART-HF Trial (Effectiveness of Surgical Mitral Valve Repair Versus Medical Treatment for People With Significant Mitral Regurgitation and Non-Ischemic Congestive Heart Failure) was planned to randomize subjects with significant heart failure associated FMR to either OMT or OMT with surgical mitral annuloplasty. Unfortunately, this important study was terminated due to the inability to recruit sufficient numbers of patients (trial NCT00608140, www.clinicaltrials.gov).

What does all this mean? We need randomized data to confirm that the correction of FMR in patients with advanced LV dysfunction and significant MR does in fact result in a meaningful clinical impact. It may be that MitraClip therapy could allow patients at high-surgical risk to be treated with acceptable safety and procedural outcomes (a lower biological impact), but whether this truly benefits patients as opposed to optimal medical therapy remains to be proven.

The history of medicine is filled with the application of hopeful therapies, which based on their novelty and perceived advantages, that have been rapidly adopted with the best of intentions. The PARTNER B trial, in which inoperable patients with severe AS had improved survival with transcatheter aortic valve replacement (TAVR) when compared with medical therapy, and the PARTNER A trial, in which high-surgical-risk patients had similar outcomes with TAVR when compared with open surgery, have established the pathway for percutaneous valve therapies to prove their worth initially in inoperable or high-risk scenarios. Conversely, the perceived lack of MitraClip efficacy over mitral surgery in the randomized EVEREST II trial may have stemmed from its inclusion of primarily lower-surgical-risk patients with degenerative MR [3]. Randomized trials in higher-risk FMR populations are needed to establish an appropriate and evidence-based application of any therapy, be it surgical or percutaneous.

There is a growing consensus that FMR is not merely an innocent bystander when diagnosed in the presence of LV dysfunction and heart failure, and it is hoped that FMR correction will result in clinical benefits, which may include improved survival over time. For this to hold true, the morbidity of the therapy which corrects MR must be low enough not to overwhelm the clinical benefits of reduced MR. In addition, therapies to reduce MR will likely have to achieve an as yet undefined permanent degree of MR reduction to translate into a sustained clinical effect. The soon-to-commence COAPT Trial (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for High Surgical Risk Patients) sponsored by Abbott (Abbott Park, IL, USA) will randomize extreme high-surgical-risk patients with degenerative MR ≤3+ to either OMT or OMT with surgical mitral annuloplasty. The outcomes of this trial and other investigator-initiated FMR focused trials are eagerly awaited.

**Conflict of interest:** none declared.

**REFERENCES**


