Review Article on Novel Concepts in Cardiopulmonary and Structural Heart Disease

Mitral regurgitation: lessons learned from COAPT and MITRA-Fr

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Abstract: Recent studies about percutaneous treatment of secondary mitral regurgitation (MR) underlined the importance of left ventricular geometry and features of mitral valve as determinants of procedural and long-term success. Guideline-directed medical therapy (GDMT), transcatheter mitral valve treatment (TMVT) and surgical procedures (mitral valve replacement, mitral valve repair at level of the annulus or subvalvular apparatus) have been extensively evaluated but not adequately compared in current clinical studies. A detailed analysis of the results of the study about transcatheter mitral valve repair would allow to evaluate the safety and effectiveness of such procedure and would provide potential indications for improving the quality of percutaneous and surgical repair in patients with moderate-to-severe secondary MR. Patients with proportionate MR (i.e., MR severity is proportional to the amount of left ventricular dilatation) are prone to respond to the optimization of medical therapy, while patients with disproportionate MR (i.e., MR severity is disproportionately higher than predicted by left ventricular dilatation, with high EROA and small left ventricle) are likely to benefit from additional repair. The identification of specific subpopulation of "high responders", based on the anatomic characteristics of the mitral valve and the relative dimensions of the annulus, the regurgitation and the left ventricle, can also apply to medical therapy. However, some pivotal component of MR (such as the symmetry of tethering and the differences in biomechanical features of leaflets) are not adequately investigated in current studies and warrant further evaluation.

Keywords: Mitral valve; ischemic mitral regurgitation (MR); Mitraclip; repair; replacement

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The clinical problem

Advances in the management of acute coronary syndromes have increased survival among patients with coronary artery disease; however, secondary mitral regurgitation (MR) still affects more than 2.5 million patients per year, with a double mortality rate in case of moderate-to-severe MR (1). The main long-term manifestations of untreated secondary MR are left ventricular dysfunction and heart failure (HF), with tremendous social implications considering the large part of the population involved in the prevalence of the disease (1-3).

Landmark clinical trials have established mechanical intervention as an actual treatment for patients with moderate-to-severe secondary MR and symptoms (4,5). In these trials, although the use of Mitraclip procedure was not associated with longer survival than medical therapy alone in patients with advanced ischemic cardiomyopathy, the reduction in terms of HF-associated symptoms and the improvement in quality of life appeared important. Also, the available surgical options for secondary MR encompass valve replacement and multiple techniques of valve repair (6-8) have been shown to be a safe and effective treatment, but such options were not adequately compared or evaluated against Mitraclip or guideline-directed medical therapy (GDMT) (9), mainly due to intrinsic differences in inclusion/exclusion criteria. Risk stratification in patients with secondary MR appears to be extremely difficult, as recent studies are pointing out that geometric features of the left ventricle are more important than classic risk scores (10). Therefore, the available options to treat secondary MR (GDMT, transcatheter procedures and surgical interventions) should be tailored on each patient.

More recently, an increasing proportion of patients with moderate to severe secondary MR, HF and left ventricular dysfunction are referred to transcatheter mitral valve treatment (TMVT) using edge-to-edge repair technique (Mitraclip procedure, Abbott Vascular, Santa Clara, CA, USA) (4,5). The use of Mitraclip in COAPT and MITRA-Fr randomized controlled trials (RCTs) was designed to test the hypothesis that the use of Mitraclip plus GDMT for HF and left ventricular dysfunction would improve survival compared with GDMT alone (4,5). Besides the single results of the trials, COAPT and MITRA-Fr brought out two different phenotypes of patients, defined as proportionate and disproportionate, with an dishomogeneous response to transcatheter mitral valve repair (10). In the analysis of data from the proportionate phenotypes of patients enrolled in the MITRA-Fr study at a maximum follow-up of 12 months, the use of Mitraclip over GDMT resulted in no differences in the occurrence of death or unplanned hospitalization for HF (4,5,10). Conversely, among patients of disproportionate phenotypes enrolled in COAPT study with HR and moderate-to-severe or severe secondary MR, TMVT resulted in a reduced rate of hospitalization for HF and reduced all-cause mortality than medical therapy alone over 2 years of follow up (4,5,10).

A detailed analysis of the results of the two RCTs about transcatheter mitral valve repair, and the related existing literature, would allow to evaluate the safety and effectiveness of such procedure and would provide potential indications for improving the quality of percutaneous and surgical repair in patients with moderate-to-severe secondary MR.

Current clinical evidences

At present, no randomized trial compared medical management and surgery for moderate to severe MR related to ischemic nonischemic cardiomyopathy. Everest RCT compared the Mitraclip procedure to conventional MV surgery only in a small number of patients with functional MR due to ICM or NICM (11).

COAPT study evaluated the effect of edge-to-edge TMVT on short-term outcomes in 614 patients who had secondary MR randomly assigned to device group (302 patients) or control group (312 patients). The Mitraclip group had a significantly lower all-cause mortality than those whose MR was managed conservatively at 24 months [29.1% *vs.* 46.1%; hazard ratio (HR) 0.62; 95% CI, 0.46–0.82; P<0.001]. Recipients of device had yearly rate of hospitalization for HF of 35.8% as compared with 67.9% in those who received GDMT (HR 0.53; 95% CI, 0.40–0.70; P<0.001). Interestingly, patients who had implanted the device and discharged in GDTM showed a better quality of life (assessed by questionnaires and NYHA functional class), an improvement of dynamic functional capacity, improved MR and improved LV remodeling (assessed by LV end-diastolic volume) compared to the GDMT group (4).

In MITRA-Fr (5), patients with secondary MR and HF were randomized to edge-to-edge TMVT in addition to GDMT (N=152) or medical therapy alone (N=152). Over a median follow-up of 12 months, the linearized mortality rate associated with non-surgical treatment was 22.4%. Mechanical intervention was not associated with a reduced risk of death (HR for intervention group 1.11; 95% CI, 0.69–1.77). The unplanned hospitalization rate for HF was 48.7% in Mitraclip recipients compared with 47.4% in those who were treated with GDMT only (HR 1.13; 95% CI, 0.81–1.56). Differently from COAPT study, MITRA-Fr study has many missing values in terms of longitudinal echocardiographic outcomes, functional status, peptide levels, and quality of life measures, causing a clear reduction of the power of evaluation for this RCT. Among other things, a depressing data concern a considerable number of patients (48/152) in the intervention group in whom technical success of device implantation was achieved had recurrence of MR of grade ≥2 after 1 year (5).

However, a deep analysis of the result of COAPT and MITRA-Fr highlights some discrepancies that can be linked to differences in mortality and repeated hospitalizations. This concern is due to the fact that the study design of MITRA-Fr and COAPT are not equivalent and the two studies enrolled different cohorts of patients. The recipients of Mitraclip in the MITRA-Fr had a mean LVEDV of 252 mL and an EROA of 0.31±0.1 cm². Of these more than 50% had an EROA<0.3 cm^2, and only 16% had an EROA ≥0.4 cm² (5). Conversely, patients enrolled in the COAPT trial showed a mean LVEDV of 192 ml, with a mean EROA of 0.41±0.15 cm². A small percentage (14%) of patients had an EROA <0.3 cm² whereas 41% had an EROA ≥0.4 cm² (4). Interestingly, among patients in COAPT study EROA was ~30% greater but their LV volumes were ~30% smaller compared with those of MITRA-Fr study. As a result, two differently phenotypes of patients were evaluated, thus compromising and fogging the clinical effectiveness of the procedure. Patients in the COAPT study had severe MR and pathophysiological phenotypes of disproportionate MR compared to MITRA-FR study patients who had pathophysiological phenotypes of proportionate MR or non-severe MR (4,5,10). Also, the immediate device failure was 9% in MITRA-Fr and 5% in COAPT, as evidenced by the recurrence of MR grade 3+ or 4+ (4,5). Plasmatic values of brain natriuretic peptide (BNP) are often used in the evaluation of HF and support the differentiation of two different phenotypes of patients. In patients enrolled to receive the Mitraclip procedure and with congestive HF, BNP levels correlate with LV end-diastolic pressure (12-14) and wedge pressure (15). BNP level <100 pg/mL indicates that HR is unlikely (negative predictive value >90%), while a BNP level >500 pg/mL suggests that HR is a likely diagnosis (positive predictive value >90%) (16). The preoperative plasma level of BNP was higher in MITRA-Fr study [device group 3,407 (1,948–6,790) *vs.* control group 3,292 (1,937–6,343)] compared to COAPT study (device group 1,014.8±1,086.0 *vs.* control 1,017.1±1,212.8) suggesting for a greater number of patients who had congestive HF and higher left ventricular end-diastolic pressure in MITRA-Fr study. A considerable number of MITRA-Fr patients' who received the Mitraclip operation developed a mild-to-moderate MR from ischemic cardiomyopathy (62.5%) or nonischemic cardiomyopathy (37.5%), whereas COAPT patients showed severe MR that was attributable to severe coronary artery disease (60.9%) or evolutive nonischemic cardiomyopathy (39.1%) involving primarily the mitral valve than myocardium (4,5). Patients who develop a cardiomyopathy as primary disease may have mild to moderate MR with a normal mitral valve and can be asymptomatic for years. However, the increasing grade of MR, even among asymptomatic patients, determines a volume overload on the left ventricle, that, if sustained over time, results in ventricular dilatation and ultimately leads to HF (17-19).

Everest II (Endovascular Valve Edge-to-Edge Repair Study) is an RCT which evaluated the effect of Mitraclip on 5 year outcomes in 279 patients who had MR grade 3+ or 4+ (11). The 80 patients undergoing conventional MV surgery had a significantly better 5-year rate of the composite endpoint (freedom from all-cause death, reintervention, or recurrent MR grade 3+ or 4+) in the as-treated population than those whose MR was managed with the percutaneous repair (44.2% versus 64.3%, P=0.01). During a follow-up of 5 years, the mortality rate associated with TMVT repair was 20.8% and 26.8% for surgery. This result was not confirmed in multivariable analysis highlighting that treatment strategy was not associated with survival.

The increased recurrence rates of 3+ to 4+ MR was higher in recipients of TMVT repair compared with conventional MV surgery (12.3% *vs.* 1.8%; P=0.02) as well as the proportion of patients who required reoperation (27.9% *vs.* 8.9%; P=0.003). The early repeat (within the first 6 months from procedure) of mechanical intervention after percutaneous repair occurred in 78% of patients (11).

To our knowledge, there are also no randomized trials comparing MV repair with TMVT associated with GDMT. However, data from observational studies suggest a benefit with transcatheter Alfieri edge-to-edge mitral valve repair. The TRAMI (Transcatheter Mitral Valve Interventions study) (20) evaluated Mitraclip in 1,064 patients from 20 German centers (525 patients ≥76 years, 539 patients < 76 years). In this largest published registry, 87% of patients had NYHA functional class III or IV, 69% had reduced LVEF, and in 71% of cases MR etiology was deemed to be secondary. Although the median STS mortality score was 10, logistic EuroSCORE was higher among elderly patients [25% (15–40%) *vs.* 18% (10–31%), P<0.001] and the ratio of women was greater (47.2% *vs.* 29.3%, P<0.001). During a median follow-up of 3 months, 12% died and 12% were hospitalized for HF, although two third of patients remained in NYHA functional class I or II. In detail, elderly patients who received Mitraclip had a greater incidence of preserved LV ejection fraction (40.1% *vs.* 21.8%, P<0.001) and degenerative MR etiology (35.3% *vs.* 25.6%, P<0.01) (20).

However, in this study the advanced age was the most frequent reason for non-surgical treatment (69.4% *vs.* 36.1%, P<0.001). Secondly, the intra-hospital MACCEs (composite of death, myocardial infarction or stroke) rates were low in both groups (3.5% *vs.* 3.4%, P=0.93) and, finally, the proportion of non-severe MR at discharge was comparable (95.8% *vs.* 96.4%, P=0.73). These data were not confirmed with a logistic regression model that showed the significant impact of age on acute efficacy and safety of TMVT among elderly patients (20). Also, the better results reported by Everest study compared with TRAMI study might be related to a lower percentage of patients with FMR (27% *vs.* 71%) and enrollment of younger patients [67.3±12.8 *vs.* 75.0 (70.0–81.0)] in the Everest study (11,20).

Proportionate and disproportionate MR

Grayburn *et al.* (10) recently revised the geometric features of patients with secondary MR and, based on results of COAPT and Mitra-Fr, introduced the terms "proportionate" and "disproportionate" MR, and this classification is related to the ratio between the effective regurgitant orifice (EROA) and left ventricular end-diastolic volume (LVEDD), and clinically represents whether the significance of MR can be described by the degree of LV dilatation.

Depiction of MR as proportionate or disproportionate to LVEDV is critical for proper patient selection (10): patients with proportionate MR (i.e., patients whose MR severity is proportional to LV dilatation) are likely to respond to optimized medical therapy, while patients with disproportionate MR (i.e., MR that is disproportionately—exaggeratedly—higher than predicted by LV dilatation, with high EROA and small left ventricle) would be most likely to benefit from additional repair. As a corollary, patients with an EROA / LVEDV ratio below the line of proportionality has non-severe MR and would not benefit from any MV-directed intervention (10).

The presenting features of proportionate and disproportionate phenotypes of patients are not similar (10). In proportionate condition, ischemic-nonischemic cardiomyopathy (ICM-NICM), is the primary pathophysiologic illness that causes secondary MR and HF. In disproportionate condition, geometric distortion of mitral valve due myocardial ischemia or infarct as well as non-ischemic cardiomyopathy (NICM) leads to secondary MR that evolves with adverse left ventricular remodeling and HF. The natural history of the two conditions depends on the initial clinical disorder that led to secondary MR (4,5,10).

Common causes of proportionate condition include ischemia (irrespective of myocardial infarction) and NICM, recrudescence of chronic systolic or diastolic HF, and dysfunction of a normal mitral valve. Although these patients have an history of paroxysmal nocturnal dyspnea or orthopnea suggesting for secondary MR (5), a history of silent myocardial infarction or occult diastolic dysfunction may also manifest as HF due to secondary MR (5). In contrast, disproportionate condition is associated primarily with functional mitral disorder, including posteroinferior and lateral displacement of papillary muscles, leaflet tethering and malcoaptation, worsening of LV sphericity index with involvement to an adverse left ventricular remodeling and HF (4). The patient history should focus on signs of coronary artery disease and acute coronary syndrome, a decrease in the left ventricular wall motion function associated with need of revascularization (by means of percutaneous coronary intervention or CABG operation). Unfortunately, as evidenced in COAPT and MITRA-Fr RCTs, the history is not always reliable in differentiating proportionate from disproportionate phenotypes of patients (4,5). For example, an ischemic-nonischemic cardiomyopathy (suggesting proportionate phenotypes) may be complicated by syncope or sudden cardiac arrest that requires a cardiac implantable electronic device. Conversely, in patients with severe ischemic MR and coronary targets affected by high-grade proximal lesions that compromise ischemic but viable myocardium (suggesting disproportionate phenotypes), the benefit of surgical revascularization is undisputed.

Current and future clinical use

Patients with secondary MR who are suitable for edge-to-edge TMVT should undergo a careful assessment of symptoms, electrocardiography and echocardiography to assess mechanism and severity of functional MR, LV size and function. For completeness, quantitative Doppler assessment are recommended to define severe MR more precisely (regurgitant volume >60 mL, a regurgitant fraction > 50%, and an EROA >40 mm^2). Patients with symptomatic moderate-to-severe MR or with LV dysfunction or dilatation (LV end-systolic diameter >40 mm) should be provided mechanical intervention with percutaneous repair or conventional MV surgery (19,21-23). Similarly, asymptomatic patients without left

ventricular dysfunction/dilation but with atrial fibrillation or pulmonary hypertension should be listed for systematic control and considered for mechanical intervention when worsening of the NYHA class or rehospitalization for HF are more frequent (21,24,25). Before the advent of edge-to-edge TMVT, conventional mitral valve surgery was the preferred procedure for severe MR. Given the uncertain risk–benefit ratio, conventional MV surgery is not the preferred treatment in patients who do not require associated CABG (17,18,23). As a result, in aging population with significant comorbidities and poor candidates for conventional MV surgery, lower-risk procedures based on transcatheter technologies have been developed to reduce the severity of MR and treat secondary MR (26). The use of the Mitraclip follows the surgical technique named Alfieri stich in which the two prolapsed scallop (P2 and A2) of the mitral valve are brought back in place with the creation of a double mitral orifice (27-29). The objectives of transcatheter MV repair are to obtain a proper line of coaptation on both leaflets and to preserve the subvalvular apparatus (4,5,11,20,26,30). In COAPT and MITRA-Fr RCTs, the of Mitraclip for MV repair is recommended in patients with significant comorbidities, such as advanced respiratory or renal dysfunction, depressed left ventricular function or recent cerebrovascular events but no marked extracardiac arteriopathy. In patients with coexisting coronary artery disease, CABG surgery or percutaneous coronary intervention were previously performed before percutaneous mitral valve repair (4,5).

The improved clinical outcomes obtained by transcatheter interventions are at risk of being compromised by the failures of the results of single studies. The clinical benefit associated with the use of Mitraclip seemed more evident in patients with less compromised ventricles (with non-dilated ventricles, e.g. LVEDV <195 mL) and more pronounced MR (EROA >0.3 cm^2) as the correction of MR results in greater improvement of adverse reverse remodeling. The sex was not found to be a significant effect modifier (4,5). Because the attrition rate of survival and rehospitalization for HF may increase almost exponentially with time, it is not yet known whether the clinical differences in outcome that is apparent between the groups at 1 years could be more significant through a longer follow-up, and this can be a drawback on the safety and effectiveness of the procedure.

Translating phenotypes in the use of medical therapy

Since COAPT and MITRA-Fr are based on the use of GDMT in both control arms of RCTs, all patients received medical treatment for chronic HF with reduced LV ejection fraction (17-19,23,31).

The use of neurohormonal antagonist administration results in relevant difference between proportionate and disproportionate MR (32-37). The treatment with neurohormonal antagonist reduces morbidity and mortality in patients with secondary MR and chronic HF leading to a decreased of LVEDV even more when the degree of MR is proportionate to the LVEDV. In these cases, the patients showed a reduction of MR. The effect of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin receptor blockers (ARB) seemed more effective in decreasing the degree of MR primarily in patients with mild/moderate MR that are largely enrolled in MITRA-FR than in COAPT study (34). The use of a neprilysin inhibitor combined to ARB (Sacubitril/Valsartan) improved MR in patients who have LVEDV>200 mL and mild-to-moderate MR as reported in a recent double blinded randomized trial (36).

The same pharmacological behavior is noted with the use of beta-adrenergic blockade (38-45). One study enrolled the patients in a double-blind placebo-controlled trial and showed that metoprolol was effective in ameliorating functional MR (40% *vs.* 20%) where there was reduced ejection fraction and LVEDV ~200 mL (39). Another RCT revealed that the use of metoprolol reduced LV end-diastolic diameter from 73 mm to 64 mm and decreased the MR grade (40).

The use of carvedilol improves the reverse remodeling with a reduction of MR ratio improving functional MR in patients with ICM or NICM primarily in mild-to moderate MR and reduced LVEF (41-44). Another report revealed that the carvedilol improves LVEDV and the severity of MR with a significant reduction in EROA in 30% of patients (44).

To note that the action of beta-blocker was most pronounced in LV end-diastolic indexed diameter > 37 mm/m^2 that corresponds to a LVEDV of ~250 mL (42). A great percentage of patients (80%) with chronic HF due to idiopathic cardiomyopathy had improvements in MR

12 months year after the administration of carvedilol (LVEDV of 230.5±80.7 mL, and MR estimated at 2.15±1.09) (44). The use of B-blocker reduced EROA dimension by 80% in a study of patients with chronic HF (17 dilated/ischemic *vs.* 28 NICM) with severe MR with low ejection fraction (24%±7%) at 6 months follow-up (45).

Areas of uncertainty and future directions

We are not aware of any randomized studies that compared the geometric modifications after mitral valve repair with the Mitraclip procedures and conventional MV surgery for secondary MR and it is essential that this trial will be conducted in the near future (9,17,18,23,46). Therefore, the current recommendation for the use of TMVT edge-to-edge in the treatment of moderate-to-severe secondary MR is based on two RCTs and several observational data (4,5,23). It is unclear whether patients who have the improvement of severe MR without the normalization of interpapillary muscle distance and anteroposterior annular should undergo better result over time without a significative reduction of posteroinferior and lateral tethering (8,47-57).

The excellent results reported by Stone (4) are based only on the correction of coaptation length by creation of a double orifice (28,29). It is not clear whether these benefits are related to the correction of the asymmetric or symmetrical type of tethering, which determines a different jet for the new assumed location of the coaptation point after posteromedial papillary muscle migration (8,47,52,54,55).

Some investigators have found evidence of greater effect due to an improvement of remodeling with losartan treatment on anterior leaflet of mitral valve than the posterior one (58) whereas others have demonstrated that the biomechanical features of anterior leaflet are different than posterior one (59-63). As a result, the safety and effectiveness of "one size fits all" mechanical intervention could lead to worse results (52).

Also, there is growing experience with minimally invasive TMVT edge-to-edge performed through transesophageal echocardiographic guidance (>15,000 implants in 2015 TVT registry). This approach requires further investigation with respect to widespread use and cost-effectiveness, and it is currently performed only in few specialized centers (64).

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