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I prefer the MitraClip in these cases: the 5-year COAPT data

Antonio L. Bartorelli[1,2]*, Luca Grancini[1], Giovanni Monizzi[1], Emanuele Gallinoro[1], Angelo Mastrangelo[1], Vincenzo Mallia[1], Franco Fabbiocchi[1], and Daniele Andreini[1,2]

[1]IRCCS Ospedale Galeazzi-Sant'Ambrogio, Milan; and [2]Department of Biomedical and Clinical Sciences, University of Milan, Milan

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The COAPT 5-year data demonstrate that compared with medical treatment transcatheter edge-to-edge repair (TEER) with the MitraClip in symptomatic patients with Grade 3+/Grade 4+ secondary mitral regurgitation (SMR) reduced by nearly half the annualized hospitalization risk (33 vs. 57%), by almost 30% the death rate (57 vs. 67%) and achieved significant and durable SMR reduction in 95% of patients. Control patients who crossed over to TEER at 2 years had better prognosis, but nearly half of them died before reaching crossover eligibility. Death or hospitalization for heart failure (HHF) occurred in 73.6% of TEER patients and 91.5% of controls within 5 years, pointing to a need for further study to address left ventricle (LV) dysfunction, the underlying cause of patient's disease. MTRA-FR targeted SMR using the same device and did not improve the composite endpoint of all-cause mortality or HHF at 12 months. Possible reasons for the discrepancy include enrolment of patients with more severe MR and less-advanced LV disease (dilation/dysfunction), less-procedural complications, and higher success in reducing MR in COAPT compared with MITRA-FR. Thus, the ideal patient for MitraClip treatment would be one with severe MR, but with no too severe LV dilation/dysfunction, which is what differentiates COAPT patients from those in MITRA-FR.

Introduction

Mitral regurgitation (MR) is the most common valve disease[1] with a prevalence of ~2% in the general population and increasing frequency in elderly patients.[2,3] Moderate or greater MR severity is present in <1% of people <50 years, but is found in nearly 1 out of 10 people aged >75 years.[3] Primary (e.g. degenerative or organic) MR is caused by abnormalities in one or more mitral valve (MV) components, such as leaflets, chordae, or papillary muscles.[4] Secondary MR (SMR), also referred to as functional because the MV is in itself normal, occurs as a result of annular dilatation and geometrical distortion of the subvalvular apparatus secondary to left ventricle (LV) dysfunction and dilatation associated with ischaemic or non-ischaemic heart failure (HF) in about 9 out of 10 cases.[4] In the remaining 1 out of 10 cases, SMR may be due to left atrial myopathy owing to longstanding atrial fibrillation. Severe SMR is a predictor of poor outcomes due to more hospitalization for heart failure (HHF) depressed quality of life and shortened survival.[5] Death rates of 20% at 1 year and 50% at 5 years have been reported, respectively.[6] Moreover, there is a direct relationship between SMR severity and death. Indeed, 1-year mortality ranges from 45 to 57% in patients with moderate-to-severe MR.[7] Although SMR can be surgically corrected with MV repair or replacement, the surgical approach has never clearly been demonstrated to alter the SMR natural history or to improve survival.[8] Another important limitation of surgery is that up to 50% of patients may not meet eligibility criteria due to high operative risk associated with advanced age, impaired LV function, and multiple comorbidities. This may explain why most HF patients with SMR are treated conservatively.

*Corresponding author. Email: antonio.bartorelli@grupposandonato.it

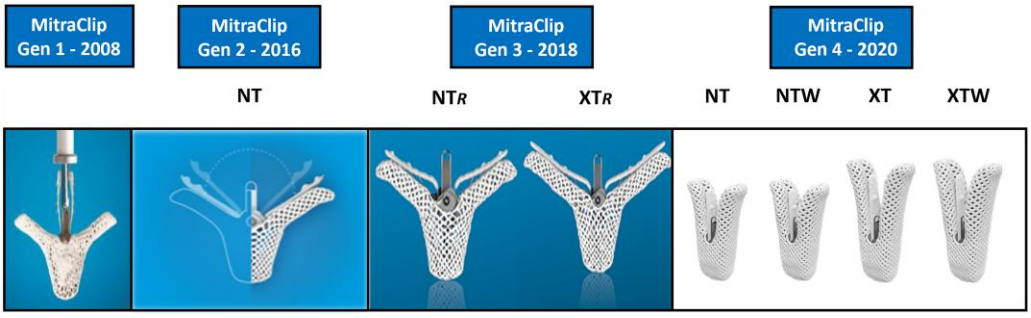

Figure 1 Evolution of the MitraClip from G1 to G4. Compared with G1, G2 featured sleeve steering enhancement and increased drop angle of the nitinol grippers leading to better leaflet grasping. In G3, two clip sizes were introduced with longer clip arms in XT_R, grasping was further improved, coaptation surface was increased, and steering accuracy and ease-of-use were enhanced. G4, which is currently on the market, allows tailored mitral valve repair with four clip sizes, wider clip arms in NTW and XTW, independent leaflet grasping, and left atrial pressure monitoring. Gen, generation.

Transcatheter treatment

Transcatheter repair provides an alternative minimally invasive technique to surgery for treating MR with a percutaneous approach.[9] Currently, transcatheter edge-to-edge repair (TEER) for SMR include the MitraClip™ (Abbott Vascular, Santa Clara, CA, USA) and the PASCAL™ (Edwards Lifesciences, Irvine, CA, USA). Other percutaneous devices, whose utility is still limited, are the Carillon Mitral Contour System™ (Cardiac Dimensions, Kirkland, WA, USA), which performs indirect annuloplasty, the Cardioband Mitral System™ (Edwards Lifesciences), which performs direct annuloplasty and the Mitralign™ (Tewksbury, MA, USA), which attempts to mimic surgical suture annuloplasty. The ESC/EACTS guideline recommend TEER with the MitraClip™ for SMR patients who remain symptomatic despite guideline-directed medical therapy (GDMT).[10]

The MitraClip system

The transcatheter MitraClip procedure is based on the Alfieri edge-to-edge surgical technique and is intended for repairing MR through fixed approximation of leaflet tissue and creation of a double mitral orifice using a percutaneous venous approach and transseptal crossing. The MitraClip System allows for real-time clip positioning and repositioning under transoesophageal guidance to optimize MR reduction. The first-generation MitraClip underwent several device iterations (*Figure 1*) that further expanded anatomical indications and enhanced procedural success, MR reduction, and likely result durability, including some form of annuloplasty effect. The MitraClip System received CE mark in 2008 and US Food and Drug Administration approval for PMR in 2013 and for SMR in 2019. The device has over 16 years of clinical experience with >200 000 patients treated in more than 78 countries.

The COAPT trial

The multicentre, randomized, parallel-controlled, open-label COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation trial) enrolled 614 patients between 27 December 2012 and 23 June 2017 at 78 centres in the USA and Canada.[11] Patients with Grade 3+/Grade 4+ SMR, confirmed by an independent echocardiographic laboratory, symptomatic despite maximal GDMT were randomized (1:1) to undergo MitraClip + GDMT ($n = 302$) or GDMT alone ($n = 312$). Symptoms were still present despite 36% of patients underwent prior cardiac resynchronization therapy. Among inclusion criteria, patients also had to have ≥1 HHF within 12 months and/or brain natriuretic peptide (BNP) ≥ 300 pg/mL or N-terminal pro b-type natriuretic peptide (NT-proBNP) ≥ 1500 pg/mL. Mean age was 72 years and 43% of device-treated and 48% of control patients were females. At baseline, patients had non-ischaemic (39.1%) or ischaemic (60.9%) cardiomyopathy and were in NYHA Classes II–IV (about 60% of patients were in NYHA Class III/IV). At echocardiography, EROA (effective regurgitant orifice area) was 0.41 cm^2, LV end-systolic diameter 53 mm, LV end-diastolic diameter 62 mm and LV ejection fraction (LVEF) 31.3%, while tricuspid regurgitation ≥2 + was present in 16%. The mean STS PROM (Society of Thoracic Surgeons Predicted Risk of Mortality) score for surgical replacement was 8.1 and ≥8% in 42% of patients. The primary efficacy outcome was all HHF within 2 years, including recurrent events in patients with more than one event. Secondary efficacy outcomes included MR ≤2+, all-cause death, death or HHF, and all-cause hospitalizations at 1 and 2 years. Clinical and echocardiographic follow-up was performed at 30 days, 6 months, 1 year, 18 months, and 2, 3, 4, and 5 years. Drug use was similar between groups during follow-up, although inhibitors of the renin-angiotensin axis were used more frequently in the device group. The average daily dose of medications was similar and major drug changes were infrequent in both groups. Patients randomized to GDMT alone were not allowed to 'crossover' to the MitraClip arm prior to 24 months, when they were permitted to do so if they continued to meet the trial eligibility criteria. MitraClip + GDMT was significantly superior to GDMT alone across all endpoints at each time point regardless of patient age, sex, MR severity, LV function and volume, cardiomyopathy aetiology, and surgical risk. Indeed, TEER was superior to GDMT alone in reducing annualized rates of HHF at 2 years. Unexpectedly, mortality powered as a

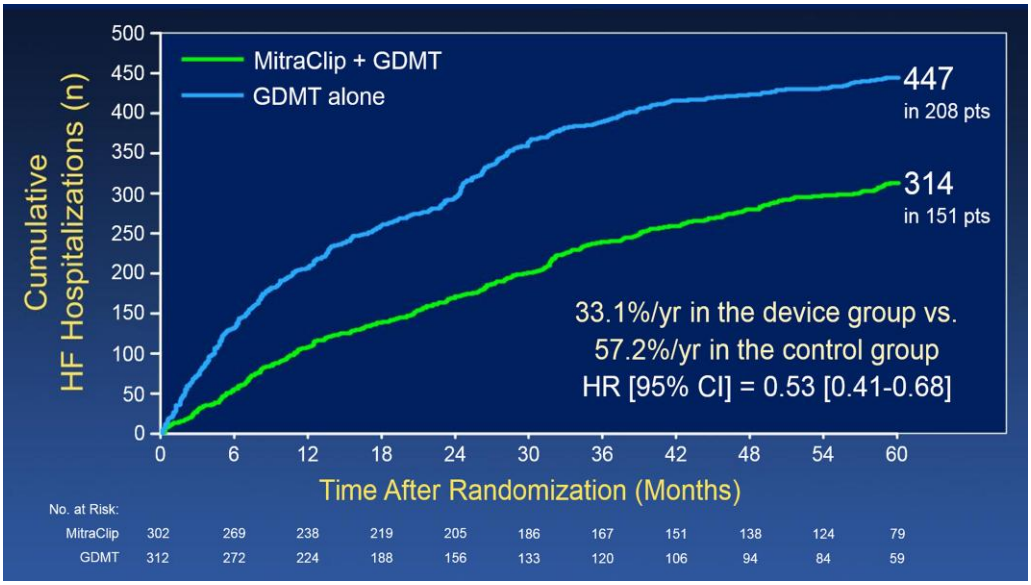

Figure 2 Primary endpoint of all heart failure hospitalization at 5-year follow-up. CI, confidence interval; GDMT, guideline-directed medical therapy; HF, heart failure; HR, hazard ratio.

pre-specified secondary endpoint was also significantly lower among MitraClip-treated patients. Reduced mortality predominantly emerged >1 year after treatment, a delayed effect consistent with long-term benefits from a durable decrease in the severity of LV volume overload. The primary safety endpoint, freedom from device-related complications (device detachment, embolization, endocarditis, and severe MV stenosis requiring surgery) was 96.6%. Only 4 (1.4%) complications occurred within 30 days and none afterwards. The strongly positive COAPT results at 24 months, with a number needed-to-treat to avoid hospitalization and mortality of 3.1 and 5.7 only, respectively, were reflected by the recent ESC/EACTS guidelines.[10] If SMR patients meet COAPT inclusion criteria, a IIa recommendation for TEER with the MitraClip was given, while a IIb recommendation was assigned to this treatment after careful evaluation of other therapeutic options if these criteria were not met. Among the 260 MitraClip-treated patients undergoing echocardiography at discharge, MR grade was ≤1+ in 214 (82.3%) and 2+ in 33 (12.7%). At 1 year, the proportion of patients with MR grade ≤2+ was significantly higher in the MitraClip + GDMT arm compared with the GDMT alone arm (94.8 vs. 46.8%; $P < 0.001$). A positive trend towards reverse LV remodelling was also observed at 1 year. LV end-diastolic volume (LVEDV) change from baseline was −3.7 mL in device-treated arm vs. +17.1 mL in control arm ($P = 0.004$). At 1 and 2 years, 72.2 and 59.2% of MitraClip patients were in NYHA Class I or II compared with 49.6 and 39.3% of control patients ($P < 0.001$), respectively. It is noteworthy that 67 (21.5%) GDMT only patients ultimately underwent TEER, 5 before 2 years and 62 afterwards, representing 44.9% of control patients who survived to 2 years. However, patients with 'delayed' TEER showed improved outcome in terms of subsequent death or HHF [hazard ratio (HR), 0.53], similarly to the initial MitarClip cohort.

COAPT 5-year results

Follow-up through 5 years was completed in 89.4% of device patients and 84.6% of control patients.[12] The composite outcome of death and HHF at 5 years was lower among MitraClip-treated patients compared with those receiving GDMT alone. These events occurred in 213 (73.6%) and 266 (91.5%) patients [HR, 0.53; 95% confidence interval (CI), 0.44–0.64], respectively, and were consistent across all subgroups. At least one HHF occurred in 151 (50%) device patients and 208 (66.7%) control patients, with a total number of 314 and 447 HHF within 5 years, respectively. In an analysis of time to first HHF out to 5 years, it occurred at a rate of 61% in the device arm compared with 83% in the medical therapy arm (HR, 0.49; 95% CI, 0.4–0.61), while the annualized HHF rate was 33.1% vs. 57.2% (HR, 0.53; 95% CI, 0.41–0.68; *Figure 2*), respectively. Of note, the rate of HHF from baseline to 3 years was 46.8% in the device arm and 76.4% in the medical therapy arm (HR, 0.46; 95% CI, 0.36–0.57), whereas from year 3 to year 5, HHF rate was 30.7% and 34.3%, respectively (HR, 0.85; 95% CI, 0.55–1.33), a shift that may be explained by the crossover trial design. Indeed, a multivariable analysis of patients who crossed over to TEER at 2 years showed a significant reduction of death and HHF compared with medical therapy alone (HR, 0.53; 95% CI, 0.36–0.78), improved NYHA class and durable repair of SMR throughout the 5-year follow-up. Although this suggests that it is never too late to treat patients with moderate-severe or severe SMR, the large proportion (42.7%) of control patients who had already died before they gained eligibility for treatment crossover further underlines the disease severity in this population. All-cause mortality through 5 years occurred in 162 (57.3%) patients in the device group and 189 (67.2%) in the control group (HR, 0.72; 95% CI, 0.58–0.89). On echocardiography at 5 years, MitraClip-treated patients

Table 1 Main differences between COAPT and MITRA-FR in echocardiographic profile and procedural results

Echocardiographic profile	COAPT ($n = 614$)	MITRA-FR ($n = 304$)
EROA, mm^2 (mean ± SD)	41 ± 15	31 ± 10
<30 mm^2	14% (80/591)	52% (157/301)
30–40 mm^2	46% (270/591)	32% (95/301)
>40 mm^2	41% (241/591)	16% (49/301)
LVEF, % (mean ± SD)	31 ± 9	33 ± 7
LVEDVi, mL/m^2 (mean ± SD)	101 ± 34	135 ± 35
Procedural results		
No clip or ≥3+ MR	5%/5%	9%/9%
≥1 Clip implanted	95.0% (287)	90.8% (138)
Procedural complications	8.5%	14.6%
12-month ≥3+ MR after MitraClip	5%	17%

EROA, effective regurgitant orifice area; MR, mitral regurgitation; LVEF, left ventricle ejection fraction; LVEDVi, indexed left ventricle end-diastolic volume; SD, standard deviation.

had less severe MR but slightly higher mean MV gradient and smaller MV orifice area. However, none of them required surgery or intervention for severe MV stenosis and the symptomatic status and NYHA class were improved in all. Still, despite the favourable risk-benefit profile of the MitraClip, adverse outcomes continued to accrue within 5 years in both groups such that 73.6 and 91.5% of device and control patients had either died or required HHF, while mortality was 57.3 and 67.2%, respectively. These event rates emphasize illness severity and the need for early identification of appropriate candidates for TEER, use of additional therapies to address the underlying LV dysfunction, which is the major risk, including GDMT optimization and close follow-up by trained HF specialists, and new strategies for HF prevention.

Which patient I prefer to treat after the 5-year COAPT data

The COAPT trial results were clearly different from those of the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation prospective clinical trial) that randomized more than 300 HF patients with severe SMR to TEER with the MitraClip along with medical therapy or medical treatment alone.[13] The 12-month primary clinical endpoint, a composite of death from any cause or unplanned HHF, was negative showing no significant difference between the intervention and control groups (54.6 vs. 51.3%, odds ratio, 1.16, 95% CI, 0.73–1.84, $P = 0.53$). Trying to understand why COAPT won while MITRA-FR failed may help in the precise selection of patients who could benefit from TEER. What is evident is that there were clear differences between the two trials regarding patient selection, medical treatment optimization, procedural success and most importantly MR severity and LV volume index parameters (*Table 1*). In the MITRA-FR trial, the majority of patients had more dilated LV, defined by indexed LVEDV (LVEDVi = 135 ± 35 mL/m^2), and average EROA of 30 mm^2 and EROA <30 mm^2 in 52% of them, which suggest moderate rather than severe MR, a condition that has been defined as proportionate MR. On the contrary, in the COAPT trial the majority of patients had disproportionate MR (average EROA 40 mm^2, EROA <30 mm^2 in 14% only), indicating truly severe MR, and lower LVEDVi (101 ± 34 mL/m^2). Of note, the only COAPT subgroup that did not benefit from MitraClip + GDMT comprised patients who had an EROA <30 mm^2 in the setting of a more dilated LV (LVEDVi >96 mL/m^2). This suggests that the MitraClip procedure added to medical therapy optimization does not seem to have significant beneficial effects in patients with moderate MR and too advanced LV disease (dilation and/or dysfunction). From a procedural point of view, more patients in COAPT had more than one clip implanted compared with MITRA-FR patients and showed a lower residual MR ≥3 + both acutely (5 vs. 9%) and at 12 months (5 vs. 17%). The aforementioned concept of disproportionate vs. proportionate MR suggests that patients with a COAPT-like profile (more MR and less remodelling) are more likely to respond to TEER, an intervention that directly reduces MR and only indirectly affects the LV.[14,15] A cut-off of 0.14 for the ratio of EROA to LVEDV has been proposed to separate proportionate from disproportionate MR. Overall, both trials help us in appropriately selecting SMR patients for MitraClip therapy who could benefit most from the intervention. They have to remain symptomatic despite optimal GDMT with substantial MR (EROA >30 mm^2) and LV dysfunction, but not too much dysfunction (LVEF ≥20%), a not very dilated LV, and preserved right ventricle function without severe pulmonary artery hypertension (*Table 2*). Thus, patient selection, medical management, and procedural timing are keys for clinical success. An important secondary implication of the COAPT trial is that waiting until the patients have been observed for several years is futile because a lot of them are going to die every single year. Thus, many of those deaths may be prevented and HHF reduced by identifying appropriate patients for MitraClip treatment despite optimal GDMT as soon as possible. Whether some subcategories of COAPT-ineligible patients, who represent a substantial proportion of those referred for potential TEER in

Table 2 **COAPT-like criteria to identify** secondary mitral regurgitation **patients who have a better prognosis after** transcatheter edge-to-edge repair **with the MitraClip**

Absence of severe LV impairment	Absence of RV impairment and/or severe PH	Absence of haemodynamic instability
LVEF ≥20%, and	TAPSE ≥15 mm or PSV ≥8 cm/s by tissue Doppler imaging, and	No advanced HF refractory to GDMT, and
LVESD ≤70 mm	Less than severe TR, and	No need for i.v. drugs or mechanical circulatory support
	PASP ≤70 mmHg	

All three criteria should be fulfilled to define a COAPT-like profile.
HF, heart failure; GDMT, guideline-directed medical therapy; LV, left ventricle; LVEF, left ventricle ejection fraction; LVESD, left ventricle end-systolic diameter; PASP, pulmonary artery systolic pressure; PH, pulmonary hypertension; RV, right ventricle; TAPSE, tricuspid annular plane systolic excursion.

clinical practice, would still benefit from MitraClip treatment has not yet been extensively assessed. However, recent data indicate that patients with only one vs. multiple COAPT exclusion criteria and no hemodynamic instability had lower adverse events at 2 years compared with drug-treated patients (55 vs. 69%).[16] Finally, it should be noted that the MitraClip used in COAPT and MITRA-FR trials was the first-generation device, while now already an iterated fourth generation is available, adding several features further enhancing procedural success, MR reduction and result durability.

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Data availability

No new data were generated or analysed in support of this research.

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