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MitraClip: How Do We Reconcile the Inconsistent Findings of MITRA-FR and COAPT?

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Abstract

Purpose of Review Secondary mitral regurgitation (MR) is a common valvular disorder in patients with left ventricular (LV) dysfunction and is associated with worse morbidity and mortality. New data on percutaneous mitral valve (MV) repair suggest that targeting the valve itself may improve outcomes. Our objective is to review two recent trials (MITRA-FR and COAPT) with regard to percutaneous MV repair. We will dive into their methodology and results and propose potential explanations for their divergent outcomes.

Recent Findings MITRA-FR and COAPT studied the MitraClip plus guideline-directed medical therapy (GDMT) versus GDMT alone in patients with secondary MR. COAPT found an overwhelming benefit in reduction in HF hospitalization and mortality whereas MITRA-FR found no difference between treatment groups. Patient selection, differences in procedural outcomes, and smaller LV dimensions may explain these diametrically opposed results.

Summary Secondary MR is a common valvular disorder with complex pathophysiology. There are certain patients who will not benefit from percutaneous MV repair. The results of MITRA-FR and COAPT suggest that percutaneous MV repair may benefit carefully selected individuals with secondary MR on maximum tolerated doses of GDMT.

Keywords Mitral regurgitation · Transcatheter repair · COAPT · MITRA-FR

Introduction

Mitral regurgitation (MR) is a common valvular disorder. Primary mitral regurgitation is due to a structural abnormality of the valve itself. In contrast, secondary mitral regurgitation is a consequence of left ventricular dysfunction, and the valve itself is typically structurally normal. Of these two types of mitral regurgitation, the most common is secondary, or functional, MR. [1] Secondary mitral regurgitation is associated with worse morbidity and mortality. At present, management of secondary mitral regurgitation is primarily focused on medical therapies targeted at an ailing left ventricle. Surgical and percutaneous repair of MR have mixed outcomes and are not currently routinely recommended. Before discussing newer percutaneous options for secondary MR, it would be helpful to briefly review the pathophysiology and natural history of this condition.

Secondary mitral regurgitation can be secondary to an ischemic or non-ischemic etiology. In either instance, the mechanism of mitral regurgitation is largely the same. With non-ischemic cardiomyopathy, left ventricular dilatation leads to apical and lateral displacement of the papillary muscles. The primary cause of mitral regurgitation is an increased effective regurgitant orifice (ERO) due to annular dilatation and loss of annular contraction [2]. The mitral valve leaflets exhibit normal motion (Carpentier type I).

Similar to non-ischemic cardiomyopathy, in ischemic cardiomyopathy either ventricular dilatation or localized scar leads to this same apical and lateral displacement. When the papillary muscles are displaced, there is a loss of the normal tethering forces of the mitral valve leaflets [3]. Left ventricular and atrial enlargement also leads to mitral annular dilatation, further preventing adequate coaptation of the mitral valve leaflets. Mitral regurgitation due to ischemic cardiomyopathy is frequently associated with inferior/posterior wall motion

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abnormalities and tethering of the posterior leaflet (Carpentier type IIIb) or global wall motion abnormalities from multivessel coronary artery disease leading to displacement of both papillary muscles resulting in a centrally directed mitral regurgitation jet [4].

Numerous studies have shown that secondary mitral regurgitation in both ischemic and nonischemic cardiomyopathy is associated with increased morbidity and mortality [5–8]. Prospective studies have shown that it is not only the presence of mitral regurgitation but also the degree of mitral regurgitation that correlates with worse outcomes. Patients with severe mitral regurgitation have higher all-cause and cardiac mortality and increased hospitalizations compared to those with moderate or less severe MR. [5–8] The presence of secondary mitral regurgitation has traditionally been thought to be a marker of a failing left ventricle. At the same time, it is unclear if the presence of mitral regurgitation is simply a sign of worsening systolic function or is contributing to the progressive impairment of left ventricular function. Several studies have shown that the presence of secondary mitral regurgitation and ejection fraction are independent determinants of congestive heart failure [6]. In other studies, secondary mitral regurgitation was associated with increased heart failure hospitalizations and all-cause mortality, independent of baseline characteristics, including left ventricular function [7, 8]. Whether mitral regurgitation is the cause or consequence of left ventricular dysfunction, it has implications for therapy. At present, guideline recommendations for secondary mitral regurgitation focus on medical and device therapies targeted at the failing left ventricle and do not target the mitral regurgitation itself [9, 10].

The mainstay of treatment for this condition thus far has been guideline-directed medical therapy, aimed at promoting reverse remodeling of the left ventricle. Neurohormonal blockade is central to the management of systolic heart failure. Inhibition of the renin-angiotensin system with angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) reduces morbidity and mortality in patients with reduced left ventricular systolic function [11–19]. Beta blockade has proven efficacy in the management of heart failure. Several studies have demonstrated significant morbidity and mortality benefit with beta-blocker use, with a NNT of 14–26 in the initial large beta-blocker studies [11–14]. Other important medications include spironolactone and, more recently, angiotensin receptor-neprilysin inhibitors (ARNIs) [15]. In appropriate patients with systolic heart failure, cardiac resynchronization therapy (CRT) improves quality of life and decreases heart failure hospitalizations and all-cause mortality [16–20].

Data are conflicting regarding the benefits of surgical mitral valve repair. This problem is further compounded by the heterogeneity of repair techniques used, whether repair was accompanied by coronary artery bypass grafting (CABG), and lack of randomized clinical trial data. At present, data and guidelines (class IIb) do not strongly support surgical mitral valve repair alone for functional MR. [21]

Transcatheter mitral valve repair approximates the techniques utilized in surgical mitral valve repair. Percutaneously implanted mitral valve annuloplasty rings and edge-to-edge repair using the MitraClip are two novel transcatheter options of treatment of secondary mitral regurgitation. Transcatheter repair of mitral regurgitation with the MitraClip is efficacious in individuals with primary mitral regurgitation [22]. In the EVEREST trial, percutaneous mitral valve repair with the MitraClip for primary mitral regurgitation was not as effective as surgery in reducing the degree of mitral regurgitation. However, it had a superior safety profile and similar clinical outcomes [22]. At 5 years of follow-up, there were durable results with percutaneous mitral valve repair though less so compared to surgical mitral valve repair (81 vs 97% respectively) [23]. Despite differences in durability, the majority of patients reported continued improvement in their heart failure symptoms with no significant difference between percutaneous and surgical repair groups (91 vs 97%, $p = 0.19$) [23].

Initial data on MitraClip use in secondary mitral regurgitation was largely from European registries. In the TRAnscathter Mitral Valve Interventions (TRAMI) registry, the majority of patients were in NYHA class III and IV and had an LVEF $\leq 50\%$. The majority of patients had improvement in their mitral regurgitation severity and improvement in their heart failure symptoms, with as high as 77% of patients in NYHA class I or II at 1-month follow-up [24, 25]. The ACCESS-EU registry showed that these findings persisted at a follow-up of 1 year [26]. Observational studies also showed an improvement in left ventricular dimensions and global longitudinal strain after MitraClip placement [27].

It is against this background that two landmark trials assessing the role of MitraClip in patients with secondary MR were conducted.

MITRA-FR

The MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial enrolled individuals with severe, secondary mitral regurgitation and depressed left ventricular systolic function to percutaneous mitral-valve repair in addition to guideline-directed medical therapy (GDMT) versus GDMT alone. The primary outcome was a composite of death from any cause or unplanned heart failure hospitalization at 12 months.

A total of 307 patients were randomized. Individuals enrolled in MITRA-FR were largely in New York Heart Association (NYHA) class II or III and had severely depressed LV systolic function and severely dilated left ventricles

(Table 1). Participants met criteria for severe mitral regurgitation by both effective regurgitant orifice area and regurgitant volume (Table 1). Enrolled individuals were high risk for surgery, as defined by the EuroSCORE II.

MITRA-FR found no difference between the two study arms in the composite primary outcome of death or heart failure hospitalization at 12 months (54.6% vs 51.3%, OR 1.16, 95% CI 0.73–1.84, $p = 0.53$) [28•].

COAPT

The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial enrolled individuals with moderate to severe or severe secondary mitral regurgitation, who remained symptomatic despite maximal tolerated doses of guideline-directed medical therapy, to percutaneous mitral valve repair plus GDMT versus GDMT alone [29•]. The primary endpoint was hospitalization for heart failure at 24-month follow-up.

The COAPT trial enrolled 607 participants. Most individuals were in NYHA class II or III. Trial participants all had severely depressed LV systolic function, severe mitral regurgitation by EROA, and dilated left ventricles (Table 1). All individuals were high surgical risk, with a mean STS score of 7.8 ± 5.5 in the device and 8.5 ± 6.2 in the control arm.

COAPT found a significantly lower rate of hospitalization for heart failure at 24 months in the device group compared to control (35.8 vs 67.9%, HR 0.53, 95% CI 0.40–0.70, $p < 0.001$). Additionally, the trial was positive for all prespecified secondary endpoints, including mitral regurgitation grade ≤ 2+, 6-minute walk distance, quality of life (assessed via the Kansas City Cardiomyopathy Questionnaire, KCCQ), left ventricular end diastolic volume, and all-cause mortality at 24 months (29.1% vs 46.1%, HR 0.62, 95% CI 0.46–0.82, $p < 0.001$).

Reconciling MITRA-FR and COAPT

The diametrically opposed results of these two landmark trials have resulted in significant debate. It is unlikely that there is a single reason for this. Reconciling these two trials requires a detailed understanding of differences in patient selection, procedural outcomes, left ventricular structure, and severity of MR.

On the face of it, MITRA-FR and COAPT enrolled similar patient populations. However, there were important differences. For instance, while all patients had significant

Table 1 Comparison of key characteristics of the MITRA-FR and COAPT trials

	MITRA-FR ($n = 307$)		COAPT ($n = 614$)	
	Device + GDMT	GDMT	Device + GDMT	GDMT
Trial enrollment period	2013–2017		2012–2017	
Age, years	70.1 ± 10.1	70.6 ± 9.9	71.7 ± 11.8	72.8 ± 10.5
Male sex, %	78.9	70.4	66.6	61.5
LV ejection fraction, %	33.3 ± 6.5	32.9 ± 6.7	31.3 ± 9.1	31.3 ± 9.6
LVEDVi, mL/m^2	136.2 ± 37.4	134.5 ± 33.1	Not reported	
LVEDV, mL	Not reported		194.4 ± 69.2	191.0 ± 72.9
LVESD, mm	Not reported		53 ± 9	53 ± 9
EROA, mm^2	31 ± 10	31 ± 11	41 ± 15	40 ± 15
RVol, mL	45 ± 13	45 ± 14	Not reported	
NT-proBNP, ng/L	3407 [1948–6790]*	3292 [1937–6343]*	5174.3 ± 6566.6	5943.9 ± 8437.6
ACEi/ARB, %	73.0	74.3	67.6	60.0
ARNI, %	10.0	12.1	4.3	2.9
Beta-blockers, %	88.2	90.8	91.1	89.7
MRAs, %	56.6	53.0	50.7	49.7
CRT-D, %	30.5	23.0	38.1	34.9
Event rates				
HF hospitalization, %	48.7	47.4	35.8	67.9
All-cause mortality (12 months), %	24.3	22.4	19.1	23.2
All-cause mortality (24 mos.), %	Not reported		29.1	46.1

Values are mean ± SD; those with denoted with asterisk represent median [IQR]

functional MR, the severity of MR was likely different between the two trials. Per respective protocols, MITRA-FR enrolled patients with severe MR and COAPT enrolled patients with moderate to severe or severe MR. It is important to note that the definition of "moderate" and "severe" MR has not been consistent between the European and American guidelines. MITRA-FR defined severe MR as an EROA > 20 mm^2 and/or regurgitant volume ≥ 30 mL, in accordance with the 2012 European guidelines [30]. COAPT enrolled patients with at least 3+ MR, using the 2003 American guidelines, corresponding to an EROA > 30 mm^2 and/or regurgitant volume ≥ 45 mL [31]. The mean EROA was lower in MITRA-FR compared with COAPT (31 vs 41 mm^2). This resulted in a much larger proportion of individuals enrolled in MITRA-FR with more moderate MR rather than severe MR (EROA ≤ 30 mm^2: 52% vs 14%) Therefore, though both trials were aimed at a similar patient population, MITRA-FR enrolled patients with less severe MR than COAPT.

Another important difference was LV size. MITRA-FR had no restrictions on LV size, while patients with LVESD > 7 cm were excluded from COAPT. Thus, the mean LVEDD at baseline in MITRA-FR was 6.9 cm, while it was 6.2 cm in COAPT. Indexed end-diastolic volumes were similarly larger in MITRA-FR vs COAPT: 135 vs 101 mL/m^2. Therefore, MITRA-FR likely had more patients with less/non-recoverable ventricles compared with COAPT.

Further, putting these two characteristics together, a post hoc COAPT analysis suggested that in those patients with LVEDVI > 96 mL/m^2 (median) and EROA ≤ 30 mm^2 (10.2% of total cohort), there was no benefit of MitraClip over GDMT for the primary endpoint (27.8% vs 33.1%, $p = 0.83$), while in the rest of the cohort the beneficial effect was concordant with the overall results.

Packer and Grayburn proposed a new paradigm based on these two characteristics: they posit that secondary MR may occur by two distinct mechanisms [32••]. In the first, progressive enlargement of the left ventricle, and subsequent dilatation of the mitral valve annulus, results in tethering of the mitral valve leaflets leading to mitral regurgitation. In this case, a linear relationship exists between LV end-diastolic volume and EROA—thus, this form of secondary MR has been designated "proportionate mitral regurgitation" [32••, 33]. In the case of "proportionate mitral regurgitation," the degree of mitral regurgitation is commensurate to the degree of left ventricular dilatation, and thus mitral valve annular dilatation. In other words, as the left ventricle dilates, the mitral valve annulus dilates leading to mitral regurgitation, and progressive dilatation leads to increasing mitral regurgitation severity in a direct, linear relationship. These individuals derive the most benefit from therapies targeted at reducing left ventricular volumes and reverse remodeling of the left ventricle. In the second mechanism, dyssynchronous LV contraction, from either electrical dyssynchrony or regional wall motion abnormalities, again leads to abnormal tethering of the papillary muscles and mal-coaptation of the mitral valve leaflets leading to mitral regurgitation. In this instance, LVEDV is lower than expected for the degree of MR severity—thus, these individuals have "disproportionate mitral regurgitation" [32••, 33]. In these individuals, while there is a degree of left ventricular dilatation, it is less than expected for the degree of mitral regurgitation present. In other words, there is no direct, linear relationship between degree of left ventricular dilatation and mitral regurgitation severity. Therapies aimed at the mitral valve itself are more beneficial in this cohort, and interventions aimed at reverse remodeling of the left ventricle volumes may be less efficacious [32••]. Using this conceptual framework may also help better understand the disparate results of the two trials [33]. Individuals enrolled in MITRA-FR had proportionate MR given their degree of LV dilatation; thus, percutaneous mitral valve repair is less likely to benefit this cohort. Conversely, COAPT participants had disproportionate MR. Therefore, it is perhaps unsurprising that a therapy aimed at the mitral valve leaflets showed significant benefit in this cohort.

Baseline GDMT use was similar between both trials, with slightly higher cardiac re-synchronization therapy use in COAPT (Table 1). While both specified that patients be on maximal doses of guideline-directed medical therapy, this was more strictly evaluated and enforced in COAPT. In COAPT, potential subjects were evaluated by a site Heart Team, consisting of a heart failure specialist, interventional cardiologist, and cardiothoracic surgeon, for eligibility and to ensure that the patient was on maximum tolerated doses of GDMT. After being deemed eligible by the Heart Team, they were then evaluated by a central Eligibility Committee to determine appropriateness for enrollment. At any point, randomization could be approved or denied (screen failure rate 58%) [34]. Individuals enrolled in MITRA-FR were on appropriate guideline-directed medical therapy, as determined by the local site, but did not undergo the same degree of scrutiny prior to enrollment compared to COAPT. There was also very little uptitration/change to GDMT in COAPT during the conduct of the trial (1.8–6%). Therefore, it appeared that the MitraClip was implanted on a more intensive medical therapy background in the COAPT trial. COAPT enrolled patients over 5 years at 78 sites (September 2012–June 2017) compared with MITRA-FR (3.5 years between December 2013–March 2017, 37 sites), suggesting that patients in COAPT may have been more selectively enrolled, while MITRA-FR enrolled more unselected functional mitral regurgitation (FMR) patients.

Successful MitraClip implantation was more frequent in COAPT versus MITRA-FR (98.0% vs 95.8%). Additionally, while more patients in COAPT received > 1 clip (61.8% vs 54.3%), fewer patients required three or more clips (8.2 vs 9.4%). Some have speculated that this in indicative of more

meticulous intra-procedural imaging to guide optimal clip placement and ensure adequate reduction of mitral regurgitation at the time of the procedure [35]. Indeed, at the time of discharge, more individuals in the COAPT device arm had MR grade 2+ or lower (95% vs 91.5%), a difference that persisted at 1-year follow-up (95% vs 83%) [33]. This also correlates with an improvement in LV volumes noted at 1 year in COAPT with MitraClip compared with GDMT (17.1 vs -3.7 mL, $p = 0.003$). Prospective, observational studies have shown frequent recurrence of mitral regurgitation after surgical mitral valve annuloplasty [36, 37]. Surgical data has failed to demonstrate a mortality benefit when using surgical repair for functional mitral regurgitation, likely due to this lack of durable repair [38]. Accordingly, less durable results in the MITRA-FR trial may explain the lack of benefit seen at 1 year.

In MITRA-FR, there was a 14.6% peri-procedural complication rate at 1-year follow-up, driven mostly by device implantation failure (4.2%) and hemorrhage or vascular complication (3.5%). It is possible that this complication rate is due in part to the relative inexperience of some enrolling sites, with a site needing only five prior MitraClip implants to qualify as a site for the study. In contrast, COAPT sites were required to have extensive prior experience with MitraClip implantation, and reported a 96.6% freedom from device-related complications at 1-year follow-up. Unfortunately, the lack of consensus in how peri-procedural complications are defined, and reported, between these trials and registry data precludes a direct comparison for specific adverse events.

Other considerations include a larger sample size of COAPT compared with MITRA-FR, and a longer duration of follow-up (2 vs 1 year).

What lessons do these disparate trial results have for clinical practice? First, it clearly demonstrates that FMR is not just a marker of functional outcomes, but likely has a causal role. Moreover, treating appropriate patients (COAPT-"like") with FMR can actually improve patient outcomes, independent of the use of GDMT. It also proves that the disease process in the left ventricle reigns. As demonstrated by COAPT and MITRA-FR, all FMR is not the same, and ultimately it is the degree of dilatation of the left ventricle and its proportionality to the EROA that dictates whether or not mitral valve intervention is likely to be beneficial. From a policy and societal standpoint, there are three critical issues. It highlights the role for a highly functioning and expanded multidisciplinary team in the care of these patients. For instance, such a team needs to have a detailed understanding of the mechanism and proportionality of MR in a given patient. A thorough evaluation and input from HF-trained/specialized physicians who can attest to adequate GDMT (and CRT when appropriate) will similarly be paramount. Ultimately, the team will have to decide: "is this a MITRA-FR-like patient or a COAPT-like patient?" Payers, industry, and legislators will also have to pay attention to this issue. Rational and thoughtful dispersion of technologies such as TAVR has been critical to their success, where real-world practice has been able to match the beneficial results noted in clinical trials [39, 40]. For MitraClip, the issue is much more complex, and an indiscriminate dispersion/utilization of MitraClip in all-comers with FMR is more likely to provide "MITRA-FR-like" results in real-world practice rather than COAPT-like, with implications for health-care cost, wastage, and even harm to certain patients. For this particular reason, once/if MitraClip use in FMR is approved for payment by CMS (currently, it is USFDA approved for FMR, but not reimbursable by CMS), the role of national registries such as the STS/ACC TVT registry will be critical to understanding real-world outcomes and impact. Finally, complications will be higher and procedural success lower among less established operators and sites, with clear implications for new and existing sites, as well for training pathways.

Conclusions

Secondary mitral regurgitation is common in patients with left ventricular systolic dysfunction, and its complexity has not been fully appreciated until now. The divergent results of the MITRA-FR and COAPT trial have taught us several important lessons, and it is more apparent now that not all secondary MR is the same. In fact, it is the heterogeneity of the secondary MR disease process that may explain the discordant results not only in MITRA-FR and COAPT but also prior surgical and percutaneous studies for functional MR. [32••] Future studies are needed on how best to identify appropriate patients for this procedure, and outline the optimal timing of mitral valve intervention (i.e., at what degree of left ventricular dilatation).

Compliance with Ethical Standards

Conflict of Interest Rina Mauricio and Dharam J. Kumbhani declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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