Why Did COAPT Win While MITRA-FR Failed? Defining the Appropriate Patient Population for MitraClip

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Abstract

In 2018, the world of functional mitral regurgitation changed with the presentation of two trials – Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR) and Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT). The trials, which seemed to point in two different directions, raised significant questions for the field. This article looks at the differences in effective regurgitant area, guideline-directed medical therapy, patient selection, technical clues and other reasons why the trials had similar aims but very different findings.

Keywords

Mitral regurgitation, functional mitral regurgitation, secondary mitral regurgitation, heart failure, congestive heart failure, COAPT, MITRA-FR, effective orifice area, optimal medical therapy

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In patients with heart failure and reduced left ventricular ejection fraction (LVEF), secondary (functional) mitral regurgitation, in which the mitral valve leaflets and chordae are essentially normal, is the result of functional and structural alterations of the left ventricle (LV). Severe secondary mitral regurgitation (MR) is a predictor of poor clinical outcomes in this patient population due to more hospitalisations for heart failure (HF), poor quality of life and shortened survival times.[1–4] While guideline-directed medical therapy (GDMT) may have an impact on LV function, symptomatology and functional MR severity, there has been no data to show that surgical treatment of secondary MR is associated with lower incidence of death or hospitalisation.[5]

Percutaneous transcatheter treatment can be used to reduce MR where the anterior and posterior mitral valve leaflets are approximated with the MitraClip device (Abbott Vascular). In the Endovascular Valve Edge-to-Edge Repair Study II (EVEREST II) trial, Feldman et al. showed that although the MitraClip was safer than surgical mitral valve repair, the transcatheter option was not as effective in reducing MR severity among the study group, who mostly had primary MR.[6] Prospective clinical trials with hard clinical outcomes on the beneficial effect on secondary MR of enhancing GDMT with percutaneous transcatheter mitral valve repair had not been shown until now.[7]

At the 2018 Transcatheter Cardiovascular Therapies 30th Scientific Session Conference, Gregg Stone presented the long-awaited and ground-breaking results of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) randomised prospective clinical trial. COAPT showed that in more than 600 patients with heart failure and severe functional MR, transcatheter percutaneous mitral valve repair using the MitraClip device in conjunction with GDMT when compared with GDMT alone, not only significantly reduced the primary endpoint of heart failure rehospitalisations by 47%, but also mortality at two years by 38%.[7] Additionally, all 10 secondary endpoints met statistical significance in favour of the MitraClip with GDMT over GDMT alone. The reaction of the audience when the primary endpoint results slide was displayed on the screen was enormous, with an audible gasp followed by cheering and clapping. It had been difficult to imagine the clinical outcome of the COAPT trial due to slow enrolment, a lengthy time to complete, but mostly due to ominous predictions in light of the outcomes from the Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR) clinical trial.

The COAPT trial results were clearly different from the negative results of the MITRA-FR randomised prospective clinical trial presented by Jean François Obadia a month earlier at the 2018 European Society of Cardiology Congress.[8] In the MITRA-FR trial, more than 300 HF patients with severe MR were randomised to be treated with medical treatment alone or with percutaneous transcatheter mitral valve repair (MitraClip) along with medical therapy. All the participants were evaluated for a

primary clinical endpoint at 12 months of a composite of death from any cause or unplanned hospitalisation for HF.[8] Dr Obadia discussed the MITRA-FR trial's negative primary outcome results at 12 months, showing no significant difference in the rate of death or unplanned HF hospitalisations in the intervention and control groups (54.6% versus 51.3%, OR 1.16, 95% CI [0.73 to 1.84], p=0.53).[8]

The big question was why there was such a significant difference in the results between the MITRA-FR trial and the COAPT trial. Why was the COAPT trial successful where the MITRA-FR trial seems to have failed? There has been much debate about this issue in the cardiovascular world since the two trials were presented.

A Tale of Two Trials

Recruitment

What is evident is that there were clear differences between the two trials regarding patient selection, medical treatment optimisation, the severity parameters of MR and the setting of the LV volume index parameters. Some of this is due to differences between European and American guidelines. In addition, these differences were only found in a post-hoc analysis and are therefore subject to inherent limitations.

Nevertheless, in the MITRA-FR trial, the majority of patients had an average effective regurgitant orifice area (EROA) of 30 mm^2 which suggests moderate MR rather than severe, whereas in the COAPT trial, the majority of patients had an average EROA of 40 mm^2 which is truly severe MR. The only COAPT subgroup that did not benefit from MitraClip with GDMT was the patients who had an EROA <30 mm^2 in setting of a dilated LV (>96 ml/m^2). A significant number of patients (52%) with moderate MR (EROA <30 mm^2) were enrolled in the MITRA-FR trial, whereas only 14% of patients with this parameter were enrolled in the COAPT trial. This suggests that the MitraClip procedure added to medical therapy optimisation does not seem to have a significant beneficial effect on patients with moderate MR and dilated LV cardiomyopathy.

The patient recruitment process was more selective in the COAPT trial compared with the MITRA-FR trial, as indicated by the slow enrolment and length of time of the trial. One review article describes the difference as proportionate mitral regurgitation (MITRA-FR) and disproportionate mitral regurgitation (COAPT) to the degree of LV dilatation, with the COAPT trial enrolling patients with EROA about 30% higher and LV volumes about 30% smaller than the MITRA-FR trial.[9]

Medical Therapy and Optimisation

The 'guideline-directed' medical therapy used in the two trials differed significantly. The COAPT patients were under more strict evaluation with HF specialists overseeing the maximal doses tolerated for all medications, before and at the time of the MitraClip intervention. Several critiques of the COAPT trial have pointed out that even at the highest enrolment centre, Cedars-Sinai Medical Center in Los Angeles, with 46 enrolled patients total, that would average about one study patient per month receiving the MitraClip intervention. Only about 1–12% of patients had medication changes during the trial.

The highly stringent patient selectivity in the COAPT trial is the obvious difference between the two trials. The MITRA-FR trial was designed to be more true to life in terms of medical therapy and optimisation. The rates of drug use and medication titration throughout the MITRA-FR trial course were not tracked, and although these were guideline directed, they may not have been guideline optimised.

Yet the story does not end here – the percentage of drugs used in MITRA-FR was higher than COAPT even if dose optimisation was not checked by a selection committee. In addition, although there were a significant number of HF hospitalisations in the COAPT trial, the doses of medications were not changed significantly.

Size of Study and Study Design

The number of patients and follow-up were different between the two trials. The MITRA-FR trial enrolled about 300 patients, 150 in each arm; and the COAPT trial enrolled about 600, 300 in each arm. Perhaps an effect size may not have been seen in MITRA-FR that was seen in COAPT. Although hospitalisations differed early on between the two patient groups in the COAPT trial (partly due to a more rigorous medical arm), mortality did not differentiate until the second year. The follow-up period for MITRA-FR was only 1 year. Perhaps the positive nature of COAPT could be partially down to better design, probably due to more accessible funding.

Technical Success and Procedural Safety

Technical success and procedural safety may be different between the two trials. Residual MR class ≥3+ was higher post-clip for MITRA-FR compared with COAPT, both acutely (9% versus 5%) and at 12 months (17% versus 5%); procedural complications – although low and improving with current experience – were higher in MITRA-FR than in COAPT (14.6% versus 8.5%), and residual MR class ≥3+ was higher post-clip for MITRA-FR compared with COAPT, both acutely (9% versus 5%) and at 12 months (17% versus 5%).[7–8]

It is important to note that there was no common core lab evaluation of both trials. More patients in COAPT had more than one clip implanted compared with patients in the MITRA-FR trial. This raises questions over the use of 3D imaging during the procedure. 3D imaging is better than 2D imaging at identifying location of jets, perpendicularity, post-clip leak and mitral valve area. For procedural complications, there was about a twofold higher rate of device implant failure, cardiogenic shock, stroke and tamponade in MITRA-FR compared with COAPT, which may be due to different patient populations or patients who are at different stages of the disease. These are significant issues that are likely to be associated with negative primary outcomes.

Selecting Patients Who Will Benefit From MitraClip

Overall, how did the COAPT and MITRA-FR trials help in selecting the most appropriate patient with secondary (functional) MR to receive MitraClip therapy? The COAPT trial shows us that patients have to be symptomatic, have substantial MR and have LV dysfunction (but not too much dysfunction) and be on the highest tolerated doses of HF medications. Patient selection, medical management and procedural timing is key for success. This means that HF physicians will need to be involved (and incentivised) members of the evaluation and management team for mitral valve disease. Periprocedural imaging and procedural technique needs to be optimised and patients with only one clip should be evaluated closely. Patients with at least a 2-year expected lifespan after the procedure may do better from a mortality standpoint, which should be part of the initial screening.

The Future

There are still some unanswered questions from these trials. Some of these are based on COAPT subsets to better identify patients who will benefit from the intervention, such as effects based on patients with or without frailty, medical changes during the trial period, postprocedural high gradient and more.

How do we improve the medical and procedural treatment for those in MITRA-FR who are outside the range of COAPT? Will other therapies,such as rings and valve replacement, provide better outcomes, and for which patients? These are questions worthy of consideration and we will undoubtedly see more data in the coming years. At this time, both trials provide guidance we may use to get maximal results in practice, and create opportunities for other mitral valve therapies to also work in the COAPT and MITRA-FR patient spaces. It is important to remember that MR and HF are a vast frontier for us to explore and these two trials are just the beginning. We have neither won nor lost at this time – we are still gathering information about this important disease process, and our patients will look to us for answers in the years ahead. ■

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