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Correspondence

Futile MITRA-FR and a positive COAPT trial: Where does the evidence leave the clinicians?

Garima Arora [a], Nirav Patel [a], Pankaj Arora [a,b,*]

[a] Division of Cardiovascular Disease, University of Alabama at Birmingham, Birmingham, AL, USA
[b] Section of Cardiology, Birmingham Veterans Affairs Medical Center, Birmingham, AL, USA

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Secondary mitral regurgitation (MR) in dilated ventricles is a cardiovascular disease condition that has an enormous population burden and significantly contributes to the high mortality in heart failure with reduced ejection fraction (HFrEF) patients. Moreover, cardiovascular physicians and scientists have been struggling to find a therapeutic answer for secondary MR in HFrEF patients over the last few decades. Previous randomized controlled trials (RCTs) looking for an annular surgical solution (e.g., an undersized annuloplasty ring) to a ventricular problem (i.e., left ventricular dysfunction causing annular dilatation and secondary MR) have been largely negative [1]. Recently, the results of the COAPT trial [2] comparing a percutaneous mitral-valve repair therapy (using a MitraClip device) plus medical therapy to medical therapy alone in carefully selected HFrEF patients with more than moderate secondary MR were published. The absolute risk reduction in all-cause mortality in patients receiving the MitraClip in the COAPT trial [2] was 17% which translated to a number needed to treat (NNT) of 6 to prevent one death over two years, similar NNT was observed with the use of renin-angiotensin inhibitors in HFrEF. Not only that, the results showed similarly impressive reductions in all-cause mortality across the various pre-specified subgroup analyses in the COAPT trial [2]. Success and effect size of this magnitude does not happen frequently, and this certainly should be considered as welcoming news to the clinicians and patients alike. But a key question to consider is that if an effect size like this is biologically plausible? Especially when our percutaneous approach of treatment using the MitraClip device is fundamentally similar to what our surgical colleagues have done with an annuloplasty ring over the last few decades. In both the percutaneous (MitraClip) and the surgical approach, we are not directly treating the sick ventricles, which is traditionally thought to be the cause of the problem. In addition, these unanticipated COAPT trial [2] results were presented on the background of a similar RCT (MITRA-FR) [3] in which the MitraClip therapy failed to show any survival benefit over medical therapy during the one year follow up period. Treatment for secondary MR has now become a classic example in science where extreme caution should be exercised, and successful results from the COAPT trial [2] need to be replicated prior to widespread adoption of a procedure such as MitraClip in routine clinical practice.

Ever since the publication of the COAPT trial [2] results, it has been widely speculated among the thought leaders in the cardiology community that the neutral results of MITRA-FR trial [3] were because of the fact that the ventricles were too sick for any intervention to work. On the other hand, the COAPT trial [2] has been positive because patients were not that sick and were taken for their MitraClip implantation procedure at just the "right time" during the course of the disease. Comparing the control arms of the COAPT [2] and MITRA-FR trials [3] at one-year time point reveals that rates of all-cause mortality were similar (23% and 22% respectively), which argues against the patient population enrolled in the two RCTs being drastically different. Were the ventricles on which the MitraClip procedures were performed different among the two trials? The mean ejection fraction in the MitraClip implantation arm was quite similar (31.3% in COAPT [2] vs. 33.3% in MITRA-FR [3]). Notably, the indexed left-ventricular end-diastolic volume was higher in MITRA-FR [3] (135 ± 37 ml/m^2) and lower in COAPT [2] (101 ± 34 ml/m^2) trial. However, both these indexed left-ventricular volumes would be considered as severely dilated ventricles as per the echocardiographic guidelines. More importantly, subgroup analyses in COAPT trial [2] in patients with left ventricular volumes similar to MITRA-FR [3] showed similar reductions and therefore may not explain the discordant results. Lastly, N-terminal pro-B-type natriuretic peptide levels (a well-accepted surrogate marker of left ventricular stress) were higher at baseline in the COAPT trial [2] population which makes the claim of optimization of goal-directed heart failure medications prior to recruitment in the trial as a possible cause of astounding success less credible.

If none of the above factors were responsible, what can one really attribute the success of COAPT trial [2]? Rigorously screening patients in a non-blinded trial undoubtedly increase the chances of selection bias but may not explain the dramatic effect sizes noted in the COAPT trial [2]. Sponsor's role and participation in site selection, management,

* Corresponding author at: Division of Cardiovascular Disease, 1670 University Blvd., Volker Hall B140, University of Alabama at Birmingham, Birmingham, AL 35294-0019, USA.
E-mail address: parora@uabmc.edu (P. Arora).

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and data analysis as was the case with the COAPT trial [2] and not with the MITRA-FR trial [3] will also be examined, but the extent to which it can impact the NNT is more of an ethical or a philosophical question. More than 30% of patients in both arms of the COAPT trial [2] were not included in the denominator of the 24-month visit, likely due to ongoing follow-up which is not ideal and makes the NNT less stable. This makes the long-term (5 years) follow up results of the COAPT trial [2] even more valuable. How about the significant baseline differences in the functional class of heart failure (6% class IV in MitraClip arm vs. 11% class IV in the control arm) and significant differences in use of renin-angiotensin receptor inhibitors (71.5% MitraClip arm vs. 62.8% control arm) in the COAPT trial [2] participants? The COAPT [2] investigators reported that the primary results remained robust even after adjusting for these baseline differences, which is reassuring.

As we strive to improve our ability to provide cardiovascular care for our heart failure patients, we should also fortify our capacity to implement restraints. In a recent article in lay press [4], MitraClip implantation and COAPT trial [2] success have already been claimed as a "huge advance" for treatment of severe heart failure. As clinicians, we should wait for the results of COAPT trial [2] to be replicated in additional RCTs such as RESHAPE-HF2 [5], and clinical wisdom should prevail for decision making. Certainly, the COAPT trial [2] results should not be extrapolated to a broader secondary MR patient population with HFrEF. In a shared decision-making model, only carefully selected patients using a heart-team approach should undergo the MitraClip procedure for treatment of secondary MR. Not to mention in a procedure such as MitraClip, operator experience is of paramount importance, and one would wonder if the procedure should only be limited to high-volume centers, at least that's what the failure of MITRA-FR trial [3] (where multiple small centers recruited the trial participants) has definitively taught us. One probable approach for the cardiovascular clinicians is to make sure that the valve team at their institutions can verify eligibility based on an exhaustive list of exclusion criteria outlined by the COAPT [2] investigators. This will make the population in which the MitraClip can or should be performed appropriately largely restrictive. Whether the discordant results of the MITRA-FR [3] and COPAT trials [2] are really a case of intervening early or late in the course of the disease remains to be established. Until then we should reserve our emphatic celebrations for secondary MR HFrEF patients that meet the COAPT trial criteria!

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