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The trials and tribulations of MitraClip: we got there in the end

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Take Home Messages

- The topic is important because Mitraclip has the potential to revolutionise our management of a challenging condition with a poor prognosis
- This editorial provides a critique of recent Mitraclip trials, with an attempt to rationalise conflicting results
- Going forward, the astonishing results of the COAPT trial may launch Mitraclip into the mainstream
- My opinion is that we will look back at COAPT as a seminal moment in structural intervention which proves as defining for Mitraclip as the PARTNER trials were for TAVI.

'Blockbuster', 'breathtaking' and 'spectacular' are the sorts of adjectives usually employed to describe the latest big-screen Hollywood hit. However, in this case they are taken from quotes describing the results from the recently published COAPT trial. As physicians, we are used to seeing small, incremental, and sometime obscure gains from new drugs and interventions in supposedly landmark trials; being charitable, we tend to cite the law of diminishing returns as the explanation. Therefore, when a trial comes along with genuinely marked improvements in meaningful, hard endpoints, it gets lauded as a seminal moment and significant changes in practice tend to follow. There is little doubt that we will look back upon COAPT, a study comparing MitraClip to medical therapy in the treatment of severe, secondary mitral regurgitation (MR), as a turning point within the field of structural interventional cardiology. However, in amongst all of the adulation it is easy to forget that MitraClip has had a somewhat tumultuous time in the preceding years. Indeed, it wasn't so long ago that the outlook for this nascent technology was relatively bleak. Here we have a brief overview of the technique itself, as well as the other MitraClip trials that have taken place.

MitraClip

MR is the second most frequent indication for valvular surgery in Europe, and is a condition whose prevalence increases with age [1]. It is generally classified as either

primary, where there exists a morphological abnormality of one or more components of the mitral valve (MV) apparatus, or secondary, where an anatomically normal MV fails to coapt adequately due to left ventricular (LV) remodelling, papillary muscle displacement and annular dilatation [2]. Both forms engender a poor prognosis, and are amenable to operative correction. However, up to 50% of eligible patients with severe MR, irrespective of aetiology, are never referred for surgery. Reasons for this usually include a combination of advanced age, multiple co-morbidities and LV systolic dysfunction conferring prohibitively high operative risk [3]. As such, there is a significant need for minimally invasive techniques to reduce MR severity for patients deemed unsuitable for surgery.

The principle underpinning MitraClip is an elegant surgical technique called the Alfieri stitch, where the central part of the anterior and posterior MV leaflets (A2 and P2) are sutured together, thus converting one large orifice into two smaller ones [4]. With the MitraClip, rather than being sutured together, the two leaflets are grasped and clipped into place. The procedure is undertaken via the femoral venous route, with trans-septal puncture allowing passage into the left atrium (LA) [2]. The clip is delivered by a steerable guide catheter, and advanced through the MV under guidance of transoesophageal echocardiography (TOE). It is then withdrawn back towards the LA until the MV leaflets have been grasped. The process of grasping the leaflets can be repeated if the initial positioning is unsatisfactory. Once suitably positioned, the clip is released and the result checked using TOE. If significant MR persists due to inadequate coaption of leaflets, multiple clips can be deployed to further reduce the regurgitant orifice.

MitraClip gained CE mark approval in 2008 and has been used to treat both primary and secondary MR since then. Unsurprisingly there has been a great deal of interest surrounding its use and development, and so it has been studied in a number of observational registries and randomised controlled trials (RCTs).

The early trials (and tribulations)

The EVEREST study was a multi-centre registry designed to assess the feasibility, efficacy and safety of the MitraClip device. A total of 107 patients with severe primary or secondary MR were included (79% and 21% respectively), and the study demonstrated use of the device to be safe and effective, with 66% of treated patients remaining free from death, ≥moderate MR or MV surgery at 12 months [5]. The follow-up to this promising result was EVEREST 2, the first MitraClip RCT. In this trial, 258 patients with severe primary or secondary MR were randomised in a 2:1 fashion to either MitraClip or conventional MV surgery (repair or replacement). The results were mixed, with use of MitraClip shown to be less effective than surgery at reducing MR, but associated with superior safety and similar improvements in clinical outcomes [6].

Despite the decidedly equivocal trial data up until this point, use of the MitraClip device in Europe and the USA became more widespread. Whether or not this was justified is arguable, but the upshot has been increasing amounts of registry data. Results from ACCESS-EU, a European all-comers multi-centre registry with over 500 patients treated with MitraClip for severe primary or secondary MR, were encouraging. The population consisted mainly of elderly, high-risk patients and significant improvements were noted in MR severity and functional class, coupled with low rates of peri-procedural adverse events and mortality [7].

Analysis of the results from EVEREST 2, ACCESS-EU and other registry-based studies highlighted an interesting trend; the best results were seen following use of MitraClip in patients with secondary MR. This contrasts with the evidence for MV surgery, where best outcomes are reserved for those with primary MR. Indeed, the management of secondary MR has long been an area of contention, with little evidence for benefit with any treatment or intervention. In this context, the observation that use of MitraClip improves outcomes in this cohort was unexpected but welcome. On this backdrop came the MITRA-FR trial, a RCT comparing MitraClip and medical therapy to medical therapy alone in patients with severe, secondary MR. Much was expected, but the results which were published earlier this year proved disappointing. Following 12 months follow-up of 304 patients, no differences were noted in rate of death or

unplanned hospitalization for heart failure [8]. Given the initial promise, this trial represented a significant fall from grace for MitraClip. Indeed, it led some to question whether this was the end of the road for the device [9]. Fortunately for Interventional Cardiologists, an emphatic comeback was just around the corner….

COAPT: the blockbuster trial

With the negative findings of the recent MITRA-FR trial still fresh in our minds, the results of COAPT seemed to take on greater significance. The trial was ostensibly similar to MITRA-FR, once again comparing MitraClip and medical therapy to medical therapy alone in patients with severe, secondary MR. However, the contrast in the results of the trials was staggering. Where MITRA-FR showed no benefit with use of MitraClip, COAPT demonstrated significant improvements in rate of hospitalisation for heart failure and all-cause mortality after 24 months' follow-up [10]. It was the magnitude of the improvement that was perhaps most surprising, with a number needed to treat (NNT) of only 3.1 to a prevent hospitalisation for heart failure and 5.9 to prevent a death. To put that in perspective, the NNT to prevent one death in the PARADIGM-HF trial, arguably the last landmark study in Cardiology, was 36…. [11].

The big question following COAPT is why the findings are so different to those from MITRA-FR. When Dr Gregg Stone, lead investigator for the trial, was questioned about this at TCT this year, he pointed to the fact that COAPT was a bigger study (614 patients) and that the operators had greater experience with the MitraClip device. It is also worth noting that the patient populations were subtly different, with those enrolled in COAPT generally having more severe MR and less advanced heart failure; the average effective regurgitant orifice area (EROA) for patients in MITRA-FR was 31mm^2 compared to 41mm^2 in COAPT, whilst the average end diastolic LV volume in MITRA-FR was 135ml/m^2 versus 101ml/m^2 in COAPT. Finally, whilst both trials used optimal medical therapy as the comparator, the means by which this was delivered differed; patients in the MITRA-FR trial had their heart failure medication uptitrated following randomisation, whereas those in COAPT had to be optimally managed prior to enrolment. In fact, each patients' medication records for the 2-years prior to the trial were extensively reviewed, and any patient who was not established on the maximally

tolerated doses of all guideline-directed drugs was rejected. This incredibly stringent enrolment process is admirable, and certainly led to a very well-run study, but does make you wonder whether the more pragmatic approach used in MITRA-FR provides a more representative indicator of the real-world outcomes that we should expect based upon the way MitraClip is currently being used.

Conclusion

Ultimately, rather than being contradictory, I suspect the results from the MITRA-FR and COAPT trials are in fact complimentary. They highlight the importance of careful case selection; if used in patients with sub-optimally managed heart failure and MR which is closer to moderate than it is severe, MitraClip probably has little to add. However, if used in a specific cohort of patients with genuinely severe secondary MR, following optimised guideline-directed medical therapy, MitraClip has the potential to revolutionise our management of the disease.

Whether the results from COAPT persuade NICE to approve the use of MitraClip on the NHS remains to be seen. It is likely that a decision will be made following the outcome of the RESHAPE HF 2 trial, the final instalment of the MitraClip-in-secondary-MR RCT trilogy, which is nearing completion [12]. Needless to say, the results are keenly awaited….

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