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Letters to the Editor

Reflections on percutaneous therapies for secondary mitral regurgitation

Great enthusiasm greeted the dramatic findings of the COAPT trial [1], which evaluated the role of MitraClip in the treatment of patients with symptomatic congestive heart failure and refractory secondary mitral regurgitation [2]. The results were certainly impressive, with marked reductions in mortality, heart failure hospitalizations, and patients' heart failure symptoms. The enthusiasm was so great that it was suggested that MitraClip for treatment of secondary mitral regurgitation perhaps should be considered to be given a Class I indication by guideline writing committees, in spite of being only a single trial. This would be unusual since the standard requirement for Class A level of significance for any recommendation is that the findings were found to be replicated in more than one randomized trial. The argument was made that the COAPT trial was so large, and the results so impressive, that no other trial could be done to replicate these observations. Perhaps that is justified, but it is reasonable at this time to carefully consider the available data, especially since there may be implications on other therapies which may show benefits, but which have not yet been tested with pivotal sized trials. These therapies might not only be considered competitive, but complementary to MitraClip, as they may not only overlap, but also treat patients not eligible for COAPT, or even work synergistically with MitraClip.

Anyone looking at the COAPT trial may consider that the pronounced mortality benefit seen in that trial creates an ethical dilemma with any research option which denies a suitable patient with this life-extending therapy. However, there may be a few reasons to step back for a moment and question if this is the only perspective. For one, even though the results of COAPT were profound and dramatic, it followed shortly after a trial which was impressively negative, using the same device. In the MITRA FR study, no mortality or heart failure hospitalization benefit was seen, using the same therapy, in a somewhat similar population of patients as studied in COAPT [3]. With the release of these trials, there have been several theories as to why there were such dramatic differences in findings of the two studies. These reasons have noted differences in the level of mitral regurgitation, in the severity of the cardiomyopathic conditions, in medical management (both at entry, and throughout the study) and in the skill set of the MitraClip operators [4]. Any, or all of these may have played a role. Yet the lack of benefit does create questions which may be posed by guideline authors, heart failure specialists, regulatory bodies, etc. Does a negative trial such as MITRA FR sufficiently negate the overwhelmingly positive findings of COAPT to create enough equipoise to justify further studies? Are the findings of COAPT results going to be limited to sites with high volumes of experience, which may mean that access to this therapy might be limited?

A concerning component of COAPT was the aggressive medical therapy required for enrollment in the study [5]. This degree of medical therapy appeared to extend beyond what is usual standard of care, in that patients were required to be treated to a maximal level, which appears to have meant until side effects such as hypotension. Because these non-enrolled patients were not tracked, it is not possible to know what percentages of screened patients were benefitted versus harmed by such aggressive medical therapy. Did the unusually aggressive medical management which was done prior to enrollment in COAPT contribute to the overwhelmingly positive results? Were there negative implications in patients who were aggressively treated but not randomized into COAPT – in other words could there have been harm from too aggressive medical therapy? The reasons for this level of medical management are understandable from a trialist standpoint. This created a level playing field in this non-blinded study, minimizing the potential that patients in one group or the other may have been treated more aggressively – since both groups were maximally treated prior to enrollment. But this raises a question as to whether MitraClip should only be used in patients treated to this level (which may cause harm in some patients due to medication related hypotension, renal insufficiency, etc.). Perhaps percutaneous treatment of secondary MR might allow for lowering of medication doses, minimizing medication related side effects. This was not addressed in COAPT.

The patients benefitting from MitraClip were truly refractory, and the one subgroup in COAPT who may not have benefitted were the ones with lesser degrees of MR [4], however they were also symptomatic at the time of enrollment. Arguments have therefore been made after COAPT that only patients with more severe degrees of secondary mitral regurgitation should be treated. However, these observations should be considered hypothesis generating, not definitive. In COAPT, even though the MitraClip patients did remarkably well compared to medical therapy, there was still high mortality, heart failure hospitalization rates and symptoms [2]. In addition, only a minority of patients screened for COAPT were enrolled – and only a small number of patients treated with MitraClip in COAPT sites were enrolled in COAPT, raising additional questions as to the widespread applicability of the findings. So, the story should not be closed.

In the same session at TCT as the COAPT presentation, a smaller study using a different device, in patients with less severe degrees of secondary mitral regurgitation was presented [6]. This blinded, sham controlled study demonstrated a significant reduction in secondary mitral regurgitation at one year, with reduced left ventricular dimensions and trends towards benefits in the clinical endpoints of mortality and heart failure hospitalizations. Although not as dramatic as the larger, clinically-powered COAPT trial, the favorable results of this trial argue that it is reasonable to address patients with lesser degrees of secondary mitral regurgitation, and that it is reasonable to believe that other therapies for functional mitral regurgitation may play an important role and should not be discarded.

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This may include not only mitral valve repair strategies but mitral valve replacements as well. Perhaps there are therapies which can treat patients who were excluded from the COAPT trial, or which are effective earlier in the disease process, or which can be effective even when medical therapy is not pushed to the extreme. Or perhaps there are therapies which can complement the role of MitraClip, working synergistically - important since the event rate even in the MitraClip arm of COAPT remained high. There are still opportunities for improvement.

The COAPT trial demonstrated that there is a role for mechanical management of secondary mitral regurgitation – an issue for which there had been much controversy. This was a powerful leap forward for the field of structural heart disease, and for the large community of patients with symptomatic congestive heart failure and functional mitral regurgitation. But, whether MitraClip becomes a Class I indication for secondary mitral regurgitation or not, there is still work to do.

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