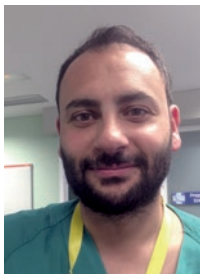

Debate: MitraClip. The interventional cardiologist perspective

A debate: MitraClip. Perspectiva del intervencionista

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Question: There is no doubt that the most significant advances made back in 2018 in interventional cardiology were the long-awaited results from clinical trials with MitraClip (Abbott Laboratories, Abbott Park, Illinois, USA): the MITRA-FR presented at the congress organized by the European Society of Cardiology and the COAPT presented at the Transcatheter Cardiovascular Therapeutics (TCT) congress. Both trials have been discussed extensively. Could you please tell us what the basic differences are in the results obtained by these two trials?

Answer: The clinical studies MITRA-FR[1] and COAPT[2] share the honor of being the very first two studies in history with a rigorous design that randomized patients with functional mitral regurgitation (FMR) to receive optimal medical therapy or optimal medical therapy plus the FMR correction device MitraClip. There were opposing results. In the MITRA-FR the device did not produce any benefits over the composite event of death or rehospitalizations after one year of follow-up. In the COAPT, the MitraClip group showed a significant reduction of hospitalizations at 2 years, and a reduced composite endpoint of death/rehospitalizations at 2 years. It seems reasonable to try to analyze the differences between both studies in an attempto to understand these opposing findings. These are the most significant differences I have seen:

Magnitude of the FMR. This is probably one of the most important aspects that may explain the differences seen. According to the clinical guidelines established by the ESC, the MITRA-FR included patients with severe FMR defined as an effective regurgitant orifice area (EROA) ≥ 20 mm^2 or regurgitation volumes > 30 mL. This brought these patients' average EROA to 31 ± 10 mm^2. On the contrary, according to the American clinical guidelines,[3] the COAPT considered significant FMR EROAs ≥ 30 mm^2 or regurgitation volumes > 45 mL (average EROA 41 ± 15 mm^2). Also, in the MITRA-FR over half of the patients (52%) showed EROAs between 20 and 30 and in the COAPT, 87% of the patients showed EROA values > 30 mm^2. In sum, the COAPT included patients with more severe FMR which would, logically, have a bigger impact on the patients' events when corrected.

- Ventricular volumes. The patients from the MITRA-FR showed higher average ventricular volumes compared to those from patients from the COAPT (end-diastolic volume index: 135 ± 35 mL/m^2 versus 101 ± 34 mL/m^2). This means that the disease was far more advanced in the French study compared to the American study. This can also be one of the keys that may explain the differences seen. Treating some FMR in patients with very dilated ventricular volumes may have no effect at all on major cardiovascular events.

- Optimal medical therapy. This is another essential aspect if we want to understand the differences seen between both trials. In the MITRA-FR, the medical treatment that patients were receiving before randomization was the one the treating physician considered optimal. Also, this treatment could be modified during follow-up without the study committee knowing about it. Thus, even though the drug doses administered to manage heart failure may have been the correct ones at the beginning of the study, they may have been modified later on. And it is well-known that optimizing drug doses has a major impact on patients' events and functional class. This effect can be seen in the functional class improvement experienced by the group that received medical treatment in the MITRA-FR. However, in the COAPT an «eligibility committee» monitored that every patient would receive the right drugs and the maximum tolerated doses before randomization. That's why there were not too many dose modifications in the COAPT follow-up compared to the beginning of the trial.

- MitraClip performance. There are substantial differences when it comes to the level of success and performance achieved by this device. In the MITRA-FR, 9% of the patients never received the device. The number of complications was higher in the MITRA-FR (14.5% versus 8.5%) and the percentage of success at one year was lower in the French trial (17 versus 5% with FMR > 2+).

- Selection of candidates. The COAPT trial paid special attention to the selection of candidates. Patients whose baseline cha-

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racteristics offered poor prognosis in the short-term and in whom the intervention wouldn't probably lead to significant clinical improvements were excluded. Irreversible pulmonary hypertension, moderate or severe right ventricular dysfunction, stage D heart failure, hemodynamic instability, and inotropic therapy were cause for exclusion from the trial. These patients were not in the exclusion list presented by the MITRA-FR. Also, all patients from the MITRA-FR should have been hospitalized, at least, one time before joining the trial, but the COAPT never considered this as a prerequisite which favors the selection of a less evolved population. The possible inclusion of these cases added to the inclusion of patients with ventricles in a far more advanced stage of the disease and not too much mitral regurgitation may have been decisive and explain the results obtained.

- Follow-up time. In the COAPT, survival curves start to separate clearly after one year of follow-up. The MITRA-FR has one year of follow-up only. We may see a different progression of these patients in time, in this study, as follow-up goes on.

- Methodological aspects. The minimum primary endpoint of the MITRA-FR was a composite of rehospitalizations or death at one year. In order to analyze this variable, the Kaplan-Meier survival analysis was used which, even though is correct from the methodological point of view, it presents us with one problem: rehospitalization is an event that may occur in time but this analysis does not take it into consideration. This is especially important here since one of the problems of this type of patients is the number of rehospitalizations. Being hospitalized once or five times a year is certainly not the same. This is something that the MITRA-FR did not pay attention to. On the other hand, the COAPT was actually designed to analyzed recurring events. As a matter of fact, the COAPT primary endpoint was the number of rehospitalizations at 2 years (not only if the patient was admitted or not). The COAPT included a composite of death/rehospitalizations as a secondary endpoint, but the way it analyzed this varies from the MITRA-FR. The events death and hospitalization are not exclusionary, but one is more relevant than the other. In the MITRA-FR, both events were considered the same and the only thing that would cancel the survival analysis was suffering from one or the other, whichever would come first. However, the COAPT had a more appropriate way to analyze this type of intercurrent events: the WIN ratio (the win/loss ratio in the treatment group). The WIN ratio analyzes the most important clinical event (death) giving it relevance even though it may have occurred after hospitalization. This way of analyzing the composite event shows differences that the traditional Kaplan-Meier model does not detect or does not detect so sharply.

Finally, we have to say that the COAPT was a more rigorous study than the MITRA-FR. In the French study, 43 patients were excluded from the protocol in the MitraClip group due to several reasons which amounts to 28% of the sample in the intervention group. Also, the numerous losses of secondary variables such as quality of life, analytical values, functional class and, most surprisingly, control echocardiograms, leaves these events un-scrutinized in the study since they may be prone to bias. In this sense, the percentage of significant FMR relapses at one year is an approximate estimate and, therefore, inaccurate.

Q.: The virtues of the COAPT trial have been praised and the limitations from the MITRA-FR brought to everyone's attention but, in your opinion, which would be the most positive aspects of the MITRA-FR and the most negative aspects of the COAPT?

A.: The positive aspects of the MITRA-FR are that it is the very first study to conduct a rigorous analysis on this issue by teaching us that choosing the optimal therapy for the management of heart failure and optimizing the maximum doses significantly improves patients and reduces their FMR (let's not forget that we're dealing with a dynamic process that can change in time). Also, maybe its most positive aspect is that it tells us what patients shouldn't probably be eligible for this therapy: patients in advanced stages with not too much mitral regurgitation and without an optimized medical treatment. This subgroup of patients may have to be overlooked.

The negative aspects of the COAPT are that it was a lab experiment: all the variables were perfectly controlled, all treatments to their maximum doses, and the MitraClip device with an almost absolute success at 2 years. It will probably be difficult to replicate all this in the real world, but there is no doubt that it is the perfect example that FMR kills and that correcting it may lead to a substantial reduction of cardiovascular events. The COAPT trial sets the ideal we should aspire to in real life.

Q.: How do both studies complement each other to define what the ideal candidate for this technique really looks like?

A.: The interesting thing about these studies is that they should be implemented together to set the foundations of how we should choose the candidates. It seems obvious that we have to forget about patients in advanced stages (greater ventricular dilation), non-severe FMR and without optimal treatments. If we want to have more positive results, our candidates need to be in the early stages of the disease, have a significant degree of FMR (that really contributes to the clinical situation), be perfectly treated, and have good results with the device (which means that the anatomical selection and the experience of the interventional team need to be high). However, we always have to be cautious with assumptions like these. These data show the «average» patient, but a COAPT trial subanalysis reveals that as long as the FMR is very relevant (EROA > 30 mm^2) there will always be a benefit, regardless of the degree of ventricular dilatation. That's why every case should be treated individually, and in my opinion, we should be very serious about the amount of FMR. On top of reducing major events, MitraClip also improves quality of life and functional class. These are goals that we should take into account when selecting patients because this may be the only therapy that will alleviate very advanced symptoms.

Q.: In the last TCT we also saw the results from a smaller clinical trial, the REDUCE-FMR, that evaluated a system of percutaneous annuloplasty. Given the results of MitraClip, which could be the role of percutaneous annuloplasty systems in patients with heart failure and severe FMR?

A.: In the COAPT study, the results from the clip were excellent because the anatomical selection of the candidates was excellent as well. However, in the real world we won't find cases like this all the time. In my opinion, in patients with great annular dilatation, so big that will prevent leaflet coaptation, the clip may have suboptimal results. It is in these cases where the role played by percutaneous annuloplasty systems may be essential - alone or in combination with the clip. According to the COAPT, the idea is that we should leave as little FMR as possible and that repair should be long-lasting, because this is what will eventually lead to less cardiovascular events. Percutaneous annuloplasty systems will complement our therapeutic arsenal to achieve this goal. However, to be taken into consideration, they need to show the same safety and efficacy profile as MitraClip.

CONFLICTS OF INTEREST

R. Estévez-Loureiro is proctor for MitraClip and declares to have received a research grant from Abbott Vascular.

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