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Editorial

MitraClip Real-World Data: What Is Missing and Looking Into the Future

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Bedogni et al. presented the results of the **GI**se registry **Of T**ranscatheter treatment of mitral valve regurgita**T**i**O**n (**GIOTTO**), confirming that in a real-world setting, functional mitral regurgitation (FMR) was the principal indication to MitraClip (MC) implantation in Italy over degenerative mitral regurgitation (DMR). This is a large registry of about 1200 patients, which included patients [1] in 22 Italian centers between February 2016 and December 2018. Of these, 64.9% were FMR patients, 24.8% were patients with DMR and 10.3% of patients had mixed etiology. The high rate (96.6%) of technical success in GIOTTO was consistent with international registries, such as ACCESS-EU. Many (>50%) patients required at least two clips to reach 87% procedural success, as measured at one month. The authors confirmed that the MC procedure was safe and effective, which is a consistent statement with all previous reports on MC.

Paradoxically, the clinical application of percutaneous mitral valve repair was introduced for clinical application in a relatively low-risk group of patients, in a reverse manner to TAVI (transcatheter aortic Valve implantation), which was applied first to high-risk or inoperable patients. The MC was also favored initially in US guidelines for DMR over FMR, although the larger and riskiest population of patients who could benefit from the procedure was FMR patients. Conversely, European guidelines rightly favored FMR indications at first, based on real-world implants in major European earlier adopters. EVEREST data demonstrated the safety and effectiveness of MC implants with a small number (27%) of FMR patients, relatively to DMR patients, who were younger and healthier. However, EVEREST results were equally encouraging for DMR or FMR patients. In the meantime, the "TAVI world" evolved clinically with a more logical and gradual approach toward lower-risk populations. The dramatic expansion to TAVI has a lot to do with such a progressive approach, along with a wider acceptance of the Heart Team concept.

The Heart Team concept is the one of the most fundamental changes in cardiovascular care from the last decade [2,3]. Most centers are now implementing percutaneous valve technology using a collegial, multi-disciplinary, inter-professional, patient-centered approach. It has allowed high-quality clinical research, which expanded clearly into new clinical applications with great and positive impact on patient care. More randomized trials were conducted with a true Heart team approach, and registries such as GIOTTO reflect this type of working collaboration, in which surgeons and interventional cardiologists are evaluating and treating the patient together, eliminating many of the historic logistical and cultural barriers.

What is still missing?

We need to: 1- (better predict the patients who do not really benefit from MC and 2-) better understand the reason(s) for an imperfect result and the impact of residual mitral regurgitation (MR) by looking at clinical and anatomical factors.

The first point is clearly more ethical and psychological. It is hard for a physician to admit to a patient the futility of a feasible, minimally invasive and low-risk procedure such as the MC. However, in the current economic and healthcare crunch due to the COVID-19 pandemic, we cannot expect healthcare administrators, funding agencies or insurance companies to let physicians ignore important economic factors such as stewardship and optimization of hospital resources. The worst outcomes in the GIOTTO registry were observed in patients having a long stay in the ICU. On the other hand, less invasive procedures with shorter hospital stay should be more attractive and efficient. Once again, the role of Heart Teams appears critical.

A difficult decision is easier coming from a team of colleagues working together without individual bias. Optimal patient selection is better achieved and accepted with a true Heart Team. Hospitals should insist on such team processes and further encourage the dissemination of team-based treatments for valve and coronary disease.

The second issue of residual MR post-MC needs more complex studies with more detailed anatomical elements and more longitudinal data, both clinical and echocardiographic. One of the remaining challenges of long-term evaluation of the MC is to understand the frequency, the anatomical reason(s) and the clinical impact of a moderate (2+) residual MR, particularly for FMR patients. Registries usually do not answer such questions, and unfortunately, randomized trials are also missing most of the information related to these critical questions. Less residual MR may actually be one reason for better COAPT results compared to MITRA-FR.

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At the same time, many COAPT patients had MR reduction overtime in the medical arm due to the variability of the disease and positive response to treatment, but we do not really know what happened anatomically. The ventricular sizes were lower in GIOTTO (left ventricular end diastolic diameter = 94 mm) compared to COAPT (101 mm) and MITRA-FR (135 mm). The combination of larger left ventricular (LV) size with low LV ejection fraction has a negative impact on outcomes. We would need for FMR to demonstrate the durability of LV improvement at least in size, if not both size and function. The same would apply to DMR, although we would then need data for longer periods, up to 10 years, in particular if we believe that the indications could extend to a younger and healthier patient population. Without evidence of long-term durability free of residual MR, MC should not be offered to low-risk patients as an alternative to surgical correction, although it may already happen in the real world.

The excellent durability of surgical repair for DMR patients has not been reproduced for FMR, although surgical correction of FMR is rather simple compared to complex reconstruction of a Barlow's valve, for instance [4]. CTS Net trials [5] demonstrated a high rate of recurrent MR at 2 years (58%) after surgical repair, with valve replacement proven much superior in that regard. Why would it be so different with MC? 30-day residual 2+ MR in GIOTTO is at 36%, and just above 57% of patients had only mild MR at 30 days. We need extensive longitudinal data to understand the discrepancies observed with residual MR in FMR patients and evaluate their true clinical impact. Understanding anatomical reasons for failure is critical, looking at valve and ventricular changes. The GIOTTO registry showed the negative impact of a mixed etiology due to the greater technical difficulties encountered in the treatment of calcified or tethered leaflets. This leads to the question of centers of expertise. High-volume centers have more experience and a higher propensity to treat sicker and more complex patients with complex anatomy.

Should they do it because they just can? Obviously, the more experienced you get at clipping a mitral valve, the faster and the more aggressive you may get with the number of clips you implant on the same valve. However, becoming a good MC team is less about “clipping and zipping” skills than the ability of the team to select well clinically and anatomically, all together. In the surgical world, the Edge-to-Edge Alfieri technique has proven more efficient on preventing residual MR when it was associated with a mitral ring implantation. Clipping the mitral valve may achieve a nice double valve orifice, but you may still need a ring to improve further and more durably the anatomical result.

Following the CTSN randomized trials on FMR, surgeons somewhat shifted from repairing to replacing FMR. In the “catheter-based world”, similarly to CTSN trials, valve replacement may show more protective value against residual MR. For this to happen, better devices are needed, easier to implant and less obstructive to the LV outflow tract. MC could then become less attractive and face more competition from percutaneous mitral valve replacement.

For now, in spite of registries and clinical trials, we are still missing good longitudinal data. Whether a center wishes, or not, to join a national or international registry, Heart Teams should definitely be committed to building rigorous institutional data collection processes, including preprocedural, intraprocedural, and postprocedural data, together with a complete longitudinal follow-up, including symptoms, medications, re-hospitalizations, and anatomical data such as degree of residual MR, valve gradients, ventricular remodelling, valve tethering/thickening, pulmonary hypertension.

Looking into the future of data science, with the advent of artificial intelligence, big data, and predicting tools, it would be great to see centers agree on a universal MC data set. This would offer a uniform wealth of data, eliminate the need for multiple registries and provide high-quality, real-world clinical information. It would be cheaper, faster, and independent from industry and provide real-time predicting tools for advanced cardiac care.

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