EDITORIAL

Chasm between the Guided-Directed Medical Therapy for functional mitral regurgitation used in the COAPT trial and present time: a major revision is mandatory

"Thinking is more interesting than knowing, but less interesting than looking"
- Johann Wolfgang von Goethe –

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Key words: **Functional mitral regurgitation; Heart failure; Transcatheter edge-to-edge mitral valve repair; Guided-directed medical therapy; Medical treatment; Randomised controlled trials.**

Palabras clave: **Insuficiencia mitral funcional; Falla cardiaca; reparación mitral borde-a-borde transcatéter, GDMT; Tratamiento médico; Estudios aleatorizados controlados.**

Cir Card Mex 2022; 7(4): 61-64.

Heart failure (HF) is one of the most common cardiovascular syndromes all over the world. In 2017, it was estimated that 64.3 million people were living with HF worldwide. The prevalence of HF in developed countries is 4.2% of the general population [1].

By definition, secondary or functional mitral regurgitation (FMR) is the result of a primary left ventricular (LV) disease that yields through the mitral valve (MV). Increase in the LV diameters, as well as sphericity, produce an outward and downward displacement (also known as "tethering") of the posteromedial papillary muscle, either alone (asymmetric tethering), or together with the anterolateral muscle (symmetric tethering). In this way, the FMR is the effect but not the cause of the disease. In patients with HFrEF (heart failure with reduced ejection fraction), depending on severity, FMR may be present to a variable degree. Moderate and severe FMR have been reported up to 27% and 19% of the series, respectively [2]. In other study by Sharma et al., 29.4% of cases following myocardial infarction had some degree of FMR. Mild was observed in 9.4%, moderate in 3%, and severe in 2% of all cases [3]. As a matter of fact, the presence of FMR can be considered as a strong marker of adverse outcomes in patients with LV dysfunction [4]. More specifically, an exponential increase in mortality directly related to the degree of FMR measured through the EROA has been identified. Thus, the hazard ratio (HR) was 2.8, 3.8 and 5.1 for EROA values of 0.2, 0.3 and 0.4 cm2, respectively [5].

Firstly, it must be well understood, that when dealing with FMR, it is not sufficient to consider the mitral regurgitation alone. We must also study in great detail, the primary condition giving rise to this pathological status of the MV. Special attention must be given to the LV sphericity and dimensions. Considering that any treatment directed to MV in FMR will only be palliative but never curative, therefore, the only curative treatment will be that directed to the LV muscle. The 2020 ACC/AHA guideline for the management of patients with valvular heart disease, for patients with severe FMR in stage D, recommend coronary artery bypass grafting if suitable in addition to MV operation as Recommendation Class 2a. On the other hand, if the patient is not a suitable candidate for coronary artery bypass grafting, with inadequate response to optimum guided-directed medical therapy (GDMT), then transcatheter edge-to-edge mitral valve repair (TEER) is indicated, as recommendation Class 2a [6].

Of particular importance, is that GDMT should always be the first-line therapy in FMR. The most detailed information giving rise to the foundation of current guideline recommendations for TEER in FMR comes from two main randomized controlled trials; namely, COAPT [7] and MITRA-FR trials [8]. In both of them, death and re-hospitalization rate for HF were compared by using medical therapy alone versus TEER plus medical treatment, which yielded

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completely opposite results. Detailed information has been provided by the disproportionate/proportionate FMR concept in order to reconcile the results between them [9]. Nevertheless, the main drawback of the disproportionate FMR concept is that the idealized limit to which one compares, is totally unrealistic. Hence, this concept is not in line with the physical laws for conservation of mass and energy. Therefore, the term should be avoided [10].

Previous surgical studies have stressed some bounds to be applied to the TEER usage [11-16]. Unfortunately, expectations for TEER are defined in terms of often-unrealistic, since TEER is a ringless therapy [11,15]. In conventional terms, the lack of an annuloplasty ring in an edge-to-edge procedure such as TEER, renders repair unstable, especially in the long -term beyond 5 years [12,13]. There is no reason why a perfect surgical technique such as edge-to-edge plus annuluoplasty ring would be unstable, when applied as a complete technique by percutaneous approach.

When comparing survival at 5-years in patients with HF in stage C and D, the numbers indicate 75% and 20%, respectively [17,18]. However, the long-term sustained effects of TEER have not yet delivered the expected results. Based upon data obtained from surgical cases of edge-to-edge without annuloplasty ring (like-TEER condition), failure as recurrent MR ≥ 3+ is found in 25%, 50% and 75%, at 5, 10 and 14 years of follow-up, respectively [11]. This indicates that the real failure rate appears after 5 years of follow-up, when no ring is used together with the edge-to-edge procedure. Considering all the aforementioned details, theoretically TEER would not be indicated for cases in Stage C, with 75% of survival at 5-years, while having an expected failure and MV reoperation rates (due to MR ≥3+) between 25% and 30% as at 5-years. All of these considerations are of paramount importance, when an achievable GDMT is feasible. The 2020 ACC/AHA guideline for the management of patients with valvular heart disease recommend a MV procedure for stage D of HF, when there is no adequate response to optimal GDMT. Thus, the only current specific indication for TEER in FMR is Stage D, with no adequate response to GDMT [6].

The 2022 current guidelines for the management of HF place special emphasis on quadruple medical therapy for those cases with HFrEF. In turn, it implies the optimal medical management for FMR. The GDMT for HFrEF now includes 4 medication classes that include sodium-glucose cotransporter-2 inhibitors (SGLT2i) (e.g. Dapagliflozin), beta blockers, angiotensin receptor-neprilysin inhibitors (ARNi) (e.g. Sacubitril/Valsatran), Mineralocorticoid Receptor Antagonists (MRA) (e.g., spironolactone) [19]. Of note, treatment of FMR with optimum GDMT, resulted in either a reduction in severity or elimination of the symptoms in nearly 40% of cases and was associated with prevention of adverse LV remodeling, leading to a better long-term prognosis [20]. In another series of FMR patients treated on Sacubitril/Valsatran, 45% improved NYHA functional class. This was directly related to the degree of MR. In 77% of them, a significant decrease in the degree of MR was observed [21]. Therefore, these patients can be categorized as Stage C, with no requirement for any other procedure to treat severe FMR. This is a very well-known concept, but it seems that it has not been completely incorporated into universally agreed best practice.

After the results from EMPEROR-Reduced and DAPA-HF trials, gliflozins as SGLT2 appeared as a new option of treatment for patients with HFrEF, including FMR [22]. The quadruple therapy (ARNi, beta-blocker, MRA and SGLT-2i) has become the new standard of care for HFrEF in 2021. Indeed, the estimated cumulative effect as a whole has been 73% of relative reduction in mortality over 2 years [23]. In summary, by using SGLT-2 inhibitors for HFrEF, they improve survival, reduce re-hospitalization rate for HF, and improve quality of life. In addition, efficacy and safety are combined with simplicity: just one pill, once per day, and no titration [24].

To bear in mind is the great disparity between the recommendation by guidelines and the situation in the real-world, regarding the GDMT for HF and FMR. In the CHAMP-HF registry of outpatients with HFrEF, 27% of eligible patients were not prescribed a renin-angiotensin system inhibitor, and 33% were without a beta-blocker. At the same time, around 25% of patients eligible for all 3 medical therapies were prescribed on this treatment, and only 1% were prescribed triple therapy at target doses [25]. The foregoing highlights the difficulty and great gap between theory and practice.

Pursuant to the above, several situations come to light. One of them is the relevance of the GDMT used in COAPT in the context of current 2022 clinical guidelines. It turns out to be incomplete and obsolete. Just to mention, in the COAPT trial, only 5% of cases were on sacubitril-valsartan (ARNi), 50% on spironolactone (MRA), and no cases on gliflozins (SGLT2i). So, we cannot transfer the COAPT results in today's optimum daily practice [26].

By narrowing the gap between ideal GDMT and the one used in the COAPT trial, we will be able to gain a better understanding of the relative difference in both trials. The fundamental objective of this writing is to highlight the paramount importance of GDMT usage, in terms and conditions stated by HF management guidelines, based upon the new quadruple therapy. In this way, patients in stage D undertreated for FMR with inadequate GDMT, can now be reassessed and their medical management optimized. Many of these cases can be cataloged as Stage C with no need for TEER, after optimization with quadruple therapy GDMT.

Of course, it must be said that this very sophisticated process based upon quadruple therapy for HFrEF and FMR is still very far from actual practice reported in the trials studying the impact of TEER in FMR. Thus, it is interesting to try to evaluate the cost we have to pay by submitting for TEER, the wrong patient on an incomplete and obsolete GDMT. It must be emphasized that it is theoretically impossible to be considered as "the top of the optimal medical

treatment", the GDMT utilized in the trials, with particular emphasis on the COAPT trial medical arm, owing to the classes and dosages involved in it. This situation could be a reason of bias in favor of TEER.

A simple approach to improving the TEER usage might be to ignore all the above, but this leads to two main objections. The first one is to consider the GDMT in the COAPT trial as a reflect the real value in our daily practice. Nonetheless, as previously stated, the GDMT in the COAPT trial is incomplete and obsolete, according to the current guidelines for HF management [26]. On this basis, a comparison would be strongly biased by the quality of the optimal medical treatment used in each trial.

The second factor is the problem of comparing two trials without considering the economic cost of the device. Much of the information supporting the TEER recommendation for FMR by guidelines largely derives from the COAPT trial. However, as demonstrated by NICE guidelines, this aforementioned trial did not consider a health economic model as part of the information to investigate the cost of the effectiveness of using TEER. To highlight this matter, in the COAPT trial, TEER was taken for granted to be cost effective at the current economic price, but the reality is quite the opposite. According to data based on 2019 USD by Rezapour A, et al. the total cost of MitraClip therapy is around $ 121,390.00 US dollars, versus $75,742.00 US dollars per medical treatment [27]. Moreover, considering the fact that life expectancy in HF patients with FMR cannot be improved by a palliative treatment such as TEER or medical treatment, results derived from indicators such as quality of life or life years gained do not represent strong evidence in favor of TEER. For this reason, TEER should not be recommended over medical treatment [28].

We may conclude that actual practice should not accept this very low efficacy of GDMT used in the trials, such as the COAPT, comparing TEER with medical treatment. Adoption of the newly proposed 4-therapy by guidelines for HF management, including gliflozins, may lead to an increase in good outcomes of GDMT as first-line therapy for FMR, in more realistic terms.

FUNDING: None

DISCLOSURE: The author has no conflicts of interest to disclose.

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