EDITORIAL

COAPT trial in the current era. *Apertis verbis* still much to be clarified

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There has been an ever-increasing interest in catheter-based techniques to treat structural heart diseases. The question of using transcatheter edge-to-edge repair (TEER) more efficiently in order to treat the severe functional mitral regurgitation (FMR) has been basically the main objective throughout the last years. Accessing novel cutting-edge technological breakthroughs may offer great promises of treatment options, but without recognizing the limitations of the TEER technique, its usage may never become a permanent part of our daily practice routine. Thus, the essential problem concerns how to implement more efficient practices such that they will be integrated in and complement other aspects of the current armamentarium at hand to treat mitral regurgitation (MR). As 2023 progresses, cardiac surgeons are finally beginning to realize the implications of an incomplete ringless therapy, such as TEER. At this point in time, it appears that cardiac surgeons are acknowledging the fact that unless a whole comprehension of TEER, unexpected results could occur in the intermediate and long-term. As a result of medical device industry involvement by sponsoring crucial RCTs, biased information and outcomes have risen drastically. Therefore, we need to be extremely discerning with the criteria governing TEER usage. In these terms, drawing a line to clearly define which are the boundaries with catheter-based techniques is mandatory. Moreover, current trends in TEER have been forcibly influenced by the results of trials whose disparity between them has not been totally elucidated yet. It appears far easier to partially solve the problem by applying a solution whose final impact in the intermediate- and long-term is not completely known. A basic problem, therefore, is to recognize and understand the shortcomings surrounding TEER. Subsequently, an evaluation is imperative to assess the extent to which they are surmountable.

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The JACC has recently published the article by Giustino et al [1], in which they analyze the impact on survival and hospitalization rates after using TEER to treat severe FMR. The authors found that there is a positive impact by reducing time-to-first-event rate to any heart failure (HF) hospitalization (34.8% vs 56.4%; HR: 0.51; 95% CI: 0.39-0.66) and fatal heart failure hospitalization rate (6.5% vs 12.6%; HR: 0.47; 95% CI: 0.26-0.85) in favor of TEER when compared with guided-directed medical therapy (GDMT) alone. Also, they found that patients who underwent TEER had two more months of life and out of the hospital than the group with GDMT alone (581 ± 27 days vs 519 ± 26 days; p=0.002) [1].

At first glance, the results appear to be quite attractive. However, we need to pay careful attention on what it really means. The results come into light after analyzing the COAPT trial [2], which has been repeatedly questioned about the certainty and reliability [3]. While this trial showed absolute favorable results in favor or TEER over medical treatment as GDMT alone in patients with severe FMR, the MITRA-FR did the exact opposite. No difference was found by using TEER over GDMT alone in severe FMR [4].

To the best of our knowledge, TEER is never used alone as a therapy. Medical therapy is the central core of the management in severe FMR, regardless TEER. Whether or not TEER is added to the FMR management, it is never the main goal of the therapy. So, when analyzing this kind of trials, we are doing for a device such as TEER in conjunction to GDMT. That being the case, several questions raise. As we have recently demonstrated, COAPT trial has many grey zones, which remain as no or only partially explained yet. Hitherto, the only to which we have had some access is exclusively for the supplementary material but not the raw data of the COAPT trial. This includes both, GDMT and echocardiographic data after TEER. As a consequence, a lack of certainty about the results of the COAPT can be argued [3]. This is especially important considering COAPT is the only

randomized-controlled trial (RCT) in favor of TEER in FMR. It is necessary to underline the fact that while MITRA-FR was mainly sponsored by the Ministry of Health of the French Government, COAPT trial was totally sponsored by Abbott. This fact has been questioned by some authors, calling into question the COAPT arguments in favor of TEER [5]. In addition, it has been widely questioned why the MITRA-FR results against the use of TEER in FMR were not included into the current guidelines for the management of the valvular heart disease [6]. All these questions still remain without a wholly satisfactory explanation.

Several attempts have been argued in order to explain the different results between COAPT and MITRA-FR, including special criteria by echocardiography. Disproportional/proportional mitral regurgitation concept has been proposed by some authors [7]. However, it has been quickly refuted because of lacking of consistent data from COAPT. The analysis by Hagendorff et al. has demonstrated that the concept of disproportionality for FMR is not in line with physical principles of preservation of mass and energy. Moreover, they emphasize that the only way to explain the disparity on results between COAPT and MITRA-FR is due to a lack of consistency in echocardiographic data reported, such as in COAPT trial [8].

Nevertheless, the most important issue in trials studying the treatment for FMR, such as COAPT and MITRA-FR, is the guided-directed medical therapy (GDMT) in all meanings. For starters, we need to make quite clear that the cornerstone in the treatment of severe FMR is the GDMT. As a matter of fact, in both American and European clinical practice guidelines for the management of the valvular heart disease, the recommendation for TEER usage is 2a, only if coronary artery bypass grafting has been ruled out, and no benefit with GDMT alone [9,10]. That being the case, a deep analysis of the medical management as GDMT in the COAPT could be helpful, at a large extent, in order to understand the controversial results.

Interestingly, more than a half of the patients diagnosed with HF can be considered as having reduced ejection fraction (HFrEF). In a study of 4,596 patients with HF, 52.8% had HFrEF [11]. By echocardiographic study in 370 cases with HFrEF, Varadarajan et al. found that FMR grade 1+, 2+, 3+ and 4+ was present in 44%, 22%, 15% and 14%, respectively. Therefore, severe MR ≥3+ can be found up to in one third of the patients with HFrEF [12]. GDMT is the central core with HFrEF. The 2022 Guidelines for the management of HF includes the four-therapy based on the simultaneous management with angiotensin receptor-neprilysin inhibitors (ARNi), beta-blockers (BB), mineralocorticoid receptor antagonists (MRA), and sodium-glucose co-transporter 2 inhibitors (SGLT2i) as the first-line therapy in HFrEF [13]. In fact, Nasser et al. [14], found that, after using only GDMT, of a total of 50 patients having HFrEF and severe FMR at baseline, 38% showed an improvement toward non-severe FMR (≤2+), at a median follow-up of 50 months. That means to say that severe FMR was successfully treated exclusively with medication in almost 40% of cases. It is worthy to highlight that ACEi/ARB (angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker) was administered in only 74% of cases, BB in 100%, and MRA in 47%. Optimal dosage was only reached in 44%, 55% and 55% of cases, respectively. Therefore, it should be stressed that there is still a big gap between optimal medical treatment and daily practice, which undoubtedly redounds to a lack of the greater potential benefit from the impact of GDMT as sufficient fist-line therapy for the conservative management of severe FMR cases.

Similar results have been reported by Januzzi et al. in the PROVE-HF study [15], in which they studied the effect of sacubitril/valsartan in 794 cases with HFrEF and severe FMR. For cases with severe FMR (14.9% of the series), the authors found an important relative reduction of the severity in FMR grade (as non-severe) of 45% (8.2% of cases) at 6 months, being sustained in 44.7% (8.4% of cases) at 1-year of follow-up. These findings indicate that by optimizing GDMT may reduce the severity of MR sufficiently to a point to avoid the necessity for any other procedure, such as TEER. In this context, a fact that usually goes unnoticed is that in the medical arm of the COAPT, up to 33% and 40% of the patients who initially did not present any improvement in terms of FMR during the first 30 days, did have a decrease in the degree of MR, evolving towards moderate or even mild MR, at 1 and 2 years of follow-up, respectively [16].

Nevertheless, despite current recommendations in guidelines for the management of HF to use the quadruple therapy [13], a high rate of underusing such medical treatment has been reported in daily practice. Despite not having a formal clinical contraindication, a large number of patients with HFrEF do not receive an optimal GDMT. Not only medial reasons are the cause for a non-optimal GDMT. Barriers to medication up-titration are multiple, including social, physiologic and economic factors [17]. The CHAMP-HF Registry reported that only 1% of patients eligible for ACE/ARB/ARNI, BB, and MRA, receiving target doses of GDMT [18,19]. In the GUIDE-IT trial, only 15.5% reached an optimal GDMT at 6 months of follow-up [20]. Indeed, GDMT in COAPT trial still leaves a lot to be desired. It has been reported as low rates utilization as <5% for ARNi, 47% for MRA, and 0% for SGLT2i in COAPT [21]. Lindfiel et al. have reported that, in the special group of HFrEF in the COAPT trial, only 3.2% received ARNi, and 54% MRA [22]. This fact becomes particularly important because more than three quarters (76.8%) of COAPT patients had HFrEF. An issue of paramount importance is that only 2% of the patients in the COAPT trial reached target full dose of the prescribed GDMT [23].

With all the aforementioned, the credibility and usefulness of the results of the COAPT trial should not have a place in the current era, where the GDMT has been thoroughly improved in all aspects. GDMT used in this trial needs to be deeply questioned and revisited. There is a profound loss of consistency between the GDMT used in the COAPT and reality.

In addition to this above, there are several points in COAPT deserving our special attention. Thirty-days after enrollment, almost 13% of the cases were withdrawn from the trial for different reasons. Out of them, 52 cases (9%) were non-included due to lack of echocardiographic study. Interestingly, this withdrawn group also had higher STS-PROM, higher natriuretic

peptide, and up to 2-thirds were most likely to be part of the TEER group [16]. It is evident from the foregoing information that a potential bias in favor of TEER arm could be easily recognized.

There could be a great difficulty to know how the residual MR after TEER was assessed by echocardiographic parameters in the COAPT trial. The importance of this issue lies in the fact that two possible MR sites can appear after TEER, with the inherent need to calculate two EROAs, two regurgitant volumes and two regurgitant fractions. This special situation makes the calculation of the residual MR very complex to a certain extent. In fact, no mention is made within the COAPT supplementary material of how the residual MR by echocardiography was calculated after TEER [21]. In the same document, MR grade ≤ 2+ at 12 months after procedure was considered as a parameter to assert effectiveness of the device [21]. As opposite to this fact, it has been shown that the residual MR 2+ does affect negatively the outcome after TEER. Buzzatti et al. have demonstrated that residual MR 2+ after MitraClip was associated with worse follow-up outcomes compared with MR ≤1+, including cardiac death (adjusted HR: 5.28 (95% CI, 2.41-11.56; p < 0.001), and development of MR ≥3+ (HR: 7.27; 95% CI, 3.34-15.80; p < 0.001) at 20.4 months of follow-up [24]. Reichart et al. found similar results. Patients with suboptimal results after MitraClip therapy, including residual MR 2+ after procedure have worse outcomes compared with residual MR ≤1+. This condition was only sustainable if residual or recurrent MR≤1+ was maintained at 12 months follow-up (all-cause mortality, p = 0.003; and the composite outcome analysis, p= 0.017) [25]. At the same time, Buzatti et al. [24] and Sugiura et al. [26] have demonstrated that residual MR ≥2+ after TEER is the most important predictor for further development of MR≥3+ (HR: 5.01, 95% IC: 2.07-9.29, p < 0.001), (HR: 3.24, 95% IC: 1.69-6.18, p < 0.001), respectively.

Another point that has not been clarified yet is the primary composite end-point used in the COAPT trial as all-cause death and re-hospitalization for HF [2]. The problem of comparing endpoints with single or multiple items is always difficult. On this basis, a composite endpoint as the primary one would be strongly biased by the produced mix of all-cause death and re-hospitalization for HF rates. Therefore, despite freedom from death from any cause was favorable for the TEER over GDMT alone at 1-year (18.8% vs 23.3%, HR: 0.79, 95% CI: 0.56-1.13, p <0.001) and 2-years (29.3% vs 47.4%, HR: 0.59, 95% CI: 0.45-0.79, p < 0.001), it should be noted that while a composite endpoint graph is shown at 2 years in the supplementary appendix as well as for the re-hospitalization for HF alone, no graph appears for all-cause death as a single item [23]. Unfortunately, analyses of this kind can be misleading due to a lack of precise and clear information about which of the two items in the composite endpoint is the strongest one to affect the final result. Based upon the great difference in favor of TEER in freedom from re-hospitalization for HF rate at 2 years, the ascribed power to the composite endpoint can be questioned by wondering why the sole re-hospitalization for HF rate was not considered as a single primary endpoint in the COAPT trial.

In addition, in order to assess the effectiveness of TEER, it has to be stressed the necessity to consider exclusively parameters that can be measured objectively, mainly by echocardiography. That is, all those subjective parameters measuring quality of life through non-objective questionnaires should be avoided. This is due to the well-known fact of bias based on the placebo effect after the TEER procedure [27]. By the same token, it has been demonstrated that the stress level on the myocardial wall stress does not consistently improve after TEER. Therefore, changes in NT-proBNP after procedure must be assessed routinely [28].

At last but not least, it remains in the air the question about the applicability of the COAPT criteria to real world patients. According to data provided by Fine et al., of 9006 cases with HF, only 101 (1%) met COAPT criteria for TEER [29].

Finally, the authors conclusion about only two more months of survival is not a strong argument in favor of TEER [1].

As a conclusion, given all the doubts previously exposed, the COAPT trial by itself would provide an incomplete assessment regarding the effectiveness of TEER in FMR. While baring many misconceptions resulting in a deliberate use of TEER, the pinpoint about in which cases TEER could be useful still remains to be elucidated. This conclusion should be extensive to all derivatives and spin-offs from the original COAPT. Otherwise, in so doing, it generally misevaluates the importance of understanding the crucial role of GDMT in FMR.

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