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Reconciling conflicting evidence in the evaluation of the MitraClip system: Assessment of and response to the MITRA-FR and COAPT trials by key stakeholders

Two clinical trials (MITRA-FR and COAPT), which were set out to evaluate the effectiveness of adding percutaneous repair (PR) for patients with severe secondary mitral regurgitation (SMR), came to very different conclusions. The MITRA-FR showed no benefit of PR,¹ while the COAPT trial reported a dramatic improvement of clinical outcomes.² We reviewed the assessment of and response to the MITRA-FR and COAPT trials by key stakeholders, whether regulators and Health Technology Assessment (HTA) bodies, or authors of publications in medical journals.

Briefly, a systematic literature search was conducted to identify documents that met the following criteria: (1) licensing/reimbursement decisions, clinical guidelines, and academic papers from top medical journals; (2) published between September 2018 and December 2023; (3) dealing with the conflicting evidence from the two trials. A total of 53 studies meeting our inclusion criteria over the period among our selected sources (details methods and details could be accessed by contacting the authors), reflecting the major controversy resulting from the publication of the two trials. The majority were authored by clinicians (46 out of 53) while five (9%) were elaborated by health services managers/HTA bodies, and two (4%) by regulatory agencies.

The main factors highlighted as potential reasons for the conflicting results were differences in terms of patients' echocardiographic characteristics ($n = 52$), the concurrent control therapy (64%), and the rate of interventional procedure success (43%). Less frequently, document authors explained the divergence in findings by focusing on the definition and measurement of outcomes ($n = 9$), or considering differences in the learning curve and/or the experience of operators ($n = 8$). Only one document (2%) mentioned the difference between industrial and academic support as a potential explanation for the discrepancy.

In 51% of cases ($n = 27$) (Table 1), authors were deemed to be in favor of the findings of COAPT when drawing conclusions while in 34% ($n = 18$) of the documents, conclusions were equivocal with authors accepting the unexplained heterogeneity in the findings. Less frequently, the conclusions were that effectiveness depended on contextual factors ($n = 5$), or were not clearly drawn ($n = 3$). None of the selected documents seemed to favor the findings of the MITRA-FR trial. All six official

documents, either originating from policymakers, managers of health services, or regulators, supported the findings of COAPT.

Irrespective of their main conclusions, 26% ($n = 14$) of authors suggested further research to be conducted, either mentioning the ongoing RESHAPE-2 RCT as an additional source of evidence or advocating for an individual-patient data meta-analysis based on the two trials ($n = 4$). In 34 cases (64%), analyses were carried out to explore reasons behind the discrepancy using data exclusively from the two trials. In the majority of these cases ($n = 20$), the authors sought to further their analysis based on a simple comparison of the baseline characteristics and inclusion criteria.² In the 14(41%) remaining cases, authors undertook or referred to additional analyses (post hoc or meta-analyses) exploring the impact of echocardiographic factors on the results. In 8 cases (16%), the reasons behind the discrepancy were explored based on data from other sources, including observational studies that have tested whether COAPT-like criteria were predictors of successful outcomes. We found generally greater acceptance and popularity of findings from the COAPT trial among the medical community as well as among regulatory or HTA stakeholders.

Our study indicated that most of the published documents tended to support the findings of the COAPT trial, and therefore accepted that PR with the MitraClip system was effective in improving outcomes. Nonetheless, these opinions did not seem to be reached without reservation. The literature that we reviewed highlighted many reflections regarding patient selection and the drug management before enrollment in the trial, which could explain the discrepancy. In more than one third of cases, authors considered that further research was necessary to draw more definite conclusions.

Among the reasons explaining the conflicting results, the concept of disproportionate-proportionate MR was repeatedly discussed. The principle³ was that those patients who had severe MR proportionate to the degree of LV dilatation, as enrolled in MITRA-FR, based on average measures of Left ventricular End-Diastolic Volume (LVEDV) and the effective regurgitant orifice area (EROA), were unlikely to respond to PR. Conversely, those patients who had disproportionately severe MR compared to LV dilatation, such as average patients enrolled in COAPT,

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TABLE 1 The conclusions based on document subtypes.

Conclusions of the documents	N (%)	Publication subtype		
		Informing relevant stakeholders	Guide clinical decision making by healthcare professionals	Produced and/or used for licensing or reimbursement decision
Favored the findings of the COAPT trial	27 (51%)	18	3	6
Equivocal	18 (34%)	18	/	/
Concluded the effectiveness depends on contextual factors	5 (9%)	4	1	/
No explicit conclusion	3 (6%)	2	1	/

were likely to achieve good outcomes after PR. This new conceptual framework sought to reconcile the conflicting findings of the two trials. It had received support in the medical community with more than 500 citations as of August 2023. However, whether this new conceptual framework was the definite answer to this controversy was yet to be formally demonstrated. A secondary analysis of the COAPT Trial,⁴ which explored the contributions of the degree of MR and LVEDV to the benefit of PR, concluded that the proportionate-disproportionate hypothesis was not supported for determining patient outcome. Similarly, a post hoc analysis from MITRA-FR failed to demonstrate a beneficial effect of PR in patients most resembling to the COAPT population based on EROA and LVEDV.⁵

The statement that optimization of medical care prior to patient selection in favor of the COAPT trial appears to be a second important factor. While the process of patient selection might have appeared more rigorous in COAPT, expert opinions had noted that the screening procedure of this trial was not really representative of “real-world” practice.⁶ For instance, a scientific eligibility committee selected the patients before enrollment in COAPT, whereas this decision was made by the centers during the MITRA-FR trial.²

A final proposition in the literature to explain the conflicting findings was that the French medical centers lacked the necessary expertise to perform the procedure. For example, in an HTA report,⁷ the surgical learning curve was identified as a factor potentially affecting effectiveness indicating that “many patients in MITRA-FR received the intervention in centres lacking adequate expertise, whereas, in COAPT, MitraClip was performed only in highly specialized medical centres.” While PR was admitted as a demanding procedure requiring highly specialized medical expertise, there was no evidence to support that MITRA-FR investigators had fewer experience than those from COAPT. In both trials, the roll-in procedures before the inclusion of first patient were low (three in COAPT and five in MITRA-FR) and all procedures were undertaken with technical proctoring by the MitraClip manufacturer.⁸ Lastly, it was suggested that the learning curve associated with PR might be situated beyond 50 cases, which exceeds by a large extent the number of cases that both MITRA-FR and COAPT investigators had performed prior to enrollment.⁹

The nature of sponsorship (industrial vs. academic) was rarely noted as a factor to explain discrepancy in findings although meta-

epidemiological analyses suggested that industry-funded trials were more likely to be associated with favorable findings.¹⁰

There was major implications for the preferential acceptance of COAPT findings in terms of dissemination of PR with the MitraClip system. Indeed, the COAPT trial was conducted with the aim to allow the clearance of the MitraClip system in SMR patients to the US population, which was by far to the largest market worldwide. Following that approval, figures reported that the sales turnover for this device reached USD 176 million in the third quarter of 2019: this implied an increase of more than 30% worldwide and more than 45% based on US market data in comparison to the previous year.¹¹

In the absence of a definite answer to reconcile the conflicting findings, the economic impact resulting from the current uncertainty was considerable, as illustrated in a recent cost-effectiveness analyses using either the COAPT or the MITRA-FR inputs.¹²


A first limitation of this review was that it was based on very selected sources of information, namely, publications from medical journals and reports by major regulatory and HTA bodies in high-income countries. This specific viewpoint could have been complemented by a more comprehensive search among the medical literature, and exploring geographical variation. However, it was likely that comparable points of discussions would have been identified in the broader literature. Similarly, considering the growing use of social media by the medical community,¹³ it could have been interesting to explore the reaction of the medical community to the publication of the two trials based on a social media analysis. Finally, a qualitative analysis to explore stakeholders interpretations could have complemented our analyses in order to better capture the full complexity of the topic.

Finally, this study analyzed key literature focusing on an important medical controversy contribution surrounding an interventional procedure that utilizes an innovative medical device. Findings demonstrating a major discrepancy in clinical evidence, such as the MitraClip case, were not uncommon.

Discordant interpretations of such evidence and different policy and practice decisions and treatment recommendations that follow had important clinical and economic impacts for patients and the population. The discussion emphasizes the need for standardized recommendations to help decision-makers under similar circumstances.

CONFLICT OF INTEREST STATEMENT

JFO is the principal investigator of the MITRA-FR study; XA is a member of the MITRA-FR steering committee. The other authors declared none.

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