THE DISPROPORTIONATE SUCCESS OF THE DISPROPORTIONATE CONCEPT

To the Editor:

A Cardiothoracic Surgical Trials Network expert panel recently discussed the treatment of functional mitral regurgitation (FMR). We agree with the authors' prudent interpretations, reiterate their words of caution, and would like to clarify certain points.

They mentioned that patients in the Cardiovascular Assessment of the Mitraclip Percutaneous Therapy (COAPT) experienced more effective and durable results, and experience of the French Prospective Randomized Trial (MITRA-FR) operators has been questioned.

- The roll-in procedures before first patient inclusion was low in both the COAPT and the MITRA-FR (3 and 5, respectively), and we agree that the learning phase requires more cases.
- In COAPT, there were more often 2 clips implanted per patient, but more often 3 clips in MITRA-FR and procedural success was similar: 98% for COAPT and 95% for MITRA-FR.
- Enrollment rate was lower in COAPT (1.7 patient/center/year) than in MITRA-FR (2.6 patient/center/year).
- The decreased complication rate in COAPT was mainly due to different definitions.
- The 5% mitral regurgitation recurrence in COAPT at 1 year (the lowest ever published for FMR) is probably due to a combination of patient selection and the technique itself. Mitral regurgitation recurrence, the Achilles' heel of surgical repair, is usually higher even than the 17% observed in MITRA-FR.[1] The edge-to-edge technique may be better suited to treat FMR than surgical downsizing annuloplasty.

Therefore, differences in technical expertise do not explain the divergent trials results. Differences in baseline characteristics have generated an intense debate.

- The larger regurgitant orifice in COAPT is undoubtedly a key element. Conversely, the finding of larger left ventricular (LV) volumes in MITRA-FR is more subtle. LV volumes, assessed by the Simpson method in both studies, matched well with regurgitant volume measured using the proximal isovelocity surface area method in MITRA-FR but not in COAPT. Larger LV volumes observed in MITRA-FR are possibly due to differences in Corelab evaluations (Table 1). Post hoc analyses including the proportionate/disproportionate theory[2] are attractive but rely on fragile evidence.
- COAPT echocardiographic selection criteria[3] were not mentioned in the initial protocol.[4]

TABLE 1. If we assume a similar flow and cardiac frequency in COAPT than in MITRA-FR, with a measured regular volume of 60 mL, the left ventricular end-diastolic volume should be 290 mL, which is more than in MITRA-FR

	MITRA-FR data	COAPT data	COAPT EDV recalculation
EDV	245 mL	193 mL	290 mL
EF	31%	31%	31%
Total LVSV	(EDV × 0.31) = 76 mL	(EDV × 0.31) = 59 mL	(Regular volume + efficiency stroke volume) 90 mL 88
Regular volume (PISA method)	45 mL	60 mL	60 mL
Effective LVSV	(LVSV – RV) = 31 mL	(LVSV – RV) = −1 mL	(2200 mL/73) = 30 mL
Regular fraction	59%	102%	59%
Fc	73 beats/min	?	73 beats/min
Q	2.2 L/min	Impossible	2.2 L/min

MITRA-FR, French Prospective Randomized Trial; *COAPT*, Cardiovascular Assessment of the Mitraclip Percutaneous Therapy; *EDV*, end-diastolic volume; *EF*, ejection fraction; *LVSV*, left ventricular stroke volume; *PISA*, proximal isovelocity surface area; *RV*, right ventricle.

The COAPT central eligibility committee was also key for COAPT success but hard to reproduce in clinical practice. Conversely, MITRA-FR was a pragmatic trial reflecting real-life practice.

Interpreting medical management is difficult, leading to more questions than answers. Guideline-directed medical therapy was compulsory for at least 3 months in both protocols,[4,5] so that patients were supposed to be stable at randomization. Mitral regurgitation decreased in both study control groups: 46.9% in the COAPT and 32.5% in the MITRA-FR. After randomization, any modification of medical treatment was discouraged in the COAPT, which may have highlighted the difference between the 2 COAPT groups. Conversely, guideline-directed medical therapy was encouraged during the follow-up in MITRA-FR with more than 80% of adaptation (data not published).

Taken together, COAPT and MITRA-FR suggest that percutaneous mitral valve repair is safe and effective and encourage the local teams to be selective. As concluded by the Cardiothoracic Surgical Trials Network panelists, there is a critical need for additional research to identify

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patient subsets who may benefit from an intervention, but for the time being, we should avoid fast and simple conclusions about this complex disease.

Jean-Francois Obadia, MD, PhD[a]
Bernard Iung, MD, PhD[b,c]
David Messika-Zeitoun, MD, PhD[d]
[a]*Hôpital Cardiovasculaire Louis Pradel*
Chirurgie Cardiothoracique et Transplantation
Hospices Civils de Lyon and Claude Bernard University
Lyon, France
[b]*APHP*
Hôpital Bichat
Paris, France
[c]*Université de Paris and INSERM 1148*
Paris, France
[d]*Division of Cardiology*
University of Ottawa Heart Institute
Ottawa, Canada

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REPLY: PROPORTIONING OUR BELIEFS TO THE EVIDENCE

Reply to the Editor:

The insightful commentary of Obadia and colleagues[1] adds to the fervent discussion of the results of 2 recently published randomized trials of percutaneous treatment of functional mitral regurgitation (MR).[2,3] In a procedurally oriented study, it is tempting to focus on technical aspects and patient selection as possible sources of differences in outcomes, yet medical adjuncts deserve equal attention. As outlined by the Obadia and colleagues,[1] it seems that technical expertise is unlikely to account for the discordant result of the trials, and the concept of "disproportionate" versus "proportionate" functional MR provides a helpful conceptual framework[4] but few firm conclusions in an attempt to reconciliate the data on the basis of differential relationships of mitral insufficiency and chamber size in the 2 studies. It is noteworthy that the rate of recurrent MR in both trials was superior to randomized surgical results with ring repair in patients with ischemic MR and less advanced myocardial dysfunction.

Although leaflet approximation may represent repair superior to isolated annular reduction, medical management of these ill patients should not be ignored. More than half of patients eligible for randomization in the COAPT trial were excluded during the run-in period, many because medical optimization had caused these patients to no longer meet inclusion criteria. Furthermore, at 1 year, 46.8% patients in the control group had moderate or less MR, suggesting significant improvement from baseline with medical therapy alone. Medical therapy in the COAPT trial was tightly controlled through the Clinical Endpoint Committee, and medication adjustments were tracked throughout the study period (Appendix Table S6 in the original COAPT article[2]). Medical therapy in the MITRA-FR trial was provided at randomization (Appendix Table S2 in the original MITRA-FR article[3]) but subsequently left to the discretion of the local treating physician. Both β-blocking and afterload-reducing agents appeared to be used with similar frequencies at randomization in the studies. In the COAPT study, however, the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or angiotensin receptor/neprilysin inhibitors was significantly lower in the control group than in the device group at baseline and at 1- and 2-year follow-ups. Whether this difference in afterload reduction contributed to the divergence in clinical outcomes in the study is feasible, although speculative. It is tempting to conjecture that less protocol-driven medical adjustment in the MITRA-FR trial resulted in its negative outcomes, but that trial also better reflects reality of clinical medicine.