Obadia reports personal fees from Abbott, Delacroix-Chevalier, Landanger, and Medtronic. Iung reports personal fees from Edwards Lifesciences, Boehringer Ingelheim, and Novartis. Messika-Zeitoun received consultant fees from Edwards. The MITRA-FR Trial is an academic study supported by the French Ministry of Health (Programme Hospitalier de Recherche Clinique - Identifier: NCT01920698) and partially by Abbott Vascular, United States.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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

^aHôpital Cardiovasculaire Louis Pradel

Chirurgie Cardiothoracique et Transplantation

Hospices Civils de Lyon and Claude Bernard University

Lyon, France

^bAPHP

Hôpital Bichat

Paris, France

^cUniversité de Paris and INSERM 1148

Paris, France

^dDivision of Cardiology

University of Ottawa Heart Institute

Ottawa, Canada

References

1. Acker MA, Parides MK, Perrault LP, Moskowitz AJ, Gelijns AC, Voisine P, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. *N Engl J Med*. 2014;370:23-32.
2. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT Trials. *JACC Cardiovasc Imaging*. 2019;12:353-6.
3. Asch FM, Grayburn PA, Siegel RJ, Kar S, Lim DS, Zaroff JG, et al. Echocardiographic outcomes after transcatheter leaflet approximation in patients with secondary mitral regurgitation: the COAPT Trial. *J Am Coll Cardiol*. 2019;74:2969-79.
4. Mack MJ, Abraham WT, Lindenfeld J, Bolling SF, Feldman TE, Grayburn PA, et al. Cardiovascular outcomes assessment of the MitraClip in patients with heart failure and secondary mitral regurgitation: design and rationale of the COAPT trial. *Am Heart J*. 2018;205:1-11.
5. Obadia JF, Armoiry X, Iung B, Lefevre T, Mewton N, Messika-Zeitoun D, et al. The MITRA-FR study: design and rationale of a randomised study of percutaneous mitral valve repair compared with optimal medical management alone for severe secondary mitral regurgitation. *EuroIntervention*. 2015;10:1354-60.

<https://doi.org/10.1016/j.jtcvs.2020.06.114>

REPLY: PROPORTIONING OUR BELIEFS TO THE EVIDENCE

Reply to the Editor:

The insightful commentary of Obadia and colleagues¹ 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 framework⁴ but few firm conclusions in an attempt to reconcile 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 article²). Medical therapy in the MITRA-FR trial was provided at randomization (Appendix Table S2 in the original MITRA-FR article³) 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.

The author reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

As always, the devil is in the details, and he has been unkind, as the seemingly similar studies differ in many small aspects that in their sum lead to contradictory results. Clearly, further investigations and data are needed, as is the willingness to change our beliefs on the basis of the scientific evidence.

Tomasz A. Timek, MD, PhD

Division of Cardiothoracic Surgery, Spectrum Health
Michigan State University College of Human Medicine
Grand Rapids, Mich

References

1. Obadia J-F, Iung B, Messika-Zeitoun D. The disproportionate success of the disproportionate concept. *J Thorac Cardiovasc Surg.* 2022;163:e7-8.
2. Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med.* 2018;379:2307-18.
3. Obadia JF, Messika-Zeitoun D, Leurent G, Iung B, Bonnet G, Piriou N, et al; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med.* 2018;379:2297-306.
4. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: a new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging.* 2019;12:353-62.

<https://doi.org/10.1016/j.jtcvs.2020.07.098>

**REPLY FROM
AUTHORS:
DISCORDANT TRIAL
RESULTS
LEAD TO
DISPROPORTIONATE LEARNINGS**

Reply to the Editor:

In response to our recent Cardiothoracic Surgical Trials Network expert consensus panel publication on functional mitral regurgitation (MR), the MITRA-FR trial investigators raise some important caveats regarding outcome interpretation.^{1,2} It is unusual in clinical research for 2 trials using the same treatment to treat the same disease in similar patients in the same time period to demonstrate widely discordant results, with one trial clearly demonstrating a therapeutic benefit and the other none.^{3,4} There have been

numerous post-hoc analyses attempting to explain the discrepancies, including differences in study size, duration of follow-up, trial end points, severity of baseline MR, left ventricular (LV) size, operator experience, degree and durability of MR reduction, and the rigor in optimization of guideline-directed medical therapy (GDMT). However, perhaps the most intriguing and clinically impactful explanation, albeit only hypothesis-generating and in need of prospective validation, is the concept of proportionate versus disproportionate MR. Distilled to the basics, patients with disproportionate MR have greater degrees of regurgitation in relationship to the size of the LV, as defined by the relationship between the effective regurgitant orifice area and LV end-diastolic volume. Patients with proportionate MR tend to have symmetrical mitral leaflet tethering from LV dilation and can reasonably be expected to respond to GDMT directed toward the LV, especially with neurohormonal antagonists.⁵ Patients with disproportionate MR have asymmetric mitral leaflet tethering due to anatomic factors such as left bundle branch block, inferobasal LV aneurysm, or severe fibrosis of the posterior leaflet, in which additional treatment needs to be directed toward the mitral valve with resynchronization therapy or valve repair. These are 2 different mechanisms of MR, and one does not lead to the other. While the confidence in a therapy increases when the results of one trial support and substantiate the findings of the other, arguably in this instance the disparate results have led to a disproportionate level of learning that would not have become apparent with either trial alone or if the results had been concordant. It is of note that a small subgroup of patients in the COAPT trial with echocardiographic parameters similar to those of patients in the MITRA-FR trial did not benefit from MV intervention.⁵ The main takeaway is that we are now better able to discriminate which patients can reasonably be expected to respond to GDMT from those who will need intervention directed toward the mitral valve to correct MR.

Michael J. Mack, MD^a

Patrick T. O'Gara, MD^b

^aCardiothoracic Surgery

Baylor Research Institute

Baylor Scott & White Health, Plano, Tex

^bCardiovascular Division

Brigham and Women's Hospital

Boston, Mass

References

1. Gelijns AC, Moskowitz AJ, O'Gara PT, Giustino G, Mack MJ, Mancini DM, et al. Transcatheter mitral valve repair for functional mitral regurgitation: evaluating the evidence. *J Thorac Cardiovasc Surg.* 2021;162:1504-11.
2. Obadia J-F, Iung B, Messika-Zeitoun D. The disproportionate success of the disproportionate concept. *J Thorac Cardiovasc Surg.* 2022;163:e7-8.