The author reported no conflicts of interest.

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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

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**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

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