JACC: CARDIOVASCULAR IMAGING VOL. 12, NO. 2, 2019

PUBLISHED BY ELSEVIER

iREVIEW

EDITORIALS AND VIEWPOINTS

Proportionate and Disproportionate Functional Mitral Regurgitation

A New Conceptual Framework That Reconciles the Results of the MITRA-FR and COAPT Trials

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ABSTRACT

Traditional approaches to the characterization of secondary or functional mitral regurgitation (MR) have largely ignored the critical importance of the left ventricle (LV). We propose that patients with secondary MR represent a heterogenous group, which can be usefully subdivided based on understanding that the effective regurgitant orifice area (EROA) is dependent on left ventricular end-diastolic volume (LVEDV). According to the Gorlin hydraulic orifice equation, patients with heart failure, an LV ejection fraction of 30%, an LVEDV of 220 to 250 ml, and a regurgitant fraction of 50% would be expected to have an EROA of ≈0.3 cm^2 independent of specific tethering abnormalities of the mitral valve leaflets. The MR in these patients is proportionate to the degree of LV dilatation and can respond to drugs and devices that reduce LVEDV. In contrast, patients with EROA of 0.3 to 0.4 cm^2 but with LVEDV of only 160 to 200 ml exhibit degrees of MR that are disproportionately higher than predicted by LVEDV. These patients appear to preferentially benefit from interventions directed at the mitral valve. Our proposed conceptual framework explains the apparently discordant results from 2 recent randomized controlled trials of mitral valve repair. The MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial enrolled patients who had MR that was proportionate to the degree of LV dilatation, and during long-term follow-up, the LVEDV and clinical outcomes of these patients did not differ from medically-treated control subjects. In comparison, the patients enrolled in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial had an EROA ≈30% higher but LV volumes that were ≈30% smaller, indicative of disproportionate MR. In these patients, transcatheter mitral valve repair reduced the risk of death and hospitalization for heart failure, and these benefits were paralleled by a meaningful decrease in LVEDV. Thus, characterization of MR as proportionate or disproportionate to LVEDV appears to be critical to the selection of an optimal treatment for patients with chronic heart failure and systolic dysfunction. (J Am Coll Cardiol Img 2019;12:353-62) © 2019 by the American College of Cardiology Foundation.

Our thinking about the pathophysiology of mitral regurgitation (MR) has long been predicated on making the distinction between "primary" versus "secondary" forms of the disease (1). The term "primary" MR refers to lesions of the valve leaflets or chordae tendineae, whereas the term "secondary" MR refers to abnormalities in the systolic tethering of structurally normal or nearly normal leaflets caused by global or regional derangements of the left ventricle (LV).

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Manuscript received October 19, 2018; revised manuscript received November 12, 2018, accepted November 19, 2018.

ISSN 1936-878X/$36.00 https://doi.org/10.1016/j.jcmg.2018.11.006

ABBREVIATIONS AND ACRONYMS

EROA = effective regurgitant orifice area

LA = left atrium

LV = left ventricle/ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

PISA = proximal isovelocity surface area

The most common cause of primary MR in developed countries is myxomatous degeneration, which can present as prolapse or a flail leaflet. Severe degenerative MR is treated by surgical repair of the mitral valve, which is associated with highly favorable and durable outcomes and a very low mortality rate (2). In contrast, post-inflammatory causes of primary MR (e.g., rheumatic heart disease, endocarditis, and radiation) typically require mitral valve replacement. The treatment options for primary MR are not controversial.

However, the management of secondary or functional MR presents significant challenges. Because this type of MR is largely related to a disease process in the LV (and not the mitral valve), therapy is primarily directed toward the underlying LV disorder. The optimal use of neurohormonal antagonists and resynchronization devices can lead to reversal of the adverse remodeling process; the resulting reduction in LV volumes can ameliorate the severity of MR in a large proportion of patients (3–5). In contrast, surgical interventions directed at the mitral valve have yielded disappointing results. In 2 randomized controlled clinical trials of patients with moderate or severe MR due to ischemic disease but with relatively preserved LV function (ejection fraction ≈40%), mitral valve repair using a downsized annuloplasty ring or chordal-sparing mitral valve replacement failed to achieve pre-specified benefits on cardiac geometry, had no long-term favorable effects on clinical outcomes, and had a high rate of recurrent MR (6,7). Consequently, the management of secondary or functional MR has focused on the restoration of LV structure and function with drugs and devices, rather than the use of direct mechanical interventions to reduce MR.

Despite the apparent consistency of these outcomes, it seems likely that patients with secondary MR represent a heterogenous group, which may include: 1) those whose MR is entirely explained by the global distortions in mitral valve function produced by marked enlargement of the LV cavity; and 2) those in whom the disease process within the LV acts to disproportionately injure the segments of ventricular muscle that support normal mitral valve coaptation. When compared with the former group, the MR in the latter group might not be adequately ameliorated by treatments that aim to achieve a reduction in LV size, and might respond to interventions that directly reduce the degree of MR through mechanical means. Accordingly, the questions that have befuddled cardiologists are: 1) if secondary MR is a disease of the LV, can interventions that target the mitral valve still help in certain patients; and 2) how can we identify the distinct subset of patients that benefits from mitral valve repair?

During the past decade, technological advances have greatly enhanced our ability to characterize the dynamics of MR, allowing quantitative estimation of regurgitant volume as well as the effective regurgitant orifice area (EROA) (8). We can also evaluate the various determinants of MR, including the positioning of the valve leaflets and the geometric and functional distortions created by LV dilatation (9). Most importantly, the results of randomized controlled clinical trials of mitral valve repair in patients with systolic dysfunction have provided critical information about the range of responses to therapeutic interventions that aim to reduce the EROA in different groups of individuals (10–13). The totality of the evidence suggests that we are now able to identify patients with functional MR that benefit from a transcatheter procedure that is directed at the mitral valve.

We propose a new conceptual framework that distinguishes amongst the heterogenous group of patients who have functional MR due to LV disease. Our novel paradigm provides a strong pathophysiological basis for selecting patients for specialized interventions, explains the apparently discordant findings from randomized trials, and can be further tested by analyzing existing databases and performing additional studies.

EVOLUTION OF OUR CHARACTERIZATION OF MR

To explain the rationale for proposing a new framework, it is useful to first consider the merits and deficiencies of existing conceptual approaches that are currently utilized to characterize and quantify MR. Traditionally, physicians have distinguished primary from secondary MR based on: 1) anatomy (i.e., identification of the specific structural defect that caused MR); or 2) time (i.e., elucidation of the sequence of events in an effort to localize the lesion that initiated the disease process). In addition, physicians have attempted to quantify the magnitude of MR either by: 1) measuring the severity of MR by echocardiography; or 2) assessing the presumed effect of regurgitant flow on the clinical course and prognosis of the patient. Each of these approaches to the characterization of MR has important limitations.

PITFALLS OF CHARACTERIZING MR BASED ON ANATOMY OR TIME. It is appealing to think that a careful delineation of anatomy should be able to guide clinical decision-making; for example, if the valve is structurally diseased, then treatment should be directed towards its repair or replacement. However, a pure focus on anatomy can be misleading. In patients with an acute ischemic rupture of the papillary muscle, the mitral valve leaflets are not diseased, but instead, a highly localized injury of the ventricular muscle precipitates the clinical presentation, and surgical replacement or repair of the mitral valve can produce dramatic clinical benefits in this disorder (14). If replacement of the mitral valve stabilizes the clinical course of patients whose principal defect resides in the LV, then any classification that rigidly links treatment to the site of the anatomical lesion may not provide a useful framework for selecting the optimal management for specific patients.

Theoretically, the conceptual difficulties raised by acute ischemic rupture of the papillary muscle could be resolved if patients with MR were classified principally based on the presumed sequence of events over time, rather than anatomy. Specifically, if it could be established that the abnormal regurgitant flow was the initiating event leading to the patient's clinical presentation, then the pathogenesis of the MR could be considered to be valvular, rather than ventricular. Conversely, if an injury to the LV leading to marked chamber enlargement preceded the onset of MR, then the regurgitant lesion might not be considered to be an important determinant of the patient's clinical course. Based on such a framework, in a patient with an acute papillary muscle rupture, the MR would be regarded as the *primary* driving mechanism, even though the disease process did not affect the valve leaflets or chorda tendinae.

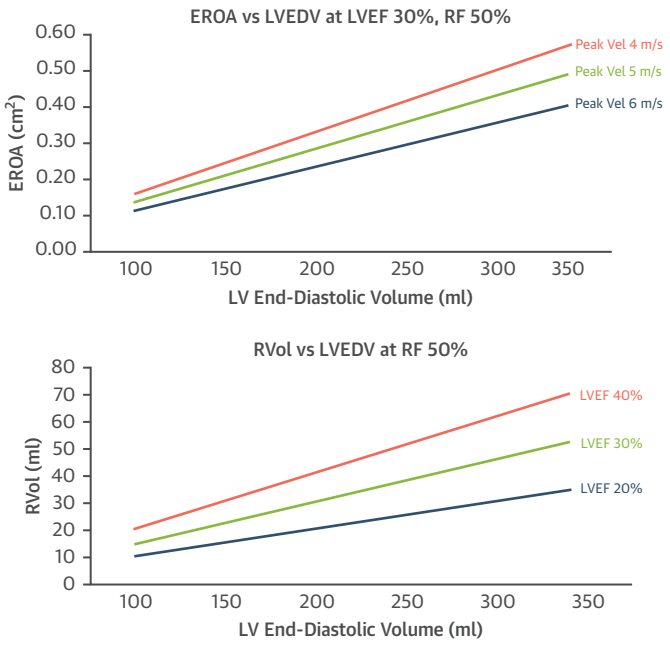
However, as in the case of a conceptual framework based on anatomy, a classification that is based on the sequence of events over *time* has important deficiencies. Many patients present to the clinician for the first time with both significant MR together with meaningful LV dysfunction, and it may be extremely difficult to accurately ascertain the sequence of events. More importantly, it is highly plausible that an LV disorder that causes cardiac dilatation might secondarily but disproportionately injure the muscle that supports normal mitral valve coaptation. In such patients, hemodynamically important degrees of MR could emerge after the onset of ventricular injury and early remodeling, but before the development of the marked ventricular enlargement that (in and of itself) would be sufficient to impair coaptation of the mitral valve leaflets.

CHALLENGES IN QUANTIFYING THE SEVERITY OF MR. Regardless of whether the regurgitant lesion is characterized in terms of anatomy or time, it is important to quantify the volume of mitral regurgitant flow. Minor degrees of MR do not require treatment, whereas severe MR can seriously compromise stroke volume, which may be particularly deleterious if systolic function is already impaired. Consensus documents defining severe MR have consistently used a regurgitant fraction of at least 50%, that is, one-half of the total stroke volume is directed backwards into the left atrium instead of forwards into the aorta (15,16). Given this threshold, we should ask: what measurements performed during 2-dimensional Doppler echocardiography identify patients with a regurgitant fraction of at least 50%?

A popular approach to the quantification of MR by Doppler echocardiography is the calculation of the EROA, most commonly by the proximal isovelocity surface area (PISA) method (15). Guidance from the American Society of Echocardiography (16) suggested that a regurgitant fraction of least 50% generally corresponded to EROA of 0.4 cm^2. However, the calculation of EROA is fraught with difficulties. The PISA method assumes a round office through a flat surface; however, this assumption is often violated in patients who have functional MR because the geometry of the regurgitant orifice is often crescent-shaped; the jets may be eccentric; the proximal convergence zone is often asymmetric; and regurgitant flow changes during systole, typically following a biphasic pattern (9). Furthermore, the EROA often cannot be calculated when the MR is mild; the EROA by 2-dimensional echocardiography may differ from that calculated by 3-dimensional methods; and meaningful changes in the calculation of EROA can be produced by tiny differences in an observer's measurement of the PISA radius (9,17,18). Accordingly, there can be substantial interobserver disagreement in the quantitative assessment of the severity of MR, even when the estimation of EROA by PISA is performed by experts (19).

In part motivated by these uncertainties, guideline documents in 2012 to 2014 proposed that the identification of patients with severe MR might best be carried out not by precise quantification of the visualized regurgitant jet on imaging, but by characterization of the presumed influence of the lesion on the prognosis of afflicted patients (20,21). If a patient with meaningful degrees of MR had a poor prognosis,

FIGURE 1 Relation of EROA and Regurgitant Volume to LVEDV



Influence of LV end-diastolic volume (LVEDV) on the effective regurgitant orifice area (EROA) **(top)** and the regurgitant volume **(bottom)** in patients with a regurgitant fraction of 50% (i.e., the threshold for severe mitral regurgitation). Relationships are depicted based on the Gorlin hydraulic orifice equation. **(Top)** Relationship between EROA and LVEDV assuming LVEF 30% and severe MR with regurgitant fraction (RF) of 50%. Note that EROA is influenced by the square root of the mean systolic pressure gradient between the LV and LA and the systolic ejection period (assumed to be 300 ms). Three different lines are shown for patients in 3 different states of heart failure: **(pink)** a patient with LV peak systolic pressure 160 mm Hg, LA pressure 16 mm Hg, and peak MR velocity 6 m/s; **(green)** a patient with LV peak systolic pressure 120 mm Hg, LA pressure 20 mm Hg, and peak MR velocity (vel) 5 m/s; and **(blue)** a patient with LV peak systolic pressure 90 mm Hg, LA pressure 26 mm Hg, and peak MR velocity 4 m/s. To be most useful, these lines should be depicted in a 3-dimensional space. Nonetheless, the EROA reaches 0.4 cm^2 only at very large LV volumes (>350 ml for **blue**, 275 ml for **green**, and 250 ml for **pink**). Additionally, the EROA is dependent on the pressure gradient between the LV and LA at a given regurgitant fraction. In a typical patient with heart failure (depicted by the **green line**) with an LVEDV 220 to 250 ml, a regurgitant fraction of 50% corresponds to an EROA of 0.30 to 0.35 cm^2. **(Bottom)** Unlike the EROA, the regurgitant volume is not dependent on pressure gradient, but it is dependent on LVEF. Note that regurgitant volume never exceeds 60 ml when the LVEF is 20% to 30%, and exceeds 60 ml in patients with a LVEF of 40% only when the LV is very dilated (i.e., LVEDV >300 ml). When the LVEDV is normal, the regurgitant volume can be below 30 ml even when regurgitant fraction is 50%. When the LVEDV is 220 to 250 ml, severe MR (defined by a regurgitant fraction of 50%) corresponds to a regurgitant volume of 45 ml when the LVEF is 40%, 35 ml when the LVEF is 30%, and <25 ml when the LVEF is 20%.

it was tempting to assume that the regurgitant lesion must be hemodynamically important, even if the calculated EROA suggested only mild-to-moderate MR. As a result, when studies suggested that patients with an EROA ranging from 0.2 to 0.4 cm^2 had similarly unfavorable clinical outcomes during follow-up (22-24), the guidelines issued in Europe in 2012 (20) and in the United States in 2014 (21) both reduced the threshold for the identification of severe functional MR from its earlier value of EROA of 0.4 cm^2 down to a new cutoff value of 0.2 cm^2. This new relaxed threshold was used to define the eligibility criteria for the MITRA-FR randomized controlled trial of transcatheter mitral valve repair (12).

However, any isolated interpretation of the calculated estimate of EROA in an individual patient—whether it is based on echocardiography or its presumed association with clinical outcomes—suffers from the same deficiency: both approaches overemphasize the assessment or importance of events taking place at the level of the mitral valve, and they ignore the critical contribution of LV volume, pressure, and function in determining the hemodynamic severity and long-term prognosis of patients with functional MR (9,25).

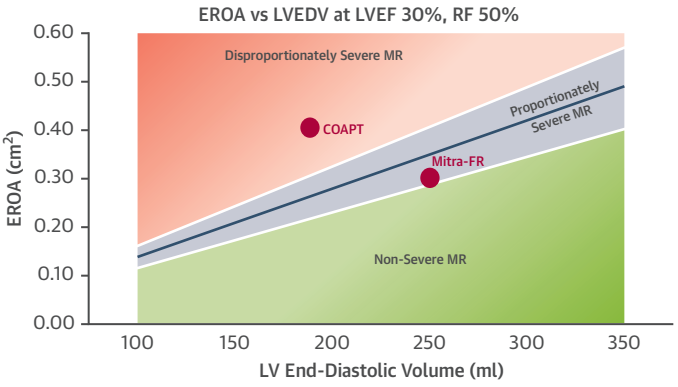
As we have described previously (9), for any given regurgitant fraction, the EROA is dependent on both the left ventricular end-diastolic volume (LVEDV) and the left ventricular ejection fraction (LVEF) (**Figure 1**). If we assume an LVEF of 30% and an LVEDV in the normal range, a regurgitant fraction >50% can be associated with an EROA as low as 0.2 cm^2. However, most patients with chronic heart failure with an LVEF of 30% have meaningful degrees of LV dilatation (e.g., an LVEDV of 200 to 250 ml); in these patients, an estimated EROA of 0.2 cm^2 reflects only modest degrees of MR. In patients with systolic dysfunction and a typically enlarged LV, the regurgitant fraction exceeds 50% only when the EROA is at least 0.3 cm^2. Even higher thresholds of EROA are needed to identify severe degrees of MR if the LVEF is <30% or the LVEDV is over 300 ml. Furthermore, the relationship between EROA and LVEDV is influenced by the mean systolic pressure gradient between the LV and left atrium (LA). Patients with chronic heart failure—who typically have lower systolic blood pressures but higher LA pressures—require very high thresholds for the EROA (e.g., 0.4 cm^2) to reliably identify patients whose regurgitant fraction is at least 50%.

The relationships depicted in **Figure 1** lead to an important conclusion: in patients with a depressed LVEF, meaningful degrees of chamber enlargement, and systolic blood pressures <120 mm Hg, values for EROA of 0.2 cm^2 would indicate the *absence* of hemodynamically important degrees of MR. An EROA of ≤0.2 cm^2 is the inevitable consequence of any degree of impaired leaflet coaptation due to LV enlargement in a nonhypertensive patient who has chronic heart failure with a reduced LVEF. This degree of MR is unlikely to be clinically relevant, in light of evidence that transcatheter mitral valve repair of

patients with functional MR has favorable effects on LV remodeling of a magnitude similar to mitral valve replacement even when the degree of residual MR is 1+ or 2+ following a successful procedure (26).

Ignoring the contribution of LV size and function also can profoundly distort the interpretation of any study that relies on the clinical course of individual patients to estimate the severity of mitral valve dysfunction (16). If meaningful degrees of MR are seen in a patient whose LV has not adversely remodeled (i.e., he or she has an LVEDV in the normal range), the clinical course of the disease can be expected to be primarily determined by the severity of the valvular disorder. However, if the LVEDV is 200 to 250 ml (as is typical for many patients with chronic heart failure and reduced LVEF), the prognosis will be profoundly influenced by the disease process in the LV. An EROA of 0.2 cm^2 in these individuals—indicative of nonsevere MR—may well be associated with a high rate of morbidity and mortality, but the adverse outcome is not related to the degree of MR. In patients whose greatly impaired LV function is the principal cause of an early death, the degree of MR should not be automatically considered to be clinically important simply because the prognosis is poor.

FIGURE 2 Relationship Between EROA and LVEDV Illustrating Domains That Define Disproportionately Severe, Proportionately Severe, and Nonsevere Functional Mitral Regurgitation



Delineation of domains to identify patients with: 1) nonsevere MR; 2) severe MR that is proportional to left ventricular end-diastolic volume (LVEDV); and 3) severe MR that is disproportionate to LVEDV. The diagram depicts the relation between effective regurgitant orifice area (EROA) and LVEDV, assuming an LVEF of 30% with a regurgitant fraction of 50%, as in Figure 1A. The **blue line** represents the hypothetical relationship when the degree of severe MR is proportional to the LVEDV. The **gray area** approximates a degree of uncertainty that is determined by the imprecision inherent in the measurement of EROA as well as the hemodynamic state of the patient (see Figure 1). The **pink area in the upper left** depicts severe MR that disproportionate to LV dilation. The **green area in the lower right** depicts nonsevere MR. The average patient enrolled in the MITRA-FR and COAPT trials is shown by the **red dots**, based on the information made public to date.

PROPOSAL FOR A NEW CONCEPTUAL FRAMEWORK. For purposes of clinical decision-making in functional MR, the critical issue is not to determine whether the mitral valve is the site of the disease process, whether the regurgitant lesion came first, or whether the MR is associated with a poor prognosis. Instead, the principal reason to fully characterize and quantify the determinants of functional MR is to determine if an intervention directed at the mitral valve is capable of changing the clinical course of the disease. In patients with functional MR, the leaflets do not have a major anatomic defect, and the regurgitant jet may emerge late in the clinical course of the disease. However, if reducing the regurgitant volume with mitral valve repair or replacement reduces the risk of death and hospitalization, then (by definition) the magnitude of MR must have been clinically important. Conversely, if an intervention targeted to the mitral valve yields no benefit, it is not reasonable to claim that the MR was clinically significant, regardless of its anatomy or time of onset.

Viewed through this lens, the precise sequence of events that may have led to the clinical presentation of the patient becomes irrelevant. If an intervention directed at the mitral valve changes the natural history of the disease, then the MR should be considered a target for therapy, even if it is "secondary" to LV dysfunction. We propose a novel terminology for identifying such patients. In our framework, physicians should seek to determine whether the estimated degree of MR is expected or *proportionate* to the degree of LV dilatation, or alternatively, whether the severity of MR is unexpected or *disproportionate* to the degree of LV enlargement (Figure 2). Furthermore, it is important to recognize that nonsevere MR (generally corresponding to an EROA ≤0.2 cm^2) is routinely seen in patients with chronic heart failure whose LV end-diastolic volumes exceed 220 ml or 120 ml/m^2 (27,28), and such mild degrees of MR in patients with a dilated LV are not corrected by mitral valve repair (29), especially when the LV systolic dimensions are also increased (27,28). Because they failed to recognize the influence of the LV, the 2012 to 2014 European and U.S. guidelines misclassified an EROA of 0.2 cm^2 in patients with meaningful LV dilatation as severe; fortunately, this error has been corrected in the 2017 update (30).

Figures 1A and 2 normalize the calculated estimate for EROA for the LVEDV, thus making it possible to identify if the MR in a patient or in a population is "proportionate" or "disproportionate" to the degree

of LV dysfunction. Upper and lower bounds need to be defined empirically, given the imprecision of the estimation of EROA and the importance of additional hemodynamic and echocardiographic variables. Nonetheless, the overarching principles depicted in the graph are clear. A patient whose MR severity is consistent with the amount of LV dilatation would fall close to the line of proportionality, and thus, might not be expected to improve following interventions that are directed toward the mitral valve. Conversely, a patient might respond favorably to a mitral valve reparative procedure if he or she had a disproportionately large degree of MR when compared with the degree of LV dilatation. A patient with an EROA/LVEDV ratio well below the line of proportionality has nonsevere MR and would not be expected to benefit from any intervention directed at the mitral valve. Amazingly, the validity of this proposed framework appears to have been inadvertently tested in 2 recently completed randomized controlled trials of mitral valve repair in patients with chronic heart failure, systolic dysfunction, and functional or "secondary" MR.

DESIGN AND RESULTS OF THE MITRA-FR AND COAPT TRIALS

The MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial (NCT01920698) (12) randomly assigned 307 patients with chronic heart failure, a reduced LVEF, and severe secondary MR to undergo transcatheter mitral valve repair or to a control group that did not undergo the procedure. After 12 months, patients who were assigned to mitral valve repair were similar to those in the control group with respect to the risk of death or the risk of hospitalization for heart failure. The hazard ratio was 1.11 (95% confidence interval [CI]: 0.69 to 1.77) for all-cause mortality and 1.13 (95% CI: 0.81 to 1.56) for hospitalization for heart failure. Although the patients who underwent mitral valve repair experienced a short-term reduction in the degree of regurgitant flow, the use of the device did not reduce LV volumes after 1 year.

The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial (NCT01626079) (13) randomly assigned 614 patients with chronic heart failure, a reduced LVEF, and severe secondary MR to undergo transcatheter mitral valve repair or to a control group that did not undergo the procedure. After 2 years, patients who were assigned to mitral valve repair had a lower risk of death from any cause and a lower risk of hospitalization for heart failure. The hazard ratio for all-cause mortality at 2 years was 0.62 (95% CI: 0.46 to 0.82; $p < 0.001$). The hazard ratio for the annualized rate of all hospitalizations for heart failure at 2 years was 0.53 (95% CI: 0.40 to 0.70; $p < 0.001$). In contrast with the findings of the MITRA-FR trial, mitral valve repair led to a significant reduction in LV volumes after 1 year of follow-up.

How can these apparently discordant results be explained? Prior to randomization, medical therapy was supposed to be titrated to maximally tolerated doses in the COAPT trial, but such a requirement was not part of the design of the MITRA-FR study. However, neither trial has reported precisely what medical treatments were used and what doses of specific drugs were achieved. Both trials reported a high prevalence of use of classes of drugs that are known to prolong life, but the use of neprilysin inhibitors in both trials was low. Although it is possible that patients in the MITRA-FR trial received less aggressive medical therapy, we currently have little data to support such a conclusion. Even if it were true, the authors of the COAPT trial have not explained why a difference in background drug treatment would explain the discordant results across the 2 studies. Interestingly, in the COAPT trial—even though medical therapy was supposed to have been maximized prior to randomization—drug treatments were intensified to a greater degree in the device than in the control arms during the follow-up period. This degree of intensification may have been related to the fact that blood pressure increases in many patients who undergo transcatheter mitral valve repair (30), thus potentially allowing for further up-titration of medical therapy. Changes in medical therapy during follow-up in the MITRA-FR trial are yet to be reported.

It might be tempting to propose that regional differences in medical practice might have contributed to the different results of the 2 trials. The MITRA-FR trial was carried out principally by investigators in France, whereas the COAPT trial was executed primarily in the United States and Canada. Were the North American investigators more experienced and more likely to have implanted a successful device? There is no reason to support such speculation. The 2 trials used precisely the same device to reduce MR severity, and the proportion of patients with residual 3+ or 4+ mitral regurgitation immediately following completion of the procedure was <10% in both studies (12,13).

The MITRA-FR and COAPT trials were developed by distinct groups of investigators, and not

unexpectedly, the primary endpoints of the 2 trials were somewhat different, and the studies used slightly different statistical approaches to their analysis of events. The COAPT trial was larger and longer in duration than the MITRA-FR trial, and thus, it recorded more major adverse cardiovascular events. However, the strikingly different findings across the 2 trials cannot be explained by differences in trial design, length of follow-up, or statistical power.

RECONCILING THE FINDINGS OF THE MITRA-FR AND COAPT TRIALS

Intriguingly, an examination of the baseline characteristics of the patients participating in the 2 trials indicates that the studies enrolled 2 distinctly different groups. The MITRA-FR investigators enrolled patients who had striking LV dilatation but relatively modest degrees of MR. Prior to randomization, the mean LVEDV was 252 ml and the mean EROA was 31 mm^2. As can be seen in **Figure 2**, these features are consistent with a degree of MR that is severe, but proportional to the degree of LV dilatation. In contrast, the COAPT investigators primarily enrolled patients in whom the degree of MR was disproportionately great compared with the degree of LV chamber enlargement. Prior to randomization, the mean LVEDV was 192 ml and the mean EROA was 41 mm^2. Therefore, when the patients enrolled in the COAPT trial are compared with those in the MITRA-FR trial, the EROA was approximately 30% higher but their LV volumes were approximately 30% smaller. When these features are displayed in **Figure 2**, it is evident that—in contrast with the patients in the MITRA-FR trial—the patients in the COAPT study had disproportionate degrees of MR.

Differences in the entry criteria for the two trials likely explain why the studies enrolled distinctively different groups of patients. The definition of severe MR in the MITRA-FR trial was based on the 2012 definition specified in the European guidelines (20); 52% of the patients had an EROA <0.3 cm^2, and only 16% had a EROA ≥ 0.4 cm^2. Furthermore, patients with marked LV dilatation were not excluded: 70% of the patients had a LV end-diastolic dimension >65 mm. In contrast, in the COAPT trial, only 14% of the patients had an EROA <0.3 cm^2, but 41% had an EROA ≥ 0.4 cm^2. In addition, the COAPT trial did not allow participation of patients with striking degrees of LV enlargement; that is, those with an end-systolic dimension >70 mm were not eligible for randomization.

Interestingly, the requirement in the COAPT trial that patients receive maximally tolerated medical therapy may also have promoted the inclusion of patients who had disproportionate MR into the study. Effective drug and device treatments for heart failure can have profoundly favorable effects on cardiac remodeling and LV geometry, and thus, these should be expected to reduce the magnitude of MR that is related to LV dilatation (3–5). Therefore, it is possible that patients whose MR was *proportionate* to their LV volumes may have responded so favorably to medical therapy (with respect to the magnitude of regurgitant flow) that they were no longer eligible for participation in the COAPT trial. In contrast, patients with disproportionate MR might not be expected to have their regurgitation be adequately ameliorated by interventions that reduce LV volumes, and thus, these patients may have been preferentially enrolled in COAPT.

In contrast, most of the participants in the MITRA-FR trial appeared to have *proportionate* MR (**Figure 2**), that is, their regurgitant flow was related more to LV dilatation than to a reparable defect in mitral valve coaptation. If the LV is markedly dilated at the time of the procedure and remains so during long-term follow-up (as was the case in the MITRA-FR trial), it may be difficult to achieve and maintain coaptation of the valve leaflets by the use of mechanical clips. Therefore, it seems likely that the marked LV enlargement of the participants—rather than the expertise of the operators—explains the lower rates of procedural success during long-term follow-up. In the COAPT trial, the proportion of patients with 3+ or 4+ MR was 5% immediately following the procedure, and remained unchanged at 5% after 1 year. In contrast, in the MITRA-FR trial, the proportion of patients with 3+ or 4+ MR was 9% after device placement and increased to 17% after 1 year.

Importantly, the results of the 2 trials demonstrate that it is not possible to distinguish patients who have proportionate or disproportionate MR by examining their overall rates for death and hospitalization for heart failure. The annualized rates for these 2 major adverse clinical outcomes were similar in the medically-treated groups in the MITRA-FR and COAPT trials. However, the rate of these events may have been primarily related to LV dysfunction in the MITRA-FR trial but to disproportionate MR in the COAPT trial. Interestingly, in another randomized trial of patients with moderate-to-severe MR, transcatheter mitral valve repair did not reduce MR as effectively as mitral valve surgery. Yet, the percutaneous procedure yielded the most favorable comparative results in patients who had functional MR that was associated with modest impairment of LV function (10,11).

IMPLICATIONS FOR CARDIAC IMAGING

The concepts depicted in **Figure 2** represent true (not measured) values for EROA, LVEDV, and LVEF. Two-dimensional echocardiography is the most widely used imaging technique to measure these parameters in clinical practice and in most clinical trials. However, EROA may be systematically overestimated by PISA because it typically only measures the largest value in systole and assumes a constant value throughout systole (16). Furthermore, 2-dimensional echocardiography is prone to underestimating LV volumes due to foreshortening as well as due to failure to align the imaging plane to the center of the LV cavity and to identify the endocardial borders in all segments. The use of an ultrasound contrast agent can improve accuracy of LV volumes (31), and 3-dimensional echocardiography is currently recommended for LV volume measurement when image quality is good enough to allow visualization of endocardial borders (32). Cine magnetic resonance imaging provides the most accurate and reproducible measurements of LV volumes and LVEF, which can also be assessed by current multidetector computed tomography with single beat acquisition. Generally, MR is quantified by magnetic resonance imaging by comparing LV total stroke volume to forward stroke volume to obtain regurgitant volume and fraction (16,32). Both cine magnetic resonance imaging and computed tomography have been shown to be capable of measuring the anatomic EROA directly (33). Clearly, further studies are needed to determine the best methodology for distinguishing patients with disproportionate from those with proportionate secondary MR and to define optimal thresholds for measured, as opposed to theoretical, values for these parameters.

CONCLUSIONS

If we accept the results of both the MITRA-FR and COAPT trials at face value, then the totality of available evidence suggests that patients with chronic heart failure respond favorably to transcatheter mitral valve repair if they exhibit degrees of MR that are disproportionately greater than might be expected from the degree of LV chamber enlargement. The COAPT trial focused primarily on patients with "disproportionate" MR, and such patients benefitted from mitral valve repair. In contrast, the MITRA-FR trial focused primarily on patients with "proportionate" MR (which was related to LV enlargement and remodeling), and these patients did not benefit from transcatheter mitral valve repair. We should not conclude that the 2 trials enrolled similar types of patients simply because they both focused on individuals with "severe" functional MR who had comparable annualized rates of morbidity and mortality.

Further analyses of the 2 trials are well-positioned to confirm or refute our proposed framework. We expect that—when the patient-level data from the 2 trials are combined—those with disproportionate MR will be shown to benefit from transcatheter mitral valve repair, regardless of whether an individual participated in the COAPT trial or in the MITRA-FR study. We also anticipate that the pretreatment LV volume will be shown to influence the procedural success rates (as defined by absence of MR), particularly in the long-term, thus explaining the higher 1-year rates of meaningful post-procedural MR in MITRA-FR than in COAPT. We hypothesize that the ratio of EROA to LV end-diastolic volume is likely to be useful in individual clinical decision-making, that is, patients with proportionate MR might be highly likely to respond to the optimization of medical therapy, whereas those with disproportionate MR would be most likely to benefit from additional transcatheter repair (34). We look forward to having these hypotheses tested in future analyses. Until then, our proposed framework is consistent with our current understanding of the pathophysiology of MR and is fully concordant with the reported findings of the 2 randomized controlled trials of transcatheter mitral valve repair.

Our proposed framework should not be confused with the term "mixed primary and secondary" MR. The designation of a "mixed" lesion was developed to recognize the existence of more than 1 causal mechanism of MR, but without the ability to provide guidance with respect to the preferred options for treatment. In contrast, our proposal to assess the degree of proportionality or disproportionality in the evaluation of severe MR is intended to define distinct groups within the conventional category of "secondary" or "functional" MR to provide specific recommendations for clinical decision-making. Our framework makes no assumptions about causation.

If our proposed framework is confirmed, it is conceivable that the term "secondary" to characterize MR due to LV dysfunction may have outlived its usefulness. All MR is secondary to an abnormality of 1 or more components of the mitral apparatus, including the LV. "Functional" MR has also been used to

describe MR secondary to LV disease, but the term does not clarify which patients benefit from the mechanical correction of MR or might be better managed with drug or device treatments. Both the degree and the determinants of "secondary" MR are highly dynamic (**Figures 1 and 2**), and current treatments for heart failure modulate these dynamic conditions. In distinguishing valvular from ventricular contributions to MR, the critical question is not whether a lesion is "primary" or "secondary," but whether the magnitude of MR can be explained by the degree of LV dilatation. In patients with severe MR and impaired systolic function, the terms "proportionate" and "disproportionate" help identify which patients benefit from medical treatments that target the LV or from transcatheter interventions that target the mitral valve.

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REFERENCES

1. Carabello B. The current therapy for mitral regurgitation. J Am Coll Cardiol 2008;52:319–26.

2. Gammie JS, Chikwe J, Badhwar V, et al. Isolated mitral valve surgery: the Society of Thoracic Surgeons Adult Cardiac Surgery Database analysis. Ann Thorac Surg 2018;106:716–27.

3. Martens P, Beliën H, Dupont M, Vandervoort P, Mullens W. The reverse remodeling response to sacubitril/valsartan therapy in heart failure with reduced ejection fraction. Cardiovasc Ther 2018; 36:e12435.

4. Nasser R, Van Assche L, Vorlat A, et al. Evolution of functional mitral regurgitation and prognosis in medically managed heart failure patients with reduced ejection fraction. J Am Coll Cardiol HF 2017;5:652–9.

5. Stolfo D, Merlo M, Pinamonti B, et al. Early improvement of functional mitral regurgitation in patients with idiopathic dilated cardiomyopathy. Am J Cardiol 2015;115:1137–43.

6. Smith PK, Puskas JD, Ascheim DD, et al., for the Cardiothoracic Surgical Trials Network Investigators. Surgical treatment of moderate ischemic mitral regurgitation. N Engl J Med 2014; 371:2178–88.

7. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med 2014; 370:23–32.

8. Grayburn PA, Weissman NJ, Zamorano JL. Quantitation of mitral regurgitation. Circulation 2012;126:2005–17.

9. Grayburn PA, Carabello B, Hung J, et al. Defining "severe" secondary mitral regurgitation: emphasizing an integrated approach. J Am Coll Cardiol 2014;64:2792–801.

10. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364:1395–406.

11. Glower DD, Kar S, Trento A, et al. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. J Am Coll Cardiol 2014;64:172–81.

12. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018 Aug 27 [E-pub ahead of print].

13. Stone GW, Lindenfeld J, Abraham WT, et al., for the COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018 Sept 23 [E-pub ahead of print].

14. Doi T, Nagura S, Fukahara K, Yoshimura N. Surgical treatment of complete anterolateral papillary muscle rupture following acute myocardial infarction. Ann Thorac Cardiovasc Surg 2014; 20 Suppl:926–8.

15. Dujardin KS, Enriquez-Sarano M, Bailey KR, Seward JB, Tajik AJ. Grading of mitral regurgitation by quantitative Doppler echocardiography: calibration by left ventricular angiography in routine clinical practice. Circulation 1997;96: 3409–15.

16. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303–71.

17. Patel JB, Borgeson DD, Barnes ME, Rihal CS, Daly RC, Redfield MM. Mitral regurgitation in patients with advanced systolic heart failure. J Card Fail 2004;10:285–91.

18. Shanks M, Siebelink HMJ, Delgado V, et al. Quantitative assessment of mitral regurgitation: comparison between three-dimensional transesophageal echocardiography and magnetic resonance imaging. Circ Cardiovasc Imaging 2010;3: 694–700.

19. Biner S, Rafique A, Rafii F, et al. Reproducibility of proximal isovelocity surface area, vena contracta, and regurgitant jet area for assessment of mitral regurgitation severity. J Am Coll Cardiol Img 2010;3:235–43.

20. Vahanian A, Alfieri O, Andreotti F, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg 2012;42:S1–44.

21. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2438–88.

22. Grigioni F, Enriquez-Sarano M, Zehr KJ, Bailey KR, Tajik AJ. Ischemic mitral regurgitation: long-term outcome and prognostic implications with quantitative Doppler assessment. Circulation 2001;103:1759–64.

23. Lancellotti P, Troisfontaines P, Toussaint AC, Pierard LA. Prognostic importance of exercise-induced changes in mitral regurgitation in patients with chronic ischemic left ventricular dysfunction. Circulation 2003;108:1713–7.

24. Rossi A, Dini FL, Faggiano P, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and nonischaemic dilated cardiomyopathy. Heart 2011;97:1675–80.

25. Marwick TH, Zoghbi WA, Narula J. Redrawing the borders: considering guideline revision in functional mitral regurgitation. J Am Coll Cardiol Img 2014;7:333–5.

26. Grayburn PA, Foster E, Sangli C, et al. The relationship between the magnitude of reduction in mitral regurgitation severity and left ventricular and left atrial reverse remodeling after MitraClip therapy. Circulation 2013;128:1667–74.

27. Oh JK, Pellikka PA, Panza JA, et al. Core lab analysis of baseline echocardiographic studies in the STICH trial and recommendation for use of echocardiography in future clinical trials. J Am Soc Echocardiogr 2012;25:327–36.

28. Golba K, Mokrzycki K, Drozdz J, et al. Mechanisms of functional mitral regurgitation in ischemic cardiomyopathy determined by transesophageal echocardiography (from the Surgical Treatment for Ischemic Heart Failure Trial). Am J Cardiol 2013;112:1812–8.

29. Capoulade R, Zeng X, Overbey JR, et al. Impact of left ventricular to mitral valve ring mismatch on recurrent ischemic mitral regurgitation after ring annuloplasty. Circulation 2016;134:1247–56.

30. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: a report of the American College of Cardiology/American Heart Association

Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252–89.

31. Hundley WG, Kizilbash AM, Afridi I, Franco F, Peshock RM, Grayburn PA. Administration of an intravenous contrast agent improves echocardiographic determination of left ventricular volumes and ejection fraction: a comparison with cine magnetic resonance imaging. J Am Coll Cardiol 1998;32:1426–32.

32. Lang RM, Badano LP, Tsang W, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. J Am Soc Echocardiogr 2012;25:3–46.

33. Thavendiranathan P, Phelam D, Collier P, Thomas JD, Flamm SD, Marwick TH. Quantitative assessment of mitral regurgitation: how best to do it? J Am Coll Cardiol Img 2012;5:1161–75.

34. Packer M, Meller J, Medina N, Gorlin R, Herman MV. Importance of left ventricular chamber size in determining the response to hydralazine in severe chronic heart failure. N Engl J Med 1980;303:250–5.

KEY WORDS clinical trials, heart failure, mitral regurgitation