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EDITORIAL COMMENT

Guideline-Directed Medical Therapy for Secondary Mitral Regurgitation

More Questions Than Answers!*

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Secondary (also known as functional) mitral regurgitation (MR) is common in heart failure patients. Secondary MR is not caused by a primary abnormality of the mitral leaflets but rather to dilation/dysfunction of the left ventricle (LV). As a result, there is apical-lateral displacement of the papillary muscles resulting in tethering of the mitral leaflets and subsequent failure of anatomically normal leaflets to coapt (1). Secondary MR results in further LV volume overload and a resulting vicious cycle of more severe MR leading to further LV dilation and congestive heart failure. This mechanism of MR is termed type IIIb in the Carpentier classification of mitral valve leaflet motion and can be due to both ischemic and nonischemic dilated cardiomyopathies (2). The mainstay of therapy is guideline-directed medical therapy (GDMT) for heart failure including diuretics, beta blockers, aldosterone antagonists, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocking agents. It is an area of intense interest in the fields of surgery and medical device therapy because of the overall poor prognosis with medical therapy alone. Although it is widely recognized that secondary MR is associated with a worse prognosis in heart failure patients, it remains uncertain whether surgical correction of the MR and breaking the "vicious cycle" changes the dismal course of the disease.

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Some insight to the natural history of secondary MR and the response to medical therapy is provided by the study by Nasser et al. (3) in this issue of *JACC: Heart Failure*. They studied the course of patients with "severe" MR in patients with heart failure with reduced ejection fraction (HFrEF) in whom GDMT was titrated to optimally tolerated doses. Specifically, they followed 163 patients with HFrEF for a period of 56 months (range 13 to 94 months) and categorized MR as severe or nonsevere. All patients were treated with maximally tolerated doses of GDMT including diuretics, beta blockers, aldosterone antagonists, and angiotensin-converting enzyme inhibitor/angiotensin receptor blocking agents. The primary endpoint was major adverse cardiac events defined as a composite of all-cause death, need for heart transplantation or hospitalization for heart failure and/or malignant arrhythmia. Fifty patients (31%) had severe MR at baseline and 38% of these patients showed improvement in the severity of the MR. However, 18% of patients with nonsevere MR progressed to severe MR. The study found that the presence of sustained severe or worsening MR was an independent predictor of a poor prognosis and of continuing LV dilation. Nasser et al. (3) conclude that severe secondary MR can be successfully treated with medication in almost 40% of patients with prevention of LV adverse remodeling and an improved prognosis.

What are the main findings of this study, and how should these findings inform clinical management of heart failure patients?

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1. Severe secondary MR was present in 30% of this population with HFrEF treated in a heart failure clinic. This estimated prevalence is far higher than that seen in clinical practice because Nasser et al. (3) used an effective regurgitant orifice area of 0.2 cm^2 and vena contracta width of 0.4 cm, values that current guidelines define as moderate, not severe MR (4,5). Although severe MR can be present at lower values if the orifice area is crescent-shaped, or LV volumes are small (6), it is more likely that Nasser et al. (3) have evaluated differences between mild MR and moderate or severe MR. In a recent meta-analysis of 53 studies of the effects of secondary MR on outcomes, moderate and severe MR were almost always lumped together because the latter is uncommon (7).
2. Almost 40% of patients with HFrEF and "severe" MR experience reduction in MR severity with GDMT. It should be noted that this is a very small number of patients (19 of the 50 who started with more than mild MR) and, therefore, should be interpreted with caution. Conversely, almost 20% of patients with nonsevere secondary MR have progression of MR despite GDMT.
3. Even in the setting of an advanced heart failure clinic, patients can tolerate only ~50% of maximal doses of heart failure medications, such that up-titration to recommended GDMT doses was not routinely possible.
4. Diuretic therapy with fluid and salt restriction appears to play a major role in correction of severe secondary MR and prevention of further adverse LV remodeling as evidenced by improvement in the restrictive filling pattern and MR severity.
5. In <5 years, 31% of patients had died and 91 of 163 patients (56%) suffered a major adverse cardiac event. This confirms the known prognostic importance of secondary MR in HFrEF. Importantly, even mild MR confers an adverse prognosis in HFrEF, although worsening MR grade is associated with worsening outcomes (7).

What are the questions regarding the management of patients with severe secondary MR that need to be further answered?

1. Can the nonresponders to medical therapy, or patients who will undergo progression of secondary MR severity, be identified earlier in the course of their disease?
2. Is device or surgical correction of secondary MR an alternative to or perhaps additive to medical therapy for secondary MR, and is there a benefit of such therapy on survival or quality of life? Should such therapies be limited to patients who do not respond to medical therapy or progress despite medical therapy?
3. Is severe MR merely a marker of more severe LV dysfunction? In the Nasser et al. (3) study and the Sannino et al. (7) meta-analysis, LVEF was lower in patients with higher grades of secondary MR. This contradicts the known favorable hemodynamic influence of MR on LVEF, and suggests that LV myocardial contractility may be significantly worse in patients with secondary MR than can be detected by LVEF. Of note, LV volumes were larger in patients with secondary MR, but they were not included in the multivariate analysis of predictors of outcomes. This is a significant limitation.
4. Does correction of secondary MR by any means break the vicious cycle of LV volume overload and progression of LV dilation causing worsening of MR, or is it a marker of irreversible LV dysfunction?
5. Do ischemic and nonischemic dilated cardiomyopathies respond similarly?
6. Do other types of secondary MR such as those due to annular dilation associated with atrial fibrillation (Carpentier type I) with normal LVEF respond in a like manner to medical therapy or device or surgical intervention?

There are some insights as to the response of severe secondary MR to surgical intervention from the National Institutes of Health-sponsored CTSN (Cardiothoracic Surgical Trials Network) trial of severe MR (8). Patients with severe ischemic secondary MR were randomized between surgical mitral valve repair with an undersized annuloplasty ring and valve-sparing mitral valve replacement. There was no medical therapy control arm for comparison; however, the trial was able to demonstrate improvement in LV remodeling especially in patients with a durable valve repair.

Hopefully additional clinical questions can be further answered by the findings of the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; NCT01626079) trial. In this trial, 614 patients were randomized between GDMT alone and GDMT plus the MitraClip device (Abbott Vascular, Santa Clara, California) for correction of severe secondary MR. The primary effectiveness endpoint is recurrent heart failure hospitalizations over 24 months. The results of the trial will be available late in 2018 and should provide important additional information regarding the effectiveness and prognosis of secondary MR treated with GDMT, including cardiac resynchronization and

coronary revascularization in appropriate patients. Also, hopefully we can gain meaningful insight as to the role that device therapy adds to GDMT in heart failure patients with severe secondary MR. However, the dire prognosis of secondary MR has been shown in the recently reported national U.S. registry of patients treated with the MitraClip device (9). In 297 patients with secondary MR treated with MitraClip (off-label), the 1-year mortality was 31.2% and rate of a composite of death and heart failure rehospitalization was 49%. Clearly we have a lot more to learn.

In summary, secondary MR is common in HFrEF patients and portends a poor prognosis. In the Nasser et al. study (3), almost 40% of patients treated with GDMT had improvement in MR severity; whereas almost 20% had progression of MR severity. Larger studies are needed to confirm whether response of secondary MR to GDMT is an independent predictor of favorable LV remodeling and prognosis. To date, no study has convincingly shown a survival benefit to correcting secondary MR with transcatheter or surgical therapies. However, it is conceivable that stratification of patients based on response to GDMT might identify patient groups that may benefit from such therapies. Although the study by Nasser et al. (3) has helped shed further light on the treatment of these patients, we are still left with more questions than answers.

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