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EDITORIAL COMMENT

Treatment for Mitral Regurgitation

Which One Are We Talking About?*

Blase A. Carabello, MD

As emphasized in the 2014 American College of Cardiology/American Heart Association guidelines for the treatment of valvular heart disease (1), primary (degenerative) and secondary (functional) mitral regurgitation (MR) are 2 nearly separate diseases with different definitions, different therapies, and different outcomes. For primary MR, the disease is MR. Restoration of mitral competence with mitral repair removes the hemodynamic burden responsible for the eventual deterioration in left ventricular (LV) function, may restore LV function if it was already depressed, and improves both the quality of life and longevity (2–7).

In secondary MR, the MR is the consequence of other diseases that have injured the LV. Not surprisingly, curing MR does not cure the myocardial infarctions or dilated cardiomyopathy that caused the MR in the first place. Thus, restoration of mitral competence in this disease does not convincingly improve longevity, although it does improve quality of life (8–10). In a recent trial randomizing patients with secondary MR to receive mitral repair versus mitral valve replacement, the 1-year mortality was 15%, and mitral repair, the gold standard of therapy for primary MR, was no better than mitral valve replacement (10), reflecting the differences in therapy for the 2 diseases.

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With that background, 2 papers in this issue of the *Journal* report the results of percutaneous repair using the MitraClip, a device that reduces MR by apposing the two mitral leaflets at their midsections (11,12).

THERAPY FOR PRIMARY MR

As noted above, mitral valve repair is the preferred therapy for treating primary MR. Repair maintains LV function and can restore lifespan to normal when practiced in expert hands and when timed before severe LV dysfunction has been allowed to occur (5,13–15). That said, we must look at our collective selves as a cardiovascular community in the mirror. A substantial number of cardiologists do not know the importance of repair, the triggers for referral to a surgeon, or the repair rate in their own hospitals (16). Additionally, unfortunately, although some centers accomplish very high repair rates (17), a recent query of the Society of Thoracic Surgeons (STS) database found that the average U.S. surgeon repaired less than 50% of mitral valves on which they operated, and on average, U.S. surgeons performed fewer than one-half a dozen mitral operations of any kind in a year (18). Contrasting this finding with coronary revascularization, how many cardiologists would refer his/her patient to a surgeon that used the internal mammary artery to bypass the left anterior descending artery <50% of the time and performed only 6 coronary surgeries per year? Enter the MitraClip as a potential alternative to the low surgical repair rates noted above. Lim et al. (11) report the early and 1-year outcomes of 127 patients with primary MR treated with the MitraClip, who were judged to be at prohibitive risk for surgery. By far, the most impressive finding in this elderly group of very ill patients was their improvement in their quality of life. Of the 75% who survived to 1 year, SF-36 scores and NYHA functional class improved dramatically. As there was neither a medical nor surgical control group, we cannot know how "clip" therapy might have compared to those therapies. Although there is no

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From the Icahn School of Medicine, Mt. Sinai Beth Israel Department of Cardiology, New York, New York. Dr. Carabello has reported that he has no relationship with industry relevant to the contents of this paper to disclose.

medical therapy for primary MR per se, there are indeed standard therapies for heart failure. These therapies are generally recommended even when heart failure is caused by primary MR, but their success in this disease is unknown because patients with severe valvular heart disease have been excluded from heart failure trials. Although the use of these therapies is not discussed, they should at least be considered when heart failure intervenes in primary MR. How patient outcomes in this study would have compared with those of standard surgical mitral repair is obviously unknown.

The authors' determination of prohibitive risk seems fair, but pulmonary hypertension and risk of aspiration seem somewhat arbitrary as many patients with either condition can undergo an operation safely, albeit at higher than average risk. Furthermore, the fact that a few patients underwent surgery vitiates the term prohibitive because Webster defines "prohibitive" as "serving as to preclude the use of something." Obviously, surgery was not precluded. It has become obvious that no risk score fully can account for all the variables that enter into the risk of surgery, although the STS score seems to give a good, although often overestimated, appraisal of risk (19). Regardless, no score should supersede the judgment of a heart team that takes into account both the tangible and intangible factors that contribute to surgical risk, and in the patients reported here, surgery was considered infeasible. That said, we in the medical community must do a better job of standardizing our terminology. Different device trials now use the terms inoperable, extreme risk, high risk, prohibitive risk, and intermediate risk to classify risk, yet patients of similar risk in 1 trial might be categorized quite differently in another.

Mitral regurgitation was reduced but not eliminated by MitraClip therapy, but it does not necessarily have to be. Animal data demonstrate, and human data suggest, that reduction in MR severity to a regurgitant fraction of approximately one-third (moderate MR) allows for reverse remodeling and improved muscle function, if it was previously depressed (20,21). The problem with leaving the patient with this much MR is that it predicts eventual recurrence of severe MR. However, this is not of particular concern in the aged patients in this study, where impaired longevity of the patient reduced the need for repair durability. Nonetheless, we must take a cautionary note from Lim et al. (11) when severe MR remains after the procedure. When patients were discharged with grade 3+ or 4+ MR, their 1-year mortality exceeded 50%, an extraordinarily high figure. While there is no way to know if there was a cause-and-effect relationship, operators must at least consider this statistic.

THERAPY FOR SECONDARY MR

The ultimate therapy for secondary MR should be to restore the contractile elements or the force generation of those elements, thereby returning ventricular function to normal, allowing the LV to remodel in such a way as to restore mitral competence. Although such therapies hold promise for the future, they currently are unavailable for general use. Accordingly, we treat patients with secondary MR by using guideline-driven therapies for the heart failure that the patients almost inevitably have. This distinction for secondary MR patients derives from the fact that MR is not the primary cause of heart failure but rather a complication of it. Not surprisingly, surgery has produced disappointing results with regard to increasing lifespan, because it does not cure the loss of contractility that caused the MR in the first place (8–10). However, surgery does improve symptoms in some but not all cases. Thus, the bar for treating this disease is much lower than it is for primary MR. Accordingly, it is harder to draw conclusions from the paper by Glower et al. (12), where patients with the 2 different diseases were admixed (70% had functional MR) (13). High risk was defined by both the STS score and/or the presence of pre-specified risk factors. Thirty-day mortality (4.8%) and 1-year mortality (23%) were remarkably similar to the pure primary MR group reported by Lim et al. (11). Eighty-six percent had post-procedure MR severity of moderate or less. As in the study by Lim et al. (11), there was significant improvement in quality of life following the "clip" procedure. Although in this study, it was impossible to tease out differences in primary and secondary MR, which surely existed, future reports will surely be aimed at this discrimination.

WHAT HAVE WE LEARNED FROM THESE STUDIES?

The 2 studies noted above demonstrate that reduction in MR improves the quality of life in patients at increased risk for surgical repair. They clearly demonstrate the efficacy of a new tool to treat such patients. They also suggest a "threshold" phenomenon for the reduction of MR to have beneficial effects. Thus, we can treat inoperable patients without entirely correcting MR in the short run. Although allowing the persistence of mild to moderate MR is not wise in patients expected to have extended

longevity because of the likelihood of recurrent severe MR, in elderly patients and those with multiple comorbidities, the presence of post-procedure mild to moderate MR does not prevent a positive outcome. For secondary MR, where there is no proof that surgery prolongs life, this less invasive therapy would appear ideal. Two trials underway (COAPT [Cardiovascular Outcomes Assessment of the MitraClip Therapy Percutaneous Therapy for High Surgical Risk Patients] and RESHAPE [A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation]) should help clarify the therapeutic position of the MitraClip in patients with secondary MR.

In the future, to fully understand the role of percutaneous MR repair, we must study it separately in the 2 very different diseases for which it is being applied, so we can define its role in primary versus secondary MR. Furthermore, we must more precisely define our terms used to stratify risk in randomized trials to fully apply the trial results to our patients.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Blase A. Carabello, Mount Sinai Beth Israel, Department of Cardiology, Cardiology-5th Floor-Baird Hall, 350 East 17th Street, New York, New York 10003. E-mail: bcarabello@chpnet.org.

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