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EDITORIAL COMMENT

Percutaneous Direct Annuloplasty

Lessons From an Early Feasibility Trial*

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Over the last decade, advances in percutaneous therapies have resulted in more treatment options for patients with valvular heart disease. The success of transcatheter aortic valve replacement has stimulated the field of interventional treatment for other valve diseases, particularly mitral regurgitation (MR) (1). The MitraClip (Abbott Vascular, Santa Clara, California) is the only Food and Drug Administration–approved therapy for the transcatheter treatment of MR at this time, with a restricted indication for a small group of degenerative MR (DMR) patients who are at prohibitive risk for surgery (2). Functional MR (FMR), which is the more common form of MR, is the most important target for transcatheter intervention due to a clinically significant unmet need (3).

Innovation in percutaneous mitral therapies has fundamentally different requirements in comparison to aortic therapies. First, surgical treatment for FMR has not proven improved survival compared with medical management, hence surgical mitral valve (MV) repair or replacement for FMR has a Class IIb indication in most of the guidelines (4). Therefore, percutaneous mitral therapies do not have a surgical benchmark to follow. Furthermore, the treatment effect of reducing FMR on mortality may be difficult to demonstrate because survival in most FMR patients may be primarily determined by the underlying left ventricular (LV) dysfunction and not by the mitral regurgitation itself. Therefore, therapies targeting MV have to rely on showing improvement in more subjective endpoints such as New York Heart Association Class and reducing hospitalizations.

Despite these challenges, the field is rapidly progressing with several different percutaneous repair and replacement options for MR. In this issue of the *Journal*, Nickenig et al. (5) present initial safety and efficacy data from early feasibility trial of 71 patients using the novel and promising Mitralign system (Mitralign, Tewksbury, Massachusetts). Mitralign is a direct annuloplasty system whereby plication sutures are placed in the posterior annulus (P1 and P3 region) to decrease the annular size. These sutures are placed from the LV side using 14-F arterial access. Radiofrequency energy is used to deploy the needles and sutures as demonstrated by the illustration in the paper. In this feasibility study, 50 of 71 (70%) patients had implantation of at least 1 pledget. Thirty-day follow up data were presented for 45 patients (63% of initial intention-to-treat [ITT] cohort) and 6-month clinical follow-up was presented for 30 patients (42% of ITT). This is a limitation of the current manuscript where safety and efficacy endpoint analysis is not presented by ITT, which is critically important for an early feasibility study. Although some of this information is available in the supplemental material, it is difficult to understand the impact and reasoning for crossover or unsuccessful procedures in relation to the limitations of the technology or issues related to patient selection.

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To place the current data in context, and properly identify salient points moving forward in the investigation of new devices for the percutaneous treatment of FMR, we must understand the key questions:

WHICH FMR PATIENTS SHOULD BE TARGETED FOR TREATMENT?

This is an important question that requires several considerations. The design for an early feasibility or

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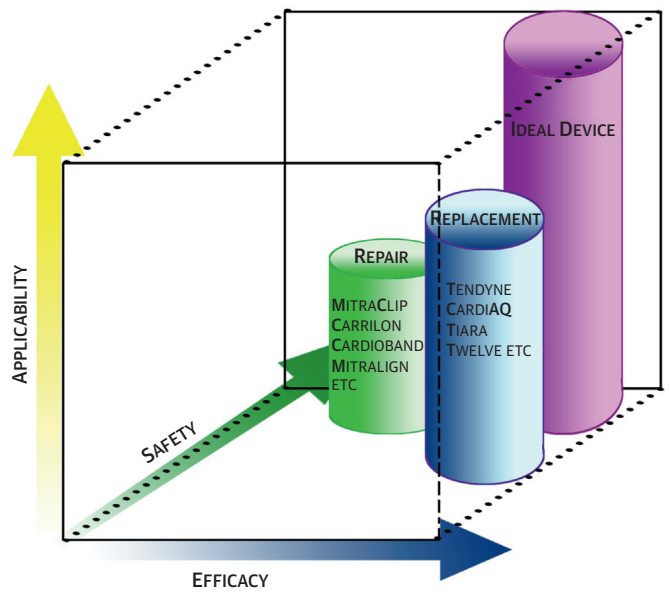
pivotal trial may be different based on the perceived safety and efficacy of the investigational device. Symptom status, FMR severity, mechanism of FMR, and cardiac comorbidities are important considerations. Early feasibility should be tested in very symptomatic patients who are the most likely to respond to the device that is being tested and have "bailout" options. In the current study, severity of symptoms was not part of the inclusion criteria (40% with New York Heart Association functional class II), and that may have impaired the ability to detect a treatment effect especially with limited follow up. The severity of MR is another important point to consider. In the current study 25% of the initial 71 patients had 2+ MR. Unlike DMR patients, FMR patients do not always have a large regurgitant volume or orifice area. Because a smaller regurgitant orifice area and/or regurgitant volume have been associated with poor outcome, the argument has been made to treat patients with moderate but "significant" FMR. This approach has led to heterogeneity in the studied populations and makes comparison between studies difficult. Furthermore, quantification of MR with different parameters is also dependent on the quality of the imaging studies and loading conditions, which add to heterogeneity.

The mechanism of regurgitation in FMR patients can be quite different. Typical mechanisms include 1 or a combination of 4 possible pathologies: 1) annular dilation due to left atrial or LV chamber enlargement; 2) apical leaflet tethering due to LV dilation; 3) leaflet tethering due to myocardial infarction (most commonly due to inferior infarct); and 4) mitral annular calcification and leaflet calcification resulting in restricted motion and malcoaptation of the leaflets. Different repair technologies may be more or less effective in certain subgroups. Therefore, it is important to take into account the specific mechanism to properly understand the strengths and limitations of a particular technology (6). In the current report, it is not clear if the Mitralign was more effective in treating a particular mechanism of MR.

Finally, FMR is associated with cardiac dysfunction at several levels including impaired contractility of LV, diastolic dysfunction, conduction abnormality, tricuspid regurgitation, atrial fibrillation, pulmonary hypertension, right ventricular dysfunction, and coronary artery disease—to name a few. It is important to standardize treatments for these abnormalities and carefully select patients based on these comorbidities to avoid confounding. This is particularly important for pivotal trials where the new treatments are compared with optimal medical therapy and functional outcomes are likely to be the primary endpoint.

FIGURE 1 Adoption of Percutaneous MV Technology Determined by Safety, Efficacy, and Applicability for Different Anatomy



The ideal device is safe and effective, and can be used for large number of patients with functional mitral regurgitation (FMR). Mitral valve (MV) replacement may be more effective and generally applicable to different FMR mechanisms than repair technologies, but risk may be higher. Larger experience with each device will allow a better determination of relative safety, efficacy, and applicability and the possibility of comparison between devices.

WHAT SHOULD BE CONSIDERED EFFECTIVE FOR FMR PATIENTS?

In FMR patients, the contribution of MR to symptoms is not always clear due to other cardiac comorbidities. Further, improvement in symptoms is very difficult to prove because of their subjective nature. Therefore, because double-blind assessment is almost impossible and there is potential for a placebo effect, symptom improvement by itself cannot be used as a sole reliable endpoint. Rehospitalization is another useful measure, but again it has limitations related to the evolving need for in-hospital treatment for heart failure exacerbations. Importantly, for the rehospitalization endpoint, adjustment of medical therapy can be viewed as a confounding factor, although effective reduction in MR with interventional devices may allow for higher doses of vasodilators and beta-blockers and this may represent device success rather than a confounding benefit from change in medical therapy. In addition, echocardiographic