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THE PRESENT AND FUTURE

CLINICAL STATEMENTS

Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 1: Clinical Trial Design Principles

A Consensus Document From the Mitral Valve Academic Research Consortium

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ABSTRACT

Mitral regurgitation (MR) is one of the most prevalent valve disorders and has numerous etiologies, including primary (organic) MR, due to underlying degenerative/structural mitral valve (MV) pathology, and secondary (functional) MR, which is principally caused by global or regional left ventricular remodeling and/or severe left atrial dilation. Diagnosis and optimal management of MR requires integration of valve disease and heart failure specialists, MV cardiac surgeons, interventional cardiologists with expertise in structural heart disease, and imaging experts. The introduction of transcatheter MV therapies has highlighted the need for a consensus approach to pragmatic clinical trial design and uniform endpoint definitions to evaluate outcomes in patients with MR. The Mitral Valve Academic Research Consortium is a collaboration between leading academic research organizations and physician-scientists specializing in MV disease from the United States and Europe. Three in-person meetings were held in Virginia and New York during which 44 heart failure, valve, and imaging experts, MV surgeons and interventional cardiologists, clinical trial specialists and statisticians, and representatives from the U.S. Food and Drug Administration considered all aspects of MV pathophysiology, prognosis, and therapies, culminating in a 2-part document describing consensus recommendations for clinical trial design (Part 1) and endpoint definitions (Part 2) to guide evaluation of transcatheter and surgical therapies for MR. The adoption of these recommendations will afford robustness and consistency in the comparative effectiveness evaluation of new devices and approaches to treat MR. These principles may be useful for regulatory assessment of new transcatheter MV devices, as well as for monitoring local and regional outcomes to guide quality improvement initiatives. (J Am Coll Cardiol 2015;66:278–307) © 2015 by the American College of Cardiology Foundation.

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Mitral regurgitation (MR) is the most prevalent valvular disease in the United States and Europe, and along with aortic stenosis, is one of the most frequent valve disorders referred for surgical correction (1–4). In contrast to aortic stenosis, which is typically characterized by severe and homogenous cusp calcification, MR is heterogeneous in etiology, mechanisms, and pathoanatomy. MR may develop either from primary pathology involving any of the components of the mitral valve (MV) apparatus (primary MR, also known as organic MR, usually due to degenerative MV disease) or arise secondarily to left ventricular (LV) dysfunction or occasionally from left atrial (LA) dilation (secondary MR, also known as functional MR) (1,2,5–7). Surgical MV repair is the recommended approach for severe primary MR, with a recently accepted role for transcatheter repair for patients who are at very high or prohibitive surgical risk (1,2,8). Conversely, secondary MR is typically treated with medications and (if indicated) biventricular pacing for heart failure, and coronary revascularization when appropriate, with the utility of MV surgery and transcatheter devices representing active areas of investigation (8). Few randomized trials, however, have been performed to evaluate the safety and efficacy of MV therapies. The introduction of transcatheter MV devices and the performance of a randomized trial comparing 1 such device to MV surgery (8) have exposed the complexities required to properly evaluate MR therapies, specifically regarding the appropriate study population and control group, background medications and procedures, efficacy and safety endpoints, learning curve issues, and analysis cohort and statistical considerations (8,9). Moreover, although the outcomes of patients with MV disorders are sometimes tracked at single centers (10,11) or in national databases (12,13), no standardized endpoints and definitions have been proposed to provide consistency and uniform interpretability of reported results.

The Academic Research Consortium was organized as a collective endeavor between leading academic research organizations and physician-scientists to reach consensus as to what constitutes meaningful clinical endpoints and definitions for evaluation of cardiovascular devices (14). In collaboration with the U.S. Food and Drug Administration (FDA) and supported by device manufacturers, prior Academic Research Consortium initiatives have addressed consensus endpoints for events following percutaneous coronary intervention and transcatheter aortic valve replacement (TAVR) (15–17), as well as

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bleeding definitions (18), and have been adopted to improve the uniformity and interpretation of clinical studies (19). The Mitral Valve Academic Research Consortium (MVARC) working group was therefore assembled to develop endpoint definitions for clinical studies of MR therapies. In addition, given the complexity of issues that must be considered for MV trials, MVARC has also developed design principles for

ABBREVIATIONS AND ACRONYMS

FDA = U.S. Food and Drug Administration

GDMT = guideline-directed medical therapy

LA = left atrial

LV = left ventricular

LVEF = left ventricular ejection fraction

MR = mitral regurgitation

MV = mitral valve

MVARC = Mitral Valve Academic Research Consortium

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

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