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Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement: Part 2: Endpoint Definitions

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;66:308–21) © 2015 by the American College of Cardiology Foundation.

Part 1 of this consensus document from the Mitral Valve Academic Research Consortium (MVARC) focused on the pathophysiology, prognosis, and clinical trial design principles recommended for investigating mitral valve (MV) disease, in particular primary and secondary causes of mitral regurgitation (MR), to ensure that completed studies provide reliable evidence for regulatory

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evaluation and to guide clinical care decision-making (1). Equally important is the assessment of clinically relevant endpoints reflecting the safety and efficacy of MR therapies and the use of consensus definitions to ensure that such endpoints are meaningful and consistent across studies (2). In addition to randomized trials, the use of consistent definitions is important for observational and administrative databases that lack a concurrent control. Academic Research Consortium (ARC) consensus endpoints have been introduced for drug-eluting stents (3), for transcatheter aortic valve replacement (TAVR) (4,5), and for bleeding complications (6), and have been adopted to improve the cross-evaluation of studies (7).

SEE PAGE 322

As discussed in part 1 of this document, MVARC recommends that all primary and major secondary endpoint events within the clinical trial framework are adjudicated utilizing pre-specified definitions by an independent committee using original source documents (1). Given the varied nature of these events, depending on the specific study, the adjudication committee should ideally include a heart failure specialist, a cardiologist specializing in MV disease, an interventional cardiologist skilled in structural heart disease interventions (ideally MV procedures), an experienced MV cardiac surgeon, an imaging specialist, and a stroke neurologist. For tracking outcomes of MV interventions in nonrandomized clinical studies or in administrative databases, for cost or logistical reasons it may not be possible to employ an independent central adjudication committee. In such cases, the use of uniform definitions will at least ensure consistency over time and across studies.

Table 1 contains the list of endpoints relevant to mitral interventions that should be collected in all patients and adjudicated, if possible. The MVARC-recommended definitions for these events are reviewed in this document. Other important secondary endpoints, including quality-of-life measures, functional performance, and echocardiographic assessments, are discussed in part 1 of this document (1). Where possible, MVARC has endeavored to align these consensus definitions with other professional society and organization efforts (with greater granularity, when necessary, specific to MR therapies), while incorporating the latest knowledge from clinical studies.

ABBREVIATIONS AND ACRONYMS

LV = left ventricular
MI = myocardial infarction
MR = mitral regurgitation
MV = mitral valve
MVARC = Mitral Valve Academic Research Consortium

DEATH

All-cause mortality is an objective endpoint without bias. The occurrence of death should be assessed through standard study processes and through supplemental interrogation of administrative registry databases to minimize the number of patients lost to follow-up and the need for imputation or sensitivity analyses. Factors contributing to the cause of death may be difficult to establish, and the relationship of death to the underlying MV disease or to the intervention may be uncertain. For these reasons, all-cause mortality is preferable compared with cardiac mortality as a primary endpoint measure. Nonetheless, adjudication of the cause of death should be performed using pre-defined criteria (**Table 2**). The cause of death is subdivided into cardiovascular and noncardiovascular causes. Although categorizing the initiating or proximate cause of cardiovascular death may be difficult, major complications contributing to death should be identified to facilitate future efforts to reduce mortality. A diagnosis of noncardiovascular death requires the primary cause to be clearly related to another condition (e.g., trauma, cancer, or suicide). All deaths that are not unequivocally related to a noncardiovascular condition are considered cardiovascular death for regulatory purposes.

Death is further classified as periprocedural if it occurs within 30 days of the intervention or beyond

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