JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2015 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER INC.

VOL. 66, NO. 3, 2015
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2015.05.049

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

Gregg W. Stone, MD,*† David H. Adams, MD,‡ William T. Abraham, MD,§ Arie Pieter Kappetein, MD, PhD,‖ Philippe Généreux, MD,*†¶ Pascal Vranckx, MD, PhD,# Roxana Mehran, MD,†‡ Karl-Heinz Kuck, MD,** Martin B. Leon, MD,*† Nicolo Piazza, MD, PhD,†† Stuart J. Head, PhD,‖ Gerasimos Filippatos, MD,‡‡ Alec S. Vahanian, MD,§§ for the Mitral Valve Academic Research Consortium (MVARC)

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

From the *Columbia University Medical Center/New York-Presbyterian Hospital, New York, New York; †Cardiovascular Research Foundation, New York, New York; ‡Mount Sinai Health System, New York, New York; §The Ohio State University, Columbus, Ohio; ‖Erasmus University Medical Center, Rotterdam, the Netherlands; ¶Hôpital du Sacré-Coeur de Montréal, Montreal, Quebec, Canada; #Hartcentrum Hasselt, Hasselt, Belgium; **Asklepios Hospital St. Georg, Hamburg, Germany; ††McGill University Health Center, Montreal, Quebec, Canada; ‡‡Athens University Hospital Attikon, Athens, Greece; and the §§Hôpital Bichat, Paris, France. For complete information on the MVARC members and participants, please see the Online Appendix. The MVARC initiative was funded by unrestricted grant support from Abbott Vascular, Boston Scientific, Cardiac Dimensions, Cordis, Edwards Lifesciences, Guided Delivery Systems Inc., Mitralign, Medtronic, Valtech. Dr. Stone has served as a consultant for AGA Medical, AstraZeneca, Atrium, Boston Scientific, Cardiovascular Systems, Inc., Eli Lilly/Daiichi Sankyo partnership, InfraReDx, InspireMD, Miracor, Osprey, Reva, TherOx, Thoratec, Velomedix, and Volcano; and has equity in the Biostar and MedFocus family of funds, Caliber, Guided Delivery Systems, MiCardia, and Vascular Nanotransfer Technologies. Dr. Adams has received royalties for intellectual property paid to his medical institution from Edwards Lifesciences and Medtronic.

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

Dr. Abraham has served as a consultant for Abbott Vascular, Novartis, and St. Jude Medical/CardioMEMS. Dr. Généreux has received grants from Cardiac Dimensions, Inc.; and serves as a consultant/speaker for Abbott Vascular, Cardiovascular Systems, Inc., and Edwards Lifesciences. Dr. Mehran has received grants from AstraZeneca, Bristol-Myers Squibb/Sanofi-Aventis, Lilly/Daiichi Sankyo, and The Medicines Company; serves as a consultant for Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, CSL Behring, Janssen (Johnson & Johnson), Maya Medical, Merck, and Regado Biosciences; and serves as an advisory board member for Covidien, Endothelix, Inc., Janssen, Merck, and Sanofi. Dr. Kuck has received grants and personal fees from Biosense Webster, Medtronic, and St. Jude Medical. Dr. Piazza has served as a consultant for Medtronic; has received grants from Medtronic and St. Jude Medical; and has equity in CardiAQ and Highlife. Dr. Head has received personal fees for lectures and product development from Medtronic. Dr. Filippatos has received grants from Abbott Vascular; and serves as a committee member or principal investigator of trials sponsored by Bayer, Cardiorentis, the European Union, Medtronic, and Novartis. Dr. Vahanian has received personal fees from and served as a consultant for Abbott Vascular, Edwards Lifesciences, and Valtech. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Saibal Kar, MD, served as Guest Editor for this paper.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

Manuscript received March 5, 2015; revised manuscript received May 5, 2015, accepted May 21, 2015.

TABLE 1 Clinical Endpoints to be Collected in All Trials of Mitral Valve Therapies

1. Mortality*
All-cause
Cardiovascular vs. noncardiovascular
Periprocedural vs. nonperiprocedural
Device relatedness (definitely related, possibly related, or unrelated)
2. Hospitalization*
For heart failure vs. other cardiovascular causes vs. noncardiovascular causes
3. Neurological events*
Stroke vs. transient ischemic attack
Etiology: ischemic vs. hemorrhagic vs. undetermined
Severity: disabling vs. nondisabling
Timing: periprocedural vs. nonprocedure related
4. Myocardial infarction*
Timing: Periprocedural vs. nonprocedure related
5. Access and vascular complications
Arterial, venous, cardiac
6. Bleeding complications
Modified VARC scale
Modified BARC scale
7. Acute kidney injury
Modified AKIN definition (also used in VARC-2)
8. Arrhythmias and conduction system disturbances
Atrial fibrillation and other atrial arrhythmias
Ventricular tachycardia and other ventricular arrhythmias
Heart block
9. Device and procedural success*
10. Specific device-related technical failure issues and complications*

*Events that should be adjudicated by an independent central adjudication committee. Other events may also be adjudicated if warranted by the specific study device or trial design.

AKIN = Acute Kidney Injury Network; BARC = Bleeding Academic Research Consortium; VARC = Valve Academic Research Consortium.

TABLE 2 Classification of All-Cause Mortality

I. Cardiovascular vs. noncardiovascular mortality
A. Cardiovascular mortality
Any of the following contributing conditions:
Heart failure (subclassified into left ventricular vs. right ventricular dysfunction)
Myocardial infarction
Major bleeding
Thromboembolism
Stroke
Arrhythmia and conduction system disturbance
Cardiovascular infection and sepsis (e.g., mediastinitis and endocarditis)
Tamponade
Sudden, unexpected death
Other cardiovascular
Device failure
Death of unknown cause (adjudicated as cardiovascular)
B. Noncardiovascular mortality
Any death in which the primary cause of death is clearly related to another condition:
Noncardiovascular infection and sepsis (e.g., pneumonia)
Renal failure
Liver failure
Cancer
Trauma
Homicide
Suicide
Other noncardiovascular
II. Periprocedural vs. nonperiprocedural mortality
Death is considered periprocedural if occurring within 30 days of the intervention or beyond 30 days in the patient not yet discharged

30 days in the patient not yet discharged. Death that occurs in a patient transferred from the index procedure hospital to an extended care facility is still considered periprocedural death, unless the patient originated in such a facility before the procedure. "Immediate" procedural mortality may be defined as death occurring within 72 h of the procedure, but this timing is somewhat arbitrary and of less certain clinical utility. Finally, the relationship between death and device failure (including direct mechanical failures and procedural complications) should be assessed and adjudicated as definitely related, possibly related, or unrelated.

HOSPITALIZATION (OR REHOSPITALIZATION)

Hospitalization is a clinically meaningful measure of morbidity, with substantial clinical and economic implications (8,9). The preferred definition of hospitalization (or rehospitalization) after discharge from an MV procedure appears in Table 3. The causes of hospitalization can be further subclassified as in Table 3. In particular, hospitalization due to new or worsening heart failure is an important metric after MV interventions that may serve as a primary endpoint in MV device trials. It is acknowledged, however, that hospitalization rates vary across different countries, regions, and hospital systems, in part due to variations in local practice patterns. The proposed definitions attempt to account for some of these variances.

HEART FAILURE HOSPITALIZATION. The mortality rate for patients hospitalized for worsening heart failure is ~4% to 7% during the in-hospital phase, ~11% to 15% at 1 month, and ~33% at 1 year (10–13). The 30-day and 1-year rates of repeat all-cause hospitalization for patients discharged for heart failure are approximately 25% and 70%, respectively (14,15). One-half of these readmissions are due to recurrent heart failure. As a clinical trial endpoint, heart failure hospitalization must be carefully defined and adjudicated by a clinical events committee using specific, objective criteria.

The definition for heart failure hospitalization requires: 1) a hospital stay for worsening heart failure for ≥24 h; and 2) administration of intravenous or mechanical heart failure therapies (Table 3). An emergency room stay for ≥24 h would qualify as a heart failure hospitalization endpoint, even absent formal hospital admission, as such a prolonged stay represents a severe episode of heart failure. The diagnosis of worsening heart failure is on the basis of: 1) symptoms of worsening heart failure such as increased dyspnea,

orthopnea, paroxysmal nocturnal dyspnea, fatigue, decreased exercise tolerance, and/or history of weight gain; 2) physical examination evidence of worsening heart failure such as neck vein distention, the presence of a third heart sound, pulmonary rales, ascites or pedal edema, and/or hypotension or signs of worsening end-organ perfusion; and/or 3) diagnostic evidence of worsening heart failure such as radiographic pulmonary congestion, natriuretic peptide levels greater than the upper limit of normal in the absence of conditions known to affect these values (e.g., renal dysfunction, infection), arterial oxygen desaturation or increasing oxygen requirements, and/or acidosis. No single finding is necessarily diagnostic, and adjudication by the clinical events committee should be on the basis of all available clinical evidence, guided by the specifics of the protocol definition.

Examples of intravenous heart failure therapies contributing to this definition would include bolus or continuous infusion of loop diuretic agents; continuous infusion of vasodilators such as nitroglycerin, nitroprusside, or nesiritide; inotropic agents such as dobutamine; inodilators such as milrinone; beta-agonists; and vasopressors such as dopamine, epinephrine, and norepinephrine. Also included would be other invasive or mechanical heart failure treatments such as ultrafiltration, cardiac resynchronization therapy, and hemodynamic assist devices including intra-aortic balloon counterpulsation or left ventricular (LV) or biventricular assist devices. Treatment with intravenous antiarrhythmic medications or electrical cardioversion and/or ablation in the absence of other intravenous or invasive heart failure treatments would not *per se* constitute criteria for heart failure hospitalization (but would qualify as a cardiovascular hospitalization). Similarly, a heart failure exacerbation that can be managed solely by augmentation of oral heart failure therapies does not meet the pre-defined criteria for heart failure hospitalization.

Patients hospitalized with heart failure meeting these criteria should further be subclassified into primary (cardiac related) or secondary (noncardiac related) heart failure. Primary heart failure may be due to any cardiac cause, including primary LV dysfunction with or without medication or dietary noncompliance, acute myocardial infarction (MI), arrhythmias, and worsening valve dysfunction. Secondary heart failure is present when a noncardiac primary condition is present such as pneumonia, urinary tract infection, or renal failure, which results in fluid overload or myocardial failure. Adjudication may be necessary to determine which diagnosis is of prevailing importance (e.g., exacerbation of chronic obstructive pulmonary disease with bronchospasm and some element of heart failure, or major heart failure exacerbation with secondary bronchospasm). Only primary heart failure should be considered a valid criterion for heart failure hospitalization, although secondary heart failure hospitalizations should also be reported and used for sensitivity analysis.

TABLE 3 Definition and Classification of Hospitalization (or Rehospitalization)

Definition
Hospitalization is defined as admission to an inpatient unit or ward in the hospital for ≥24 h, including an emergency department stay. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition.
Hospitalization Is Further Subclassified as:
I. Heart failure hospitalization: Both of the following additional criteria are present: i. Symptoms, signs and/or laboratory evidence of worsening heart failure (see text, section Heart Failure Hospitalization) ii. Administration of intravenous or mechanical heart failure therapies (see text, section Heart Failure Hospitalization) Patients hospitalized with heart failure are further subclassified as: IA. Primary (cardiac related) heart failure hospitalization IB. Secondary (noncardiac related) heart failure hospitalization II. Other cardiovascular hospitalization: such as for coronary artery disease, acute myocardial infarction, hypertension, cardiac arrhythmias, cardiomegaly, pericardial effusion, atherosclerosis, stroke, or peripheral vascular disease without qualifying heart failure III. Noncardiovascular hospitalization: not due to heart failure or other cardiovascular causes, as defined above

Finally, some trials have used a broader definition of worsening heart failure events to capture not only heart failure hospitalizations but also heart failure hospitalization "equivalents" (16). This approach includes a definition of heart failure hospitalization similar to the MVARC definition, plus heart failure-related emergency department visits and urgent (unscheduled) clinic visits requiring treatment with intravenous heart failure therapies or substantial augmentation of oral heart failure medications. These latter outpatient visits are "softer" events, are often less well documented and more difficult to adjudicate, and comprise only about 10% of all worsening heart failure events (17). As such, the MVARC recommends that they not be included in the principal endpoint definition of heart failure hospitalization. Collecting and adjudicating such events may be useful, however, for secondary sensitivity analyses and for cost/comparative effectiveness assessments. If analysis of these outpatient events is needed to comprehensively characterize device performance over time, pre-specified definitions sufficient to allow accurate data capture regarding their occurrence are required. In the future, as comprehensive outpatient management of advanced heart failure becomes more frequent, and as improvements in electronic health record infrastructure support more robust documentation, elements of outpatient heart failure control might provide more informative data supporting clinical insight into devices used for MR.

TABLE 4 Stroke and Transient Ischemic Attack: Diagnosis and Classification

Diagnostic criteria I. Acute episode of a focal or global neurological deficit with at least 1 of the following: A. Change in the level of consciousness B. Hemiplegia, hemiparesis, numbness, or sensory loss affecting 1 side of the body C. Dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke II. In addition, there is no other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) as determined by or in conjunction with the designated neurologist*
The neurological event type classification I. Stroke: duration of a focal or global neurological deficit ≥24 h OR <24 h if available neuroimaging documents a new intracranial or subarachnoid hemorrhage (hemorrhagic stroke) or central nervous system infarction (ischemic stroke) OR the neurological deficit results in death II. TIA: duration of a focal or global neurological deficit <24 h and neuroimaging does not demonstrate a new hemorrhage or infarct
Confirmation of the diagnosis of stroke or TIA requires at least 1 of the following I. Neurologist or neurosurgical specialist, or II. Neuroimaging procedure (CT scan or brain MRI)
Stroke/TIA timing classification I. Periprocedural if it occurs within 30 days of the intervention, or if beyond 30 days in the patient not yet discharged. A periprocedural stroke/TIA may be further considered immediate if it occurs within 24 h of the procedure or within 24 h of awakening from general anesthesia if beyond 24 h. II. Nonperiprocedural if it occurs beyond 30 days after the intervention and after the patient has been discharged.
Stroke/TIA etiology classification I. Ischemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue II. Hemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage III. Undetermined: if there is insufficient information to allow categorization as ischemic or hemorrhagic
Stroke severity† is further classified as I. Disabling stroke: an mRS score ≥2 at 90 days *plus* an increase in ≥1 mRS category from the pre-stroke baseline II. Nondisabling stroke: an mRS score <2 at 90 days *or* without an increase ≥1 mRS category from the pre-stroke baseline

*Patients with nonfocal global encephalopathy will not be reported as having had a stroke without unequivocal evidence of cerebral infarction based upon neuroimaging studies (CT scan or cerebral MRI). †Modified Rankin scale (mRS) assessments should be made by qualified individuals according to a certification process (20,55,56).

CT = computed tomography; MRI = magnetic resonance imaging; TIA = transient ischemic attack.

NEUROLOGICAL EVENTS

Stroke is a critical endpoint in cardiovascular clinical trials, often considered second only to mortality in importance to patients and physicians. However, until recently, studies have rarely adjudicated stroke, have not used consistent definitions or required routine neurological examination, and have not examined the effect of stroke on quality of life and survival. Factors that can affect the risk of stroke after transcatheter therapies for MR include the type of MV device and interventional procedures (given access considerations and the device's mechanism of action), underlying patient comorbidities, and other factors associated with stroke, including pre- and post-operative atrial fibrillation and use of chronic anticoagulation. If the comparator arm is MV surgery, the stroke risk in the control group can also vary according to whether MV repair versus replacement is performed and whether concomitant Maze or other cardiac procedures are performed (18). Accurate and contemporary assessment of stroke occurring in patients undergoing MV procedures is essential.

In the Valve Academic Research Consortium (VARC) and VARC-2 consensus documents (4,5), rigorous definitions, study endpoints, and processes for assessing neurological events after TAVR procedures were proposed. MVARC recommends that the basic definitions, classifications, and levels of severity for stroke and transient ischemic attack after MV procedures generally conform to VARC-2 criteria (5) and be consistent with recent standards from the American Heart Association and American Stroke Association (19), as outlined in **Table 4**. The greatest sensitivity for ascertainment of neurological events will be achieved by routine patient examination by qualified neurologists before and after procedures (both MV surgery and transcatheter therapies). In 2 recent studies of patients with aortic stenosis treated by either surgery or TAVR, systematic neurology evaluations resulted in higher rates of observed stroke than had been previously reported (20,21). To date, few studies or transcatheter MR therapies have reported stroke rates, and routine neurological evaluation was not performed (22,23). Accordingly, MVARC recommends that a qualified stroke neurologist be included in all phases of clinical trial planning, execution, and monitoring, including involvement in the clinical events adjudication committee and the data and safety monitoring board. Brain imaging (typically magnetic resonance imaging for acute and chronic ischemia and hemorrhage, and computed tomography for acute and chronic hemorrhage and chronic ischemia) should be used to supplement the clinical diagnosis of stroke (24).

Stroke may result in a range of clinical disabilities with varying effects on clinical outcomes and quality of life. For these reasons, stroke is further classified as "disabling" or "nondisabling" on the basis of a modified Rankin Scale (mRS) (25). A "disabling" stroke includes even relatively minor neurological deficits (e.g., partial visual field cut) and is defined as an mRS score ≥2 with an increase in ≥1 mRS category from an individual's pre-stroke baseline at 90 days after stroke onset. The mRS should be recorded during each outpatient visit by a trained individual certified in stroke assessment. With proper training, this need not be a physician.

Patients remain at long-term risk for ischemic stroke after MV surgery, in part due to comorbidities, atrial fibrillation, LV dysfunction, prosthetic valve material, structural valve deterioration, and for hemorrhagic stroke from chronic anticoagulant agent

use (26). Transcatheter MV therapies may also predispose to thrombus formation with embolic risk of stroke. Precise documentation of baseline patient characteristics (e.g., left atrial and cardiac function, carotid stenosis), post-operative complications (e.g., new-onset atrial fibrillation), and the use and dosage of antithrombotic and antiplatelet medications are essential to identify the contributing causes of stroke. Evaluation to determine the etiology of stroke must be comprehensive, including transesophageal echocardiography and extended monitoring for atrial fibrillation when appropriate.

In addition to documentation of stroke and transient ischemic attack, there is growing realization that subtle changes in neurocognitive function, especially in the elderly, may have important clinical consequences. Methodology for neurocognitive testing is evolving, with no standard currently accepted (27). At present, pre- and post-procedure neurocognitive testing is not routinely required in clinical trials of MV therapies, although analysis of neurocognitive data may be a worthwhile secondary endpoint for future analysis (28).

Finally, it has become increasingly recognized that, in many cases, cerebral infarction (as evidenced by new abnormalities detected by diffusion-weighted magnetic resonance imaging) may occur during surgical and interventional procedures, but be clinically silent (29–31). As the relationship between these asymptomatic defects and the development of declining neurocognitive function is uncertain (32–35), in the absence of clinical symptoms or signs of cerebral infarction, their occurrence should not currently be included in the primary endpoint of stroke in trials investigating novel transcatheter devices for MR. However, there is increasing interest to consider this endpoint as a valid measure of effectiveness in studies of adjunctive embolic protection devices, assuming such devices are also proven to have minimal risk (i.e., favorable benefit-risk profile).

MYOCARDIAL INFARCTION

For patients in clinical trials and prospective registry studies of MV surgical and transcatheter therapies, it is essential that the post-procedural degree of myonecrosis be accurately evaluated and consistently reported. This is especially true as some devices designed to treat MR work in close proximity to the coronary arteries. To date, however, the incidence and effect of periprocedural MI after MV surgery or transcatheter interventions have been inadequately studied; the definition of MI used in prior studies of MV therapies has varied (or not been reported); and the methodology to ascertain these events has often not been described (36–38).

Importantly, the optimal definition for MI after MV interventions is unknown. In this regard, the accepted definition of periprocedural MI for use in clinical trials of other interventional devices has undergone substantial evolution in the past 3 decades. In the balloon angioplasty and stent eras, the most commonly used definition was on the basis of the World Health Organization criterion of an elevation in post-procedure creatine kinase (CK) to $\geq 2\times$ the upper limits of normal (ULN), with evidence of positive MB band isoenzymes. As adjunctive pharmacology was introduced with the goal of enhancing procedural safety, smaller levels of myonecrosis (on the basis of CK-MB) were required to define a periprocedural MI, usually $\geq 3\times$ ULN. As troponin measurements were adopted, a troponin level of $\geq 3\times$ ULN was often used interchangeably with CK-MB $\geq 3\times$ ULN, despite the greater sensitivity of troponins to detect small degrees of myocardial injury. Finally, the Universal Definition of Myocardial Infarction group advocated for greater standardization of MI criteria by using the 99th percentile of the upper reference limit for each assay, which, compared with the ULN, further decreased the threshold for MI detection (39). As a result, the reported rates of periprocedural MI have increased from 2% to 3% in the early percutaneous coronary intervention era to as high as 24% more recently (40). The use of high-sensitivity troponins would further increase the rate of periprocedural MI (41,42). Given the arbitrary nature of these definitions, a task force of the Society for Cardiac Angiography and Interventions recently introduced a definition for a "clinically relevant MI," representing a level of myonecrosis that has been linked to subsequent adverse clinical outcomes (usually mortality) after adjustment for covariates associated with biomarker elevations (43). A similar evolution has taken place in biomarker interpretation after coronary artery bypass grafting, with recent recommendations to utilize comparable levels of myonecrosis after surgical and interventional revascularization procedures (43).

On the basis of these precedents, MVARC recommends that all patients in trials of MR therapies have assessment of biomarker levels at baseline and twice within 24 h post-procedure (e.g., at 8 ± 4 h and at 16 ± 4 h). If the biomarker level at either time point is elevated by $\geq 50\%$ compared with baseline, serial measures should be drawn until the peak has been reached and the levels begin to decline. CK-MB is the preferred biomarker as it has the most robust historical data relating its elevation to subsequent adverse outcomes (43). Standard troponin assays

(not high-sensitivity) may be utilized if CK-MB is not available. All patients should also have a baseline 12-lead electrocardiogram (ECG), repeated within 2 h post-procedure. For patients in large-scale observational databases, a baseline and post-procedure screening ECG within 2 h may be sufficient, with subsequent evaluation of cardiac biomarkers and imaging studies should new ST-segment changes or Q waves become evident.

Given the fact that the implications of biomarker elevations after surgical incisions of the myocardium (including transapical access) are unknown, MVARC believes that at present, a strict definition of MI in valve procedures should require additional evidence of myocardial injury, either new ST-segment elevation or depression or pathological Q waves. The extent of myonecrosis after MV surgical and transcatheter procedures that may result in (or at least be independently associated with) heart failure, arrhythmias, death, or other adverse outcomes is presently unknown. In the absence of data, we therefore recommend that a modification of the Society for Cardiac Angiography and Interventions criteria for clinically relevant periprocedural MI be adopted for clinical trial and registry reporting use (**Table 5**) (43). For nonperiprocedural spontaneous MI, the Third Universal Definition of Myocardial Infarction criteria should be adopted (**Table 5**) (39). Periprocedural biomarker elevations not meeting the criteria for MI in **Table 5** should be categorized as "myonecrosis not meeting MI criteria," and the implications of these lower levels of myonecrosis should be carefully examined. Future research should be performed to evaluate the optimal definition for a clinically relevant MI in the setting of surgical and transcatheter MV procedures, including assessment of whether the presence of ECG changes and/or new imaging evidence of infarction add important prognostic information.

TABLE 5 Definition of MI After Transcatheter and Surgical Mitral Valve Replacement

I. Periprocedural MI (≤48 h after the index procedure)*†
   A. In patients with normal baseline CK-MB (or cTn): The peak CK-MB measured within 48 h of the procedure rises to ≥10× the local laboratory ULN *plus* new ST-segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point), or to ≥5× ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB, *OR* in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the PCI rises to ≥70× the local laboratory ULN *plus* new ST-segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point), or ≥35× ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB.
   B. In patients with elevated baseline CK-MB (or cTn): The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus, new ECG changes as described.

II. Spontaneous MI (>48 h after the index procedure)‡
   Detection of rise and/or fall of cardiac biomarkers (preferably cTn) with at least 1 value above the 99th percentile URL (or ULN in the absence of URL) together with at least 1 of the following:
   A. Symptoms of ischemia
   B. ECG changes indicative of new ischemia (new ST-segment or T-wave changes or new LBBB) or new pathological Q waves in ≥2 contiguous leads
   C. Imaging evidence of a new loss of viable myocardium or new wall motion abnormality

III. MI associated with sudden, unexpected cardiac death‡
   Sudden cardiac death or cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST-segment elevation or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurs before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in the blood

IV. Pathological findings of an acute myocardial infarction‡

The use of high sensitivity (hs)-troponins is recommended for diagnosis of type II (spontaneous) MI, but has not been studied for assessment of periprocedural MI. Standard troponin assays are therefore recommended for evaluation of type I MI. *Periprocedural biomarker elevation >ULN not meeting the criteria for MI should be categorized as "myonecrosis not meeting MI criteria." †Adapted from Moussa et al. (43). ‡Adapted with permission from Thygesen et al. (39).

CK-MB = creatine kinase-MB; cTn = cardiac troponin; ECG = electrocardiogram; LBBB = left bundle branch block; MI = myocardial infarction; ULN = upper limit of normal; URL = upper reference limit.

ACCESS AND VASCULAR COMPLICATIONS

Transcatheter MV interventions may result in complications arising from access site entry, trans-septal procedures, and/or the device interacting with the MV complex and adjacent structures. Transcatheter MV procedures may involve venous, arterial, or transapical access, and the incidence and variety of associated complications will vary with each approach (44). Venous access site-related complications may include bleeding, thrombophlebitis, and pulmonary embolism. Arterial access site-related complications may include bleeding, ischemia, and peripheral emboli (45). Access site-related complications may include unintended perforation of important vascular and cardiac structures such as the inferior vena cava, aorta LV, left atrium, coronary sinus, right atrium, and right ventricle. Vascular complications directly due to malfunction of closure devices should also be recorded. Planned repair of access site entry portals such as the myocardial apex are not considered access site-related complications. Although atrial septal defects after trans-atrial procedures are not usually of hemodynamic significance and do not require repair, the criteria for a significant residual atrial septal defect should be pre-specified. **Table 6** lists MVARC recommended definitions for major and minor access-related complications.

BLEEDING COMPLICATIONS

Bleeding after surgical or transcatheter valve procedures has been strongly related to subsequent mortality (45,46). As such, bleeding events must be carefully recorded and reported in the periprocedural period as well as during long-term follow-up. Patients with MV disease are prone to bleeding because of underlying comorbidities and frequent use of chronic anticoagulation. Numerous bleeding scales have been

used in past trials of surgical and interventional therapies. VARC criteria have been developed to characterize bleeding after TAVR and surgical aortic valve procedures (4,5), and the Bleeding Academic Research Consortium (BARC) criteria have been proposed to define bleeding after coronary procedures (6). Clinical trials have identified areas for which further clarification and detail may be useful. MVARC recommends that a modified VARC-2 classification scheme be used for the primary definition of bleeding after MV procedures, in which fatal bleeding is more comprehensively defined and nonfatal bleeding is better characterized. In addition, for sensitivity analysis and in recognition that the optimal bleeding scale has not been identified, the committee recommends that a modified BARC classification of bleeding events also be reported. The modified VARC-2 and BARC bleeding scales appear in **Table 7**. In addition, in recognition that blood transfusions have been strongly associated with adverse outcomes (45,46), the timing (e.g., intraprocedural vs. post-procedural) and quantity (number of units) of each type of transfused blood product should be collected and reported, whether or not the transfusion is associated with overt bleeding.

TABLE 6 Access Site and Vascular Complications

I. Vascular complications
A. Major access site vascular complications, including:
i. Aortic dissection or aortic rupture, or
ii. Access site-related† arterial or venous injury (dissection, stenosis, ischemia, arterial, or venous thrombosis including pulmonary emboli, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect‡), irreversible nerve injury, or compartment syndrome resulting in death; hemodynamic compromise; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment, or
iii. Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage, or
iv. Unplanned endovascular or surgical interventions resulting in death; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischemia; or neurological impairment
B. Minor access site vascular complications, including:
i. Access site arterial or venous injury (dissection, stenosis, arterial, or venous thrombosis including pulmonary emboli, ischemia, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, retroperitoneal hematoma, atrial septal defect‡) not resulting in death; life-threatening, extensive, or major bleeding (MVARC scale); visceral ischemia; or neurological impairment, or
ii. Distal embolization treated with embolectomy and/or thrombectomy not resulting in amputation or irreversible end-organ damage, or
iii. Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication, or
iv. Vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)
II. Cardiac structural complications due to access-related issues
A. Major cardiac structural complications, including:
i. Cardiac perforation* or pseudoaneurysm resulting in death, life-threatening bleeding, hemodynamic compromise, or tamponade, or requiring unplanned surgical or percutaneous intervention
B. Minor cardiac structural complications, including:
i. Cardiac perforation* or pseudoaneurysm not meeting major criteria

*Including the left ventricle, left atrium, coronary sinus, right atrium, and right ventricle. †May arise from the access procedure *per se* or complications from vascular closure devices. ‡Meeting pre-specified criteria for a hemodynamically significant shunt, or requiring unplanned percutaneous or surgical closure.

ACUTE KIDNEY INJURY

Acute kidney injury (AKI) is an important complication that may occur in patients undergoing surgical or transcatheter valve repair or replacement and has been strongly related to subsequent mortality (47–49). The etiology of AKI after MV intervention is multifactorial and may include contrast-induced nephropathy; atheroemboli; drug-induced, acute tubular necrosis due to renal hypoperfusion; and other causes. Consensus of a uniform definition for AKI has not been achieved. VARC adopted the serum creatinine criteria from the modified RIFLE (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function, and End-stage kidney disease) classification but deliberately did not include the urine output criteria in defining AKI (4). VARC-2 used the Acute Kidney Injury Network definition (a modified version of RIFLE) that has been widely adopted in the nephrology community, including the Kidney Disease: Improving Global Outcomes initiative (5,50). Additionally, VARC-2 extended the timing for the diagnosis of AKI from 72 h to 7 days. In the absence of data regarding which AKI scale has the greatest prognostic utility, MVARC recommends adoption of VARC-2 criteria for AKI in MV trials and registries (**Table 8**). Serum creatinine should thus be measured pre-procedure, within 24 h post-procedure, and between 2 and 3 days post-procedure. If either of the 2 post-procedure values is increased by ≥25% or ≥0.2 mg/dl from baseline, an additional value should be drawn between 5 and 7 days, and then serial measures assessed until the creatinine is declining. In addition to reporting the occurrence of AKI, the need for ultrafiltration or hemodialysis should be separately recorded.

ARRHYTHMIAS AND CONDUCTION SYSTEM DISTURBANCES

Patients with MR and LV dysfunction frequently have atrial and ventricular arrhythmias, especially atrial fibrillation and ventricular tachycardia. The occurrence of atrial fibrillation may worsen MR, contributing to additional volume overload and further arrhythmia propensity, and result in embolic stroke. Progressive left and right ventricular dilation due to MR may predispose to lethal ventricular arrhythmias (51,52). Patients with LV dyssynchrony may be candidates for biventricular pacing, which may reduce MR (53–55). Internal defibrillators are commonly implanted in patients with reduced LV ejection fraction and improve survival (54,55). MV interventions

TABLE 7 Definition of Bleeding Complications

MVARC Primary Bleeding Scale*
I. Minor Any overt,† actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that meets ≥1 of the following: requiring nonsurgical medical intervention by a health care professional; leading to hospitalization or increased level of care; prompting evaluation; or requires 1 or 2 U of whole blood or packed RBC transfusion and otherwise does not meet criteria for major, extensive, or life-threatening bleeding.
II. Major Overt bleeding either associated with a drop in the hemoglobin of ≥3.0 g/dl‡ or requiring transfusion of ≥3 U of whole blood or packed RBCs *AND* does not meet criteria of life-threatening or extensive bleeding.
III. Extensive Overt source of bleeding with drop in hemoglobin of ≥4 g/dl‡ or whole blood or packed RBC transfusion ≥4 U within any 24-h period, or bleeding with drop in hemoglobin of ≥6 g/dl‡ or whole blood or packed RBC transfusion ≥4 U (BARC type 3b) within 30 days of the procedure.
IV. Life-threatening Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating surgery or intervention, or intramuscular with compartment syndrome *OR* bleeding causing hypovolemic shock or hypotension (systolic blood pressure <90 mm Hg lasting >30 min and not responding to volume resuscitation) or requiring significant doses of vasopressors or surgery.
V. Fatal Bleeding adjudicated as being a proximate cause of death. Severe bleeding adjudicated as being a major contributing cause of a subsequent fatal complication, such as MI or cardiac arrest, is also considered fatal bleeding.
Modified BARC Bleeding Scale (Secondary Use)§
Type 0 No bleeding.
Type 1 Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional. May include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional.
Type 2 Any overt,† actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet ≥1 of the following: requiring nonsurgical medical intervention by a health care professional, leading to hospitalization or increased level of care, or prompting evaluation.
Type 3a • Overt* bleeding plus hemoglobin drop of 3 to <5 g/dl‡ (provided drop is related to bleed) • Any transfusion with overt bleeding
Type 3b • Overt bleeding plus hemoglobin drop ≥5 g/dl‡ (provided drop is related to bleed) • Cardiac tamponade • Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) • Bleeding requiring IV vasoactive agents
Type 3c • Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation but does include intraspinal bleeding) • Subcategories confirmed by autopsy, imaging, or lumbar puncture • Intraocular bleeding compromising vision
Type 4 (periprocedural) • Perioperative intracranial bleeding ≤48 h • Reoperation after closure of incision site for the purpose of controlling bleeding • Transfusion of ≥5 U whole blood or packed RBCs within 48-h period of the index procedure • Chest tube output ≥2 l within 24-h period
Type 5a: Probable fatal bleeding. No autopsy or imaging confirmation but clinically suspicious.
Type 5b: Definite fatal bleeding. Overt bleeding, autopsy, or imaging confirmation.

*Modified with permission from VARC-2 (5). †"Overt" bleeding is defined by any of the following criteria being met: Reoperation after closure of sternotomy for the purpose of controlling bleeding; chest tube output >2 l within any 24-h period, >350 ml within the first post-operative hour, ≥250 ml within the second post-operative hour, or >150 ml within the third post-operative hour; or visible bleeding from the vascular system either at or remote from the access/surgical site. ‡Adjusted for the number of units of blood transfused (1 U packed red blood cells or whole blood is equivalent to 1 g/dl hemoglobin). §Modified from BARC (6).

BARC = Bleeding Academic Research Consortium; IV = intravenous; MVARC = Mitral Valve Academic Research Consortium; RBC = red blood cells; VARC = Valve Academic Research Consortium.

may induce new atrial or ventricular arrhythmias and may displace pre-existing leads. Conversely, reduction of MR after effective surgical or transcatheter MV interventions may theoretically improve LV ejection fraction and diminish the frequency of serious and life-threatening arrhythmias. The development of conduction disturbances after MV repair is relatively infrequent (56,57), although whether this will remain true for transcatheter MV repair and replacement procedures is unknown. Thus, assessment of the presence and burden of atrial and ventricular arrhythmias, conduction system disease, and use of therapeutic drugs and technologies is important in this patient population (**Table 9**). Pacemaker or

defibrillator lead dislodgement is also a potential risk, especially if the leads were recently positioned, and should be reported.

MEASURES OF TECHNICAL, DEVICE, PROCEDURAL, AND PATIENT SUCCESS

Technical, device, procedural and patient success are complementary metrics used to evaluate the acute and late outcomes of MV surgical and transcatheter interventions. These important parameters should be included as secondary endpoints in all prospective clinical trials and observational studies of MR therapies, and should be recorded in (or determined from) administrative databases if possible. MVARC-recommended definitions for technical, device, procedural, and patient success are shown in **Table 10**.

Technical success, measured at the time of the patient's exit from the cardiac catheterization laboratory, reflects the ability of the device to be deployed as intended and the delivery system successfully retrieved without procedural mortality or need for emergency surgery or intervention.

Device success, measured at 30 days and at all follow-up intervals thereafter, characterizes not only the acute "technical" performance of the device and delivery system, but the effectiveness of the device in reducing the severity of MR by a pre-specified amount or to a pre-specified level, as assessed by an independent echocardiographic core laboratory, without device-related complications. By MVARC criteria, "optimal" device success requires a reduction in post-procedural MR to no more than trace levels. "Acceptable" device success is defined as a reduction in post-procedure MR by at least 1 class (i.e., from severe to moderate or less; from moderate to mild or less; or from mild to none). Alternatively, if the 4+ numerical classification is used to grade MR severity, "optimal" device success is defined as a reduction in post-procedural MR to 0+ or trace, and "acceptable" device success is defined as a reduction in post-procedure MR by ≥1 grade from baseline and to an absolute level of ≤2+. Emerging data suggests that hemodynamic and prognostic improvement following transcatheter repair of MR may be realized in patients with reduction in MR severity from severe to moderate (58-60), although further studies are required to determine the prognostic effect of residual moderate (2+) versus mild (1+) versus absent MR. Device success further requires the echocardiographic absence of significant mitral stenosis (calculated valve area ≥1.5 cm^2 and transmitral gradient <5 mm Hg), and no greater than mild (1+) paravalvular MR without associated hemolysis. Note, however, that the calculated MV area and transmitral gradient vary with flow, and assessment of the degree of paravalvular MR can be subjective. Further studies are warranted to determine the prognostic effect of these measures.

Procedural success is a composite safety and efficacy endpoint measured at 30 days that is meant to characterize the early outcome of a mitral interventional procedure. For procedural success to be present, device success must have been achieved without major clinical complications, as detailed in **Table 10**.

Finally, patient success is a parameter reflecting whether the MV intervention was efficacious in improving overall clinical outcomes at 1 year. One-year patient success requires continuous device success throughout the follow-up period, with return of the patient to his or her pre-procedural living setting

TABLE 8 Definition and Stages of Acute Kidney Injury

Definition	
Maximal change in sCr from baseline to 7 days post-procedure	
Stages	
Stage 1	Increase in sCr to 150%–199% (1.50–1.99× increase vs. baseline), increase of ≥0.3 mg/dl (≥26.4 mmol/l) within 48 h, or urine output <0.5 ml/kg/h for ≥6 h but <12 h
Stage 2	Increase in sCr to 200%–299% (2.00–2.99× increase vs. baseline) or urine output <0.5 ml/kg/h for ≥12 h but <24 h
Stage 3	Increase in sCr to ≥300% (>3.0× increase vs. baseline), sCr of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of ≥0.5 mg/dl (44 mmol/l), urine output <0.3 ml/kg/h for ≥24 h, or anuria for ≥12 h; patients receiving renal replacement therapy are considered stage 3 irrespective of other criteria

Adapted with permission from Kappetein et al. (5).

TABLE 9 Arrhythmias and Conduction System Disturbances

For emerging mitral valve procedures in which the frequency of major arrhythmias and conduction system disturbances is unknown, continuous rhythm monitoring for at least 48 h in the post-procedural period is recommended to maximize the detection of arrhythmias and conduction system disturbances.

Data elements to be collected for all patients should include:

I. Baseline conduction abnormalities, paroxysmal or permanent atrial fibrillation (or flutter), ventricular arrhythmias, and the presence of permanent pacemaker and implantable defibrillators*
II. Procedure-related new or worsened cardiac conduction disturbance (including first-, second- [Mobitz I or Mobitz II], or third-degree AV block; incomplete and complete right bundle branch block; intraventricular conduction delay; left bundle branch block; left anterior fascicular block; or left posterior fascicular block, including heart block) requiring a permanent pacemaker implant; each subclassified as persistent or transient
III. New-onset atrial fibrillation (or flutter)†
IV. New-onset ventricular tachycardia or fibrillation
V. Pacemaker or defibrillator lead dislodgement

Arrhythmias and conduction system disturbances are subclassified according to:

I. The occurrence of hemodynamic instability
II. Need for therapy including electrical/pharmacological cardioversion or initiation of a new medication (oral anticoagulation, rhythm, or rate control therapy)
III. Need for new permanent pacemaker and/or defibrillator implantation, including the indication(s) and the number of days post-implant. For patients with defibrillators, the number of appropriate and inappropriate shocks should be recorded.

*The type of permanent pacemaker should be recorded (e.g., single vs. dual chamber, biventricular). †Which lasts sufficiently long to be recorded on a 12-lead electrocardiogram, or at least 30 s on a rhythm strip.

AV = atrioventricular.

TABLE 10 Technical, Device, Procedural, and Patient Success

I. Technical success (measured at exit from the catheterization laboratory)
All of the following must be present:
I. Absence of procedural mortality; and
II. Successful access, delivery, and retrieval of the device delivery system; and
III. Successful deployment and correct positioning of the first intended device; and
IV. Freedom from emergency surgery or reintervention related to the device or access procedure.

II. Device success (measured at 30 days and at all later post-procedural intervals)
All of the following must be present:
I. Absence of procedural mortality or stroke; and
II. Proper placement and positioning of the device; and
III. Freedom from unplanned surgical or interventional procedures related to the device or access procedure; and
IV. Continued intended safety and performance of the device, including:
a. No evidence of structural or functional failure (see Table 11, part I)
b. No specific device-related technical failure issues and complications (see Table 11, part II)
c. Reduction of MR to either optimal or acceptable levels* without significant mitral stenosis (i.e., post-procedure EROA is ≥1.5 cm^2 with a transmitral gradient <5 mm Hg), and with no greater than mild (1+) paravalvular MR (and without associated hemolysis)

III. Procedural success (measured at 30 days)
All of the following must be present:
I. Device success (either optimal or acceptable),† and
II. Absence of major device or procedure related serious adverse events, including:
A. Death
B. Stroke
C. Life-threatening bleeding (MVARC scale)
D. Major vascular complications
E. Major cardiac structural complications
F. Stage 2 or 3 acute kidney injury (includes new dialysis)
G. Myocardial infarction or coronary ischemia requiring PCI or CABG
H. Severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatments such as ultrafiltration or hemodynamic assist devices, including intra-aortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for ≥48 h.
I. Any valve-related dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention

IV. Patient success (measured at 1 year)
All of the following must be present:
I. Device success (either optimal or acceptable), and
II. Patient returned to the pre-procedural setting: and
III. No rehospitalizations or reinterventions for the underlying condition (e.g., mitral regurgitation, heart failure); and
IV. Improvement from baseline in symptoms (e.g., NYHA improvement by ≥1 functional class); and
V. Improvement from baseline in functional status (e.g., 6-min walk test improvement by ≥50 m); and
VI. Improvement from baseline in quality-of-life (e.g., Kansas City Cardiomyopathy Questionnaire improvement by ≥10)

*MR reduction is considered *optimal* when post-procedure MR is reduced to trace or absent. MR reduction is considered *acceptable* when post-procedure MR is reduced by at least 1 class or grade from baseline *and* to no more than moderate (2+) in severity. For clinical trials and registry studies, assessment of baseline and post-procedure MR must be made by an echocardiographic core laboratory. For large observational databases, baseline and post-procedure MR may be assessed by physicians trained in echocardiographic evaluation. †For 30-day evaluation of device success, the results from an immediate post-procedural transesophageal echocardiogram and from a transthoracic echocardiogram taken within 24 to 48 h post-procedure may be used if the 30-day echocardiogram is absent. Device success determinations at post-procedural intervals beyond the initial 30 days should reflect findings from the patient history and an echocardiographic study obtained within the relevant pre-specified follow-up window.

CABG = coronary artery bypass grafting; EROA = effective regurgitant orifice area; MR = mitral regurgitation; MVARC = Mitral Valve Academic Research Consortium; NYHA = New York Heart Association; PCI = percutaneous coronary intervention.

(e.g., home or assisted living facility), no repeat hospitalizations for the underlying condition (e.g., MR or heart failure), and sustained improvement in symptoms, functional status, and quality-of-life, as detailed in Table 10.

DEVICE-RELATED ENDPOINTS

In addition to overall device and procedural success, device-related specific endpoints that are important to consider include subcategories of device access and delivery-related success and complications, acute and chronic device function, and device-related complications. The endpoints presented in Table 11 represent a framework for device-related endpoints that should be considered, adjusted as appropriate for each particular device.

CONCLUSIONS

The ARC initiative grew out of the need for pragmatic, clinically relevant consensus definitions whose consistent use would enhance the assessment of relative safety and effectiveness in medical device evaluations (2). Although no single definition is perfect for all therapies and situations, consistent use of consensus definitions is more informative than varying ad hoc definitions across studies, and it promotes system-wide understanding of comparative health effectiveness as well as scientific progress and innovation. In this regard, the original ARC percutaneous coronary intervention definitions and VARC endpoints have been widely implemented and proven useful. MVARC has extended the ARC mission not only to provide

TABLE 11 Specific Device-Related Technical Failure Issues and Complications

I. Device failure

Device failure, defined as the absence of device success (Table 10), is subclassified as:
- Delivery failure (i.e., technical failure)
- Structural failure: the device does not perform as intended due to a complication related to the device (e.g., fracture, migration or embolization, frozen leaflet, device detachment, and so on)
- Functional failure: the device performs as intended without complication but does not adequately reduce the degree of MR (MR > moderate [2+], or fails to relieve or creates new mitral stenosis [EROA <1.5 cm^2 or transmitral gradient ≥5 mm Hg]).

II. Specific device-related technical failure issues and complications

- Paravalvular leak
  - Major: moderate or severe (2+, 3+, or 4+), or associated with hemolysis, or requiring intervention or surgery
  - Minor: trace or mild (1+), without hemolysis
- Iatrogenic atrial septal defect
  - Major: significant left-to-right shunt (Qp:Qs ≥2:1) or symptomatic requiring the need for closure
  - Minor: nonsignificant shunt that is still present at ≥6 months
- Coronary vessel compression or obstruction
  - Angiographic evidence of any reduction in coronary artery luminal diameter or coronary sinus diameter due to either external compression, thrombosis, embolism, dissection, or other cause, subclassified as:
    - Major (≥50% diameter stenosis) or minor (<50%)
    - Symptomatic or not
    - Requiring treatment or not
    - Transient (intraprocedural only, resolved at procedure end) or persistent
- Pericardial effusion
  - Major: leading to cardiac tamponade or requiring intervention
  - Minor: not leading to cardiac tamponade and not requiring intervention
- Conversion to open mitral valve surgery during a transcatheter procedure, subclassified as
  - Secondary to mitral valve apparatus damage or dysfunction, requiring surgical valve repair or replacement, or
  - Secondary to procedural complications (such as cardiac perforation, removal of an embolized device, and so on)
- Device malpositioning
  - Ectopic device placement: permanent deployment of a device in a location other than intended
  - Device migration: after initial correct positioning, the device moves within its initial position but not leading to device embolization
  - Device embolization: the device moves during or after deployment such that it loses contact with its initial position
- Device detachment
  - Partial: detachment of part of the device from the initial position without embolization
  - Complete: detachment leading to device embolization or ectopic device placement
- Device fracture
  - Major: a break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) resulting in device failure, resulting in recurrent symptoms, or requiring reintervention, or
  - Minor: a break, tear, perforation, or other structural defect in the device (stent, housing, leaflet, arm, and so on) not resulting in device failure, not resulting in recurrent symptoms, and not requiring reintervention
- Damage to the native mitral valve apparatus
  - Chords
  - Papillary muscles
  - Leaflets
  - Mitral annulus
- Interaction with nonmitral valve intracardiac structures
  - Left ventricular outflow tract obstruction (gradient increase ≥10 mm Hg from baseline)
  - Aortic valve regurgitation (≥ moderate or 2+)
  - Other
- Device thrombosis, defined as any thrombus attached to or near an implanted valve, subclassified as:
  - Major: occludes part of the blood flow path, interferes with valve function (e.g., immobility of 1 or more leaflets), is symptomatic, or is sufficiently large to warrant treatment, or
  - Minor: incidental finding on echocardiography or other imaging test that is not major
- Endocarditis
  - Any 1 of the following:
    - Fulfillment of the modified Duke endocarditis criteria (61), or
    - Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during an operation or autopsy.
  - Should be further subclassified by organism, and early (<1 yr) vs. late (≥1 yr)
- Hemolysis
  - The presence of a paravalvular leak on transesophageal or transthoracic echocardiography plus anemia requiring transfusion plus increased haptoglobin and/or LDH levels; should be confirmed by a hematologist
- Other device-specific endpoints
  - The number of devices (e.g., clips, neochords) used by intent to achieve the desired reduction in MR
  - The need for unplanned use of additional devices (e.g., valves, clips, neochords) as a result of failed device delivery, device detachment, device fracture, or other device system failure
  - If surgery is required, inability to perform mitral valve repair because of the presence of or anatomic changes from the device

LDH = lactate dehydrogenase; Qp = pulmonary blood flow; Qs = systemic blood flow; other abbreviations as in Table 10.

uniform definitions for endpoints specific to MV interventions, but also to recommend a consensus framework for the design and performance parameters of clinical studies to assess emerging transcatheter MR devices. Adoption of the principles for MR clinical trial investigation detailed in part 1 of this consensus document (1) and integrating the collection and adjudication of the

endpoints discussed herein will provide comprehensive characterization of novel MR therapies for clinical and regulatory evaluation and facilitate quality control initiatives, including assessment of operator and institutional outcomes relative to local, regional, and national benchmarks.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Gregg W. Stone, Columbia University Medical Center, Cardiovascular Research Foundation, 111 East 59th Street, 11th Floor, New York, New York 10022. E-mail: gs2184@columbia.edu.

REFERENCES

1. Stone GW, Vahanian AS, Adams DH, et al. 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. J Am Coll Cardiol 2015;66:278–307.

2. Krucoff MW, Mehran R, van Es GA, Boam AB, Cutlip DE. The Academic Research Consortium governance charter. J Am Coll Cardiol Intv 2011;4:595–6.

3. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.

4. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. J Am Coll Cardiol 2011;57:253–69.

5. Kappetein AP, Head SJ, Genereux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: The Valve Academic Research Consortium-2 consensus document. J Am Coll Cardiol 2012;60:1438–54.

6. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. Circulation 2011;123:2736–47.

7. Généreux P, Head SJ, Van Mieghem NM, et al. Clinical outcomes after transcatheter aortic valve replacement using valve academic research consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. J Am Coll Cardiol 2012;59:2317–26.

8. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 2013;127:e6–245.

9. Blecker S, Paul M, Taksler G, et al. Heart failure-associated hospitalizations in the United States. J Am Coll Cardiol 2013;61:1259–67.

10. Fonarow GC, Adams KF Jr., Abraham WT, et al. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. JAMA 2005;293:572–80.

11. Jong P, Vowinckel E, Liu PP, et al. Prognosis and determinants of survival in patients newly hospitalized for heart failure: a population-based study. Arch Intern Med 2002;162:1689–94.

12. Alla F, Zannad F, Filippatos G. Epidemiology of acute heart failure syndromes. Heart Fail Rev 2007;12:91–5.

13. Tavazzi L, Maggioni AP, Lucci D, et al. Nationwide survey on acute heart failure in cardiology ward services in Italy. Eur Heart J 2006;27:1207–15.

14. Ross JS, Chen J, Lin Z, et al. Recent national trends in readmission rates after heart failure hospitalization. Circ Heart Fail 2010;3:97–103.

15. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med 2009;360:1418–28.

16. Hauptman PJ, Schwartz PJ, Gold MR, et al. Rationale and study design of the INcrease Of Vagal TonE in Heart Failure study: INOVATE-HF. Am Heart J 2012;163:954–62.e1.

17. Bourge RC, Abraham WT, Adamson PB, et al. Randomized controlled trial of an implantable continuous hemodynamic monitor in patients with advanced heart failure: the COMPASS-HF study. J Am Coll Cardiol 2008;51:1073–9.

18. Ruel M, Masters RG, Rubens FD, et al. Late incidence and determinants of stroke after aortic and mitral valve replacement. Ann Thorac Surg 2004;78:77–83.

19. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44:2064–89.

20. Messe SR, Acker MA, Kasner SE, et al. Stroke after aortic valve surgery: results from a prospective cohort. Circulation 2014;129:2253–61.

21. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790–8.

22. Philip F, Athappan G, Tuzcu EM, et al. MitraClip for severe symptomatic mitral regurgitation in patients at high surgical risk: a comprehensive systematic review. Catheter Cardiovasc Interv 2014;84:581–90.

23. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. N Engl J Med 2011;364:1395–406.

24. Wintermark M, Albers GW, Alexandrov AV, et al. Acute stroke imaging research roadmap. Stroke 2008;39:1621–8.

25. Lyden PD, Lau GT. A critical appraisal of stroke evaluation and rating scales. Stroke 1991;22:1345–52.

26. Russo A, Grigioni F, Avierinos JF, et al. Thromboembolic complications after surgical correction of mitral regurgitation incidence, predictors, and clinical implications. J Am Coll Cardiol 2008;51:1203–11.

27. Lietz K, Brown K, Ali SS, et al. The role of cerebral hyperperfusion in postoperative neurologic dysfunction after left ventricular assist device implantation for end-stage heart failure. J Thorac Cardiovasc Surg 2009;137:1012–9.

28. Spaziano M, Francese DP, Leon MB, et al. Imaging and functional testing to assess clinical and subclinical neurological events after transcatheter or surgical aortic valve replacement: a comprehensive review. J Am Coll Cardiol 2014;64:1950–63.

29. Floyd TF, Shah PN, Price CC, et al. Clinically silent cerebral ischemic events after cardiac surgery: their incidence, regional vascular occurrence, and procedural dependence. Ann Thorac Surg 2006;81:2160–6.

30. Kahlert P, Knipp SC, Schlamann M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. Circulation 2010;121:870–8.

31. Ghanem A, Muller A, Nahle CP, et al. Risk and fate of cerebral embolism after transfemoral aortic valve implantation: a prospective pilot study with diffusion-weighted magnetic resonance imaging. J Am Coll Cardiol 2010;55:1427–32.

32. Knipp SC, Matatko N, Schlamann M, et al. Small ischemic brain lesions after cardiac valve replacement detected by diffusion-weighted magnetic resonance imaging: relation to neurocognitive function. Eur J Cardiothorac Surg 2005;28:88–96.

33. Cook DJ, Huston J 3rd, Trenerry MR, et al. Postcardiac surgical cognitive impairment in the aged using diffusion-weighted magnetic resonance imaging. Ann Thorac Surg 2007;83:1389–95.

34. Barber PA, Hach S, Tippett LJ, et al. Cerebral ischemic lesions on diffusion-weighted imaging are associated with neurocognitive decline after cardiac surgery. Stroke 2008;39:1427–33.

35. Knipp SC, Matatko N, Wilhelm H, et al. Cognitive outcomes three years after coronary artery bypass surgery: relation to diffusion-weighted magnetic resonance imaging. Ann Thorac Surg 2008;85:872–9.

36. Acker MA, Parides MK, Perrault LP, et al. Mitral-valve repair versus replacement for severe ischemic mitral regurgitation. N Engl J Med 2014;370:23–32.

37. Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. J Am Coll Cardiol 2013;62:1052–61.

38. Schillinger W, Hunlich M, Baldus S, et al. Acute outcomes after MitraClip therapy in highly aged patients: results from the German TRAnscatheter Mitral valve Interventions (TRAMI) Registry. EuroIntervention 2013;9:84–90.

39. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020–35.

40. Novack V, Pencina M, Cohen DJ, et al. Troponin criteria for myocardial infarction after percutaneous coronary intervention. Arch Intern Med 2012;172:502–8.

41. Muthu V, Kozman H, Liu K, et al. Cardiac troponins: bench to bedside interpretation in cardiac disease. Am J Med Sci 2014;347:331–7.

42. Venge P, Johnston N, Lindahl B, et al. Normal plasma levels of cardiac troponin I measured by the high-sensitivity cardiac troponin I access prototype assay and the impact on the diagnosis of myocardial ischemia. J Am Coll Cardiol 2009;54:1165–72.

43. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). J Am Coll Cardiol 2013;62:1563–70.

44. Généreux P, Webb JG, Svensson LG, et al. Vascular complications after transcatheter aortic valve replacement: insights from the PARTNER (Placement of AoRTic TraNscathetER Valve) trial. J Am Coll Cardiol 2012;60:1043–52.

45. Généreux P, Cohen DJ, Williams MR, et al. Bleeding complications after surgical aortic valve replacement compared with transcatheter aortic valve replacement: insights from the PARTNER I trial (Placement of Aortic Transcatheter Valve). J Am Coll Cardiol 2014;63:1100–9.

46. Murphy GJ, Reeves BC, Rogers CA, et al. Increased mortality, postoperative morbidity, and cost after red blood cell transfusion in patients having cardiac surgery. Circulation 2007;116:2544–52.

47. Konigstein M, Ben-Assa E, Abramowitz Y, et al. Usefulness of updated Valve Academic Research Consortium-2 criteria for acute kidney injury following transcatheter aortic valve implantation. Am J Cardiol 2013;112:1807–11.

48. Brown JR, Kramer RS, Coca SG, et al. Duration of acute kidney injury impacts long-term survival after cardiac surgery. Ann Thorac Surg 2010;90:1142–8.

49. Hobson CE, Yavas S, Segal MS, et al. Acute kidney injury is associated with increased long-term mortality after cardiothoracic surgery. Circulation 2009;119:2444–53.

50. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.

51. Hochreiter C, Niles N, Devereux RB, et al. Mitral regurgitation: relationship of noninvasive descriptors of right and left ventricular performance to clinical and hemodynamic findings and to prognosis in medically and surgically treated patients. Circulation 1986;73:900–12.

52. Kligfield P, Hochreiter C, Niles N, et al. Relation of sudden death in pure mitral regurgitation, with and without mitral valve prolapse, to repetitive ventricular arrhythmias and right and left ventricular ejection fractions. Am J Cardiol 1987;60:397–9.

53. van Bommel RJ, Ajmone Marsan N, Delgado V, et al. Cardiac resynchronization therapy as a therapeutic option in patients with moderate-severe functional mitral regurgitation and high operative risk. Circulation 2011;124:912–9.

54. Russo AM, Stainback RF, Bailey SR, et al. ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR 2013 appropriate use criteria for implantable cardioverter-defibrillators and cardiac resynchronization therapy: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, Heart Rhythm Society, American Heart Association, American Society of Echocardiography, Heart Failure Society of America, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. J Am Coll Cardiol 2013;61:1318–68.

55. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: The Task Force on Cardiac Pacing and Resynchronization Therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Eur Heart J 2013;34:2281–329.

56. Berdajs D, Schurr UP, Wagner A, et al. Incidence and pathophysiology of atrioventricular block following mitral valve replacement and ring annuloplasty. Eur J Cardiothorac Surg 2008;34:55–61.

57. Meimoun P, Zeghdi R, D'Attelis N, et al. Frequency, predictors, and consequences of atrioventricular block after mitral valve repair. Am J Cardiol 2002;89:1062–6.

58. Grayburn PA, Foster E, Sangli C, et al. Relationship between the magnitude of reduction in mitral regurgitation severity and left ventricular and left atrial reverse remodeling after MitraClip therapy. Circulation 2013;128:1667–74.

59. Lim DS, Reynolds MR, Feldman T, et al. Improved functional status and quality of life in prohibitive surgical risk patients with degenerative mitral regurgitation after transcatheter mitral valve repair. J Am Coll Cardiol 2014;64:182–92.

60. Sürder D, Pedrazzini G, Gaemperli O, et al. Predictors for efficacy of percutaneous mitral valve repair using the MitraClip system: the results of the MitraSwiss registry. Heart 2013;99:1034–40.

61. Durack DT, Lukes AS, Bright DK, et al. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Am J Med 1994;96:200–9.

KEY WORDS heart failure, mitral regurgitation, mitral valve, valve intervention, valve surgery (or cardiac surgery)

APPENDIX For complete information on the MVARC members and participants, please see the online version of this article.