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Standardized Endpoint Definitions for Transcatheter Aortic Valve Implantation Clinical Trials

A Consensus Report From the Valve Academic Research Consortium

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Objectives To propose standardized consensus definitions for important clinical endpoints in transcatheter aortic valve implantation (TAVI), investigations in an effort to improve the quality of clinical research and to enable meaningful comparisons between clinical trials. To make these consensus definitions accessible to all stakeholders in TAVI clinical research through a peer reviewed publication, on behalf of the public health.

Background Transcatheter aortic valve implantation may provide a worthwhile less invasive treatment in many patients with severe aortic stenosis and since its introduction to the medical community in 2002, there has been an explosive growth in procedures. The integration of TAVI into daily clinical practice should be guided by academic activities, which requires a harmonized and structured process for data collection, interpretation, and reporting during well-conducted clinical trials.

Methods and Results The Valve Academic Research Consortium established an independent collaboration between Academic Research organizations and specialty societies (cardiology and cardiac surgery) in the USA and Europe. Two meetings, in San Francisco, California (September 2009) and in Amsterdam, the Netherlands (December 2009), including key physician experts, and representatives from the U.S. Food and Drug Administration (FDA) and device manufacturers, were focused on creating consistent endpoint definitions and consensus recommendations for implementation in TAVI clinical research programs. Important considerations in developing endpoint definitions included: 1) respect for the historical legacy of surgical valve guidelines; 2) identification of pathophysiological mechanisms associated with clinical events; 3) emphasis on clinical relevance. Consensus criteria were developed for the following endpoints: mortality, myocardial infarction, stroke, bleeding, acute kidney injury, vascular complications, and prosthetic valve performance. Composite endpoints for TAVI safety and effectiveness were also recommended.

Conclusions Although consensus criteria will invariably include certain arbitrary features, an organized multidisciplinary process to develop specific definitions for TAVI clinical research should provide consistency across studies that can facilitate the evaluation of this new important catheter-based therapy. The broadly based consensus endpoint definitions described in this document may be useful for regulatory and clinical trial purposes. (J Am Coll Cardiol 2011;57:253–69) © 2011 by the American College of Cardiology Foundation

Since the introduction of transcatheter aortic valve implantation (TAVI) in 2002 (1), there has been increasing interest in the field of catheter-based treatment of high-surgical-risk patients with symptomatic aortic stenosis (AS) (2–7). Introduction of this new technology should ideally follow the standard bench-to-bedside evidence-based medicine pattern, starting with pre-clinical testing and advancing to clinical investigations. Unfortunately, the explosive

From the Columbia University Medical Center, Center for Interventional Vascular Therapy, New York, New York. The Valve Academic Research Consortium (VARC) consists of representatives from several independent Academic Research Organizations, several Surgery and Cardiology Societies, members of the U.S. Food and Drug Administration, and several independent experts (Appendices 1 and 2). Grants were provided to the ARC Board including representatives of The Cardiovascular Research Foundation, Cardialysis, Duke Clinical Research Institute and Harvard Clinical Research Institute to cover the costs of travel, meeting rooms, and lodging for academic attendees at the San Francisco and Amsterdam meetings by Edwards Lifesciences and Medtronic Corporation. All funds not utilized for the aforementioned travel-related purposes have been returned to the sponsors. Funding was provided by Cardialysis BV on behalf of the Valve Academic Research Consortium. The VARC meetings involved members of the Interventional Cardiology Devices Branch, of the Office of Device Evaluation, Center for Devices and Radiological Health, USFDA. The opinions or assertions herein are the private views of the authors and are not to be construed as reflecting the views of the FDA. This article is copublished in the *European Heart Journal*.

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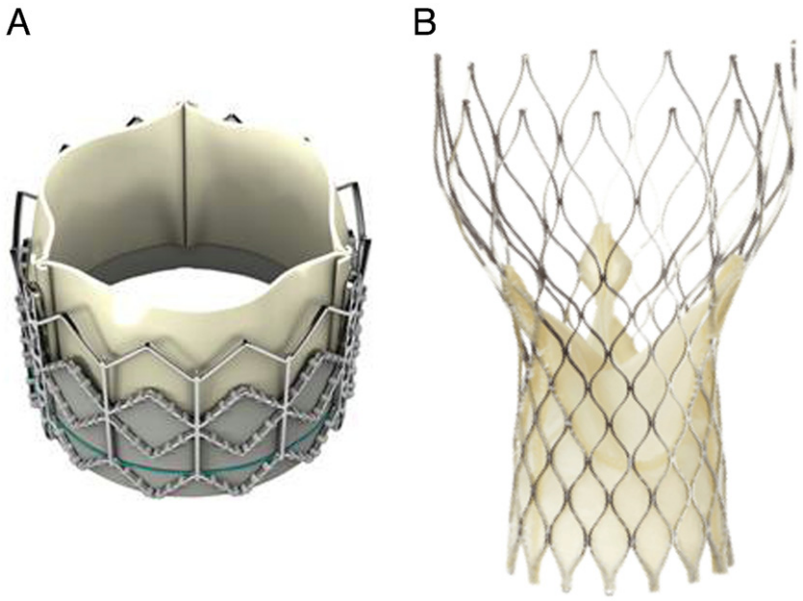

Figure 1 Current Generation Transcatheter Aortic Valve Therapies

(A) balloon-expandable, stainless steel support structure, bovine pericardial valve; **(B)** self-expanding, nitinol support structure, porcine pericardial valve.

growth of TAVI (Fig. 1) has created a 'clinical data conundrum': investigators were not prepared to optimally organize and interpret clinical data for this radically different treatment, rendering thoughtful assessment of clinical trial outcomes difficult and inter-study results comparisons problematic (8–11).

Surgical valve clinical research guidelines have been developed using a more traditional 'multi-society approach,' have been revised approximately every 10 years, incorporate not merely clinical endpoints but also issues such as structural valve deterioration and non-structural valve dysfunction, and often divide clinical events into those that are valve and non-valve related (12). Interventional cardiology has a tradition of agreed upon clinical endpoint definitions and clinical trial methodologies (13,14) and recently has incorporated a consensus process to standardize key endpoint definitions by convening an Academic Research Consortium (ARC) among Academic Research Organizations (AROs) from the USA and Europe joined by representatives from the USFDA and device manufacturers (14). The ARC process demonstrated the power of a well-managed international goal-directed academic consortium collaborating effectively with the FDA and industry to establish consensus clinical endpoint definitions and to improve the conduct of clinical research.

In the spirit of the ARC-mission statement (14), the 'Valve Academic Research Consortium' (VARC) was organized as an amalgam of the ARO and multi-society guideline models with strong participation from independent experts, the FDA, and medical device manufacturers (Appendices 1 and 2). Two in-person meetings on September 19, 2009, in San Francisco, CA, and on December 5 to 6, 2009, in Amsterdam, the Netherlands, involving VARC study group members and invited guests (including the FDA and industry representatives) provided much of the substantive discussion from which this consensus manuscript was derived.

The goals of VARC are to combine the expertise of surgeons, interventionalists, medical cardiologists, clinical trialists, and other specialists (representing relevant disciplines including echocardiography, vascular medicine, and neurology) to arrive at a consensus for: 1) *selecting appropriate clinical endpoints* reflecting device, procedure and patient-related effectiveness and safety, and 2) *standardizing definitions for single and composite clinical endpoints.*

Importantly, this first consensus manuscript was not intended as a 'guidelines statement' or a 'guidance document,' but rather should be viewed as a roadmap to facilitate the standardization of future TAVI and other aortic valve clinical research.

Principles for Selecting and Defining Clinical Endpoints for Transcatheter Aortic Valve Implantation Investigations: General Considerations

Criteria for endpoint definitions. The definitions of major clinical endpoints must follow a multi-step thought process.

- Each major endpoint should address issues that establish either the *safety and/or the effectiveness* of the proposed new therapy.

  - *Safety* is characterized by the avoidance of device-related or procedural complications.
  - *Effectiveness* is a more complex descriptor, as it encompasses both the avoidance of negative disease-related outcomes and objective measures of clinical functional benefit.

- The endpoints should relate short- and long-term *pathophysiological mechanisms* to meaningful clinical events.
- Endpoint definitions must be consistent with the body of published literature, but still reflect unique or evolving aspects of the new therapy.
- The emphasis should be on definitions that accurately represent *essential patient-oriented clinical outcomes*.
- The endpoints must be well defined (preferably through blinded adjudication processes) such that they can be to be subjected to statistical analysis.

It is helpful to reference a standardized definition format regarding: 1) the specific treatment; 2) the place of occurrence; 3) the time of occurrence; and 4) the specific type of endpoint.

Device, procedure, and patient-oriented outcomes. Endpoint definitions for TAVI will in most cases be characterized in relation to the specific implant device, the implant procedure, and the resultant patient-oriented outcomes, which can occur at any time after the procedure. During the early phases of therapy development, particular attention must be directed to the safety and performance of the device. Therefore, VARC tries to strike a compromise by also elucidating device and procedure-related events, which are essential to the understanding of a new class of catheter-based therapies.

Since TAVI is fundamentally the placement of a prosthetic aortic valve and will be compared with surgical aortic valve replacement (AVR), tradition should be respected and crucial endpoints such as all-cause mortality and device durability must be assessed longitudinally for the life of the implant (12). However, primary clinical endpoints used in pivotal clinical trials for regulatory approval of TAVI devices should incorporate a shorter time domain of 1 to 2 years after the index procedure. These recommended shorter time horizons should not discourage the standard long-term follow-up procedures for prosthetic heart valves.

Proposed Safety and Efficacy Endpoints

Mortality. All-cause mortality in surgical clinical trials has become the 'gold standard' in previously published consensus and guideline documents (12). The advantage of reporting all-cause mortality is that it is both objective (without bias) and pragmatic from the standpoint of ascertainment and adjudication. However, the use of all-cause mortality in high-risk TAVI patients may be misleading, resulting in disproportionate reporting of mortal events unrelated to either the treatment device or the procedure. Therefore, VARC proposes to use all-cause mortality as a primary clinical endpoint, but also recommends further subdivision of mortality, specifically denoting *cardiovascular mortality* as an important secondary endpoint (Table 1). Of note, 'unknown' deaths should be considered as cardiovascular in origin and to improve the ascertainment of death, the social security death index or national death registries should be utilized in cases of patients lost to follow-up.

Table 1 Cardiovascular Mortality

Any one of the following criteria:
Any death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure)
Unwitnessed death and death of unknown cause
All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
Death caused by noncoronary vascular conditions such as cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease

Consistent with surgical guidelines and surgical clinical trial practices (12), mortality should be formally assessed and reported at 30 days after the index procedure (or longer if the patient was not discharged from the treatment hospital or a secondary convalescent facility). Since there may be either unknown or under-reporting of early device failure modes, a more appropriate duration for all-cause mortality as a primary endpoint in TAVI clinical trials is 1 year after the index procedure. After 1 year, mortality should be recorded at yearly intervals for a minimum of 5 years, or ideally, for the duration of the prosthetic valve implant, in the form of well-defined post-approval surveillance registries.

Myocardial infarction. In 2007, the joint ESC/ACC/AHA/WHF task force for the redefinition of Myocardial infarction (MI) established diagnostic criteria and updated guidelines for a universal MI definition to be used in clinical trials (13). This universal MI definition is highly sensitive, relying heavily on the measurement of cardiac biomarkers (preferably troponin). Conversely, surgical valve guidelines have adopted a 'minimalist' approach to MI definitions, usually ignoring biomarker diagnoses and excluding both intra-operative and post-operative MIs, unless the MI was caused by a coronary embolus (12).

Valve Academic Research Consortium proposes a more 'centrist' approach to MI definitions after TAVI, recognizing that many patients have coexistent aortic valve and coronary artery disease (15), which requires an MI definition that does not exclude peri-procedural or late MIs that may impact patient outcomes. Valve Academic Research Consortium proposes to define *peri-procedural MI* as an acute ischaemic event that is associated with documented and *clinically significant myocardial necrosis* (Table 2). This definition does not include ischaemic events after TAVI or surgery defined solely by biomarker elevations without a clinically evident ischaemic insult. Since troponin measurements are an extremely sensitive biomarker of myocardial

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Table 2 Myocardial Infarction

Peri-procedural MI (≤72 h after the index procedure)
New ischemic symptoms (e.g., chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, or imaging evidence of new loss of viable myocardium or new wall motion abnormality), **AND**
Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure, consisting of two or more post-procedure samples that are >0.6 to 8 h apart with a 20% increase in the second sample and a peak value exceeding 10× the 99th percentile URL, or a peak value exceeding 5× the 99th percentile URL with new pathological Q waves in at least 2 contiguous leads.
Spontaneous MI (>72 h after the index procedure)
Any one of the following criteria:
Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following:
ECG changes indicative of new ischemia [new ST-T changes or new LBBB]
New pathological Q waves in at least two contiguous leads
Imaging evidence of new loss of viable myocardium or new wall motion abnormality
Sudden, unexpected cardiac death, involving 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 occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
Pathological findings of an acute myocardial infarction.

CK = creatine kinase; ECG = electrocardiographic; LBBB = left bundle branch block; MI = myocardial infarction; URL = upper reference limit.

necrosis, VARC recommends that CPK-MB should be the peri-procedural biomarker of choice in TAVI clinical trials. Biomarker samples ideally should be obtained at baseline, twice after the procedure (separated by at least 6 h), and if still elevated, daily thereafter until values are declining. Since TAVI may involve open surgical procedures (e.g., transapical access), the biomarker diagnosis of peri-procedural MI requires a >20% increase in the second post-procedure sample and a threshold elevation of ten times the upper normal range. An electrocardiogram should be collected at baseline and at least once after the procedure prior to discharge to document the presence or absence of new Q-waves. The peri-procedural interval is inclusive of all events that begin within 72 h of the index procedure. Acute ischemic events occurring after 72 h are considered spontaneous MIs and are defined in accordance with the universal MI guidelines (13), as further modified by ARC (14) (Table 2). Finally, a confirmed coronary embolus, occurring at any time, should be reported as an independent event, if biomarker changes and associated findings fulfill definition criteria.

Stroke. Recently, two reports have indicated a high frequency of new perfusion abnormalities (presumably embolic) detected by diffusion-weighted magnetic resonance imaging (MRI) studies soon after TAVI (16,17), although the clinical significance of these early perfusion defects remains unclear. Strokes during and after TAVI may occur due to embolic events from multiple sources, procedure-related aortic dissections, ischemia from hypotension, or hemorrhagic complications associated with adjunctive pharmacotherapy. Insights on stroke definitions are in a state of evolution and VARC examined viewpoints derived from several sources, including recent multi-society consensus documents (12,18,19) and multi-center randomized trials, in which stroke was an important endpoint (20–29). Valve Academic Research Consortium considered 5 important issues in arriving at clinically relevant stroke definitions, as follows: 1) a clinical diagnosis of stroke which ruled out metabolic or toxic encephalopathy, pharmacological influences, and non-central neurological symptoms; 2) the role of neuroimaging studies for confirmation of the diagnosis; 3) the distinction of stroke vs. transient ischaemic attack (TIA) (including timing); 4) categorization of stroke into major and minor events based on the degree of disability as defined by conventional neurological assessment tools; and 5) subclassification of strokes into hemorrhagic, ischaemic, and undetermined categories.

Table 3 outlines the diagnostic criteria and specific definitions for TIA and stroke as proposed by VARC. There is growing acceptance that neuroimaging is an important biomarker for the diagnosis of neuronal injury and stroke (18,19) and diffusion-weighted MRI is generally considered the procedure of choice in the context of acute neurological syndromes (30). If a stroke is reported without evidence of confirmation of the diagnosis by the methods

Table 3 Stroke

Stroke diagnostic criteria
Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
Duration of a focal or global neurological deficit ≥24 h; **OR** <24 h, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); **OR** available neuroimaging documents a new hemorrhage or infarct; **OR** the neurological deficit results in death
No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)*
Confirmation of the diagnosis by at least one of the following:
Neurology or neurosurgical specialist
Neuroimaging procedure (MR or CT scan or cerebral angiography)
Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage)
Stroke definitions
Transient ischemic attack:
New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24 h
Neuroimaging without tissue injury
Stroke: (diagnosis as above, preferably with positive neuroimaging study)
Minor—Modified Rankin score <2 at 30 and 90 days†
Major—Modified Rankin score ≥2 at 30 and 90 days

*Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies. †Modified Rankin score assessments should be made by qualified individuals according to a certification process. If there is discordance between the 30 and 90 day Modified Rankin scores, a final determination of major versus minor stroke will be adjudicated by the neurology members of the clinical events committee.
CT = computed tomography; MR = magnetic resonance.

outlined in Table 3, the event may still be considered a stroke on the basis of the clinical presentation alone, but formal adjudication by qualified neurologists who are members of, or consultants to, a clinical events committee is mandatory. Patients with a global encephalopathy will not be reported as a stroke without unequivocal neuroimaging findings. Diagnosis of stroke in patients with a previously documented neurological deficit is more problematic and requires clinical assessment by a neurologist accompanied by appropriate new CT or MRI findings. In patients with a previous stroke and persistent neurological deficits, baseline pre-treatment neurological consultation and neuroimaging studies are recommended.

The earliest time of new neurological symptoms is defined as the time of onset of the stroke or TIA. When a patient awakens or begins responding (if previously unconscious) after the index procedure with obvious new signs of a neurological deficit, the stroke or TIA is considered to have occurred during the index procedure. The diagnosis of a *transient ischemic attack* is defined as complete resolution of new neurological symptoms usually within 1 to 2 h but always within 24 h and also requires a normal neuroimaging study (18,19). A stroke fulfiling the diagnostic criteria in Table 3 is classified as a *major stroke* based upon ongoing significant clinical disability, defined as a Modified Rankin Score ≥2. Although the initial Modified Rankin Score should be recorded after 7 days or at the time of hospital discharge, the attribution of clinically significant disability requires a Modified Rankin Score ≥2 at both 30 and 90 days follow-up (allowing sufficient time for stroke disability to stabilize). The Modified Rankin Score determinations should be performed by qualified individuals who have undergone a certification process (31–34). A *minor stroke* must also fulfill stroke diagnostic criteria, with either resolution of new neurological symptoms within 24 h or persistence of symptoms >24 h and a Modified Rankin Score <2 at both 30 and 90 days follow-up. If there is discordance between the 30 and 90-day Modified Rankin Scores, the final determination of major vs. minor strokes should be adjudicated by the neurology members of the clinical events committee. For the purposes of clinical trial endpoints, VARC advocates that only major strokes should be considered as an important safety endpoint, however, all neurological events should be reported as adverse events.

Stroke will be further stratified into ischemic, hemorrhagic, or undetermined origin utilizing newly proposed definitions by an FDA consensus panel (35). Ischemic stroke is as an acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue. Hemorrhagic stroke is an acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by a non-traumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage. An undetermined stroke is a stroke with insufficient information to allow categorization as either of ischemic or haemorrhagic origin.

Table 4 Bleeding

Life-threatening or disabling bleeding
Fatal bleeding **OR**
Bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome **OR**
Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery **OR**
Overt source of bleeding with drop in hemoglobin of ≥5 g/dl or whole blood or packed red blood cells (RBCs) transfusion ≥4 U*
Major bleeding
Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g/dl or requiring transfusion of two or three units of whole blood/RBC **AND**
Does not meet criteria of life-threatening or disabling bleeding
Minor bleeding
Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening, disabling or major

*Given 1 U of packed RBC typically will raise blood hemoglobin concentration by 1 g/dl, an estimated decrease in hemoglobin will be calculated.

Bleeding complications. Bleeding is a critical safety endpoint in evaluating contemporary pharmacological agents and interventional devices (36–44). Valve Academic Research Consortium carefully reviewed several literature sources including: 1) landmark clinical trials assessing the effects of anti-thrombotic medications in stable and acute coronary syndromes (45–59); 2) a report by the Control of Anticoagulation Subcommittee of the International Society on Thrombosis and Haemostasis (60); and 3) surgery guidelines after cardiac valve procedures (12).

The definition of clinically meaningful bleeding was guided by the following principles: 1) the definition must be based on objective criteria, including an obvious source of bleeding or number of transfusions; 2) serious or meaningful bleeding must result in death, be life-threatening, be proven to be associated with increased long-term mortality, cause chronic sequellae, or consume major health-care resources. The VARC definition of bleeding complications (Table 4) is divided into life-threatening or disabling bleeding, major bleeding, and minor bleeding; anything but minor bleeding constitutes a serious or meaningful bleeding event.

Given the ample body of literature suggesting that administration of whole blood or red blood cell (RBC) transfusions in patients with cardiovascular pathology may be potentially harmful (41–44), VARC considers that any whole blood or RBC transfusion needs to be reported in the case report forms, including the number of transfused units, regardless of the presence or absence of overt bleeding. Transfusions also need to be further stratified into those associated with overt bleeding and those in the absence of overt bleeding. Bleeding complications and transfusions should also be characterized relative to the time of occurrence including during the procedure, within the index hospitalization, or post-discharge.

Acute kidney injury. The natural history of acute kidney injury (AKI) in a variety of clinical settings (61–70) is now

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Table 5 Acute Kidney Injury (Modified RIFLE Classification)

Change in serum creatinine (up to 72 h) compared with baseline
Stage 1 Increase in serum creatinine to 150% to 200% (1.5 to 2.0 × increase compared with baseline) or increase of ≥0.3 mg/dl (≥26.4 mmol/l)
Stage 2 Increase in serum creatinine to 200% to 300% (2.0 to 3.0 × increase compared with baseline) or increase between >0.3 mg/dl (>26.4 mmol/l) and <4.0 mg/dl (<354 mmol/l)
Stage 3* Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) or serum creatinine of ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l)

*Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria.

well understood, including the recognition that even small decreases in kidney function can have a dramatic impact on the risk for subsequent mortality (69,70). In recent reports, AKI has been observed in 12% to 28% of patients undergoing TAVI and was associated with a four times higher post-procedural mortality (71,72).

In defining the stages of AKI, VARC proposes adopting serum creatinine criteria from the 'modified' RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) classification (Table 5) (73). The RIFLE classification (74–76) has been validated in the setting of intensive care units and cardiac surgery (77–81) and provides practical definitions for early stages of renal dysfunction when kidney injury can still be prevented, as well as stages when the kidney has already been damaged and renal failure is established. Modifications of the original RIFLE classification include two important changes: 1) smaller changes in serum creatinine (0.3 mg/dl) are included in stage 1 ('Risk') (82); 2) the 'Loss' and 'End-stage kidney disease' categories have been removed due to a lack of uniform indications and timing of renal replacement therapy (RRT) and variability in RRT resources in different countries. An outer bound of 72 h from the index procedure for diagnosing AKI was selected based on evidence that adverse outcomes were observed when the elevation occurred within 24 to 48 h of the procedure (83) and to ensure that the process was both acute and related to the procedure itself rather than as a consequence of post-procedure multi-organ system failure. Risk, Injury, Failure, Loss, and End-stage kidney disease classifications also stress the predictive value of urine output criteria in defining AKI, but VARC has not included this measure in the definition of AKI since urine outputs may not be measured accurately or routinely in all cases.

Valve Academic Research Consortium proposes to utilize the modified RIFLE classification to: 1) capture even the earliest stages of AKI (stage 1) on case report forms; 2) define AKI as either stage 2 or 3; and 3) report any case of RRT (haemodialysis, peritoneal dialysis, or haemofiltration) occurring during the index hospitalization or within 30 days after the index procedure. Given the well-recognized damaging impact of contrast media on renal function, VARC also recommends to report the volume and type of contrast medium used during the index procedure.

Vascular complications. Recent TAVI literature indicates that major vascular complications using various non-standardized definitions (e.g., with or without including the need for blood transfusions) occur at a frequency of 4% to 34% and are associated with a two- or three-fold higher 30-day mortality (84–87). In defining vascular complications, VARC referenced the reporting standards of the Society of Vascular Surgery for defining and reporting vascular complications following endovascular aortic graft repair procedures (88).

Valve Academic Research Consortium proposes to report both major and minor vascular complications, but to only consider major vascular complications as an important clinical endpoint. Of note, the 'access site' is defined as any location (arterial or venous) traversed by a guide-wire, a catheter or a sheath [including the left ventricular (LV) apex and the aorta] and 'access related' is defined as any adverse clinical consequence possibly associated with any of the access sites used during the procedure. The VARC definitions for major and minor vascular complications are described in Table 6.

Many vascular situations require special notice. Femoral vascular access and closure in many centers is routinely achieved using surgical cut-down procedures, and therefore, pre-planned surgical access and/or closure should be considered as part of the procedure and not as a complication. Similarly, uncomplicated non-femoral (e.g., retroperitoneal, iliac, subclavian, or aortic) surgical access for sheath entry (planned or unplanned) is not considered a vascular complication, unless untoward clinical consequences are documented (e.g., bleeding complications). However, interventional or surgical repair for failed percutaneous closure of the arteriotomy site during the index procedure without other clinical sequellae (Table 6) is considered a minor vascular

Table 6 Vascular Access Site and Access-Related Complications

Major vascular complications
Any thoracic aortic dissection
Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or compartment syndrome) leading to either death, need for significant blood transfusions (≥4 U), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (e.g., hypogastric artery occlusion causing visceral ischemia or spinal artery injury causing neurological impairment)
Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage
Minor vascular complications
Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula or pseudoaneuysms requiring compression or thrombin injection therapy, or hematomas requiring transfusion of ≥2 but, 4 U) not requiring unplanned percutaneous or surgical intervention and not resulting in irreversible end-organ damage
Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage
Failure of percutaneous access site closure resulting in interventional (e.g., stent-graft) or surgical correction and not associated with death, need for significant blood transfusions (≥4 U), or irreversible end-organ damage

Table 7 Potential Failure Modes of Prosthetic Valve Dysfunction

Aortic stenosis
Stent creep
Pannus
Calcification
Support structure deformation (out-of-round configuration), under-expansion, fracture, or trauma (cardio-pulmonary resuscitation, blunt chest trauma)
Mal-sizing (prosthesis-patient mismatch)
Endocarditis
Prosthetic valve thrombosis
Native leaflet prolapse impeding prosthetic leaflet motion
Aortic regurgitation
Pannus
Calcification
Support structure deformation (out-of-round configuration), recoil, under-expansion, fracture, insufficient radial strength, or trauma (cardiopulmonary resuscitation, blunt chest trauma)
Endocarditis
Prosthetic valve thrombosis
Malposition (too high, too low)
Acute mal-coaptation
Leaflet wear, tear/perforation, prolapse, or retraction
Suture breakage or disruption
Native leaflet prolapse impeding prosthetic leaflet motion

complication. Considering the recent proliferation of vascular access approaches and the recognition that specific access sites and techniques may be associated with either increased or decreased complications, VARC strongly recommends that detailed information is recorded on the access site and technique for each procedure.

A special circumstance relates to complications associated with the left-ventricular apex site during transapical TAVI procedures. Although such complications are less frequent than transarterial vascular complications, a recent report indicates that the clinical consequences (including death) can be more serious (89). Major complications associated with transapical TAVI procedures include bleeding, pseudoaneurysm formation (with or without rupture), and haemodynamic instability requiring urgent transarterial cardiopulmonary bypass support. Valve Academic Research Consortium proposes that all such complications associated with transapical TAVI be reported in case report forms and that clinical consequences resulting from such complications be registered under the appropriate clinical endpoints (e.g., bleeding, stroke, mortality).

Prosthetic Valve Performance

The clinical presentation of patients with prosthetic valve dysfunction is usually consistent with symptoms and signs of either valvular regurgitation or stenosis. Valve Academic Research Consortium proposes only two criteria to evaluate impaired prosthetic valve performance: 1) prosthetic valve haemodynamics assessed by echocardiography and 2) associated clinical findings indicating impaired cardiovascular or valvular function (e.g., new or worsening congestive heart failure). Transthoracic echocardiography (TTE) is usually adequate to evaluate prosthetic aortic valve function (90), although transoesophageal echocardiography (TEE) may be very useful in the setting of technically challenging or complex cases. Serial echocardiography evaluations after surgical AVR and TAVI should be performed at baseline, soon after the index procedure (ideally within 24 to 48 h, but always before discharge), at 1 month (especially for TAVI), 12 months, and yearly thereafter (91,92). This follow-up schedule is more intensive than recommended in the AHA/ACC and ESC guidelines for follow-up after surgical AVR (91,92), but more frequent documentation of valve function and position is considered desirable for TAVI clinical trials.

Although the VARC definitions for impaired prosthetic valve performance discount mechanistic characterizations, valve failure mode(s) should be recorded whenever possible in case report forms (Table 7). In addition to echocardiography, multi-slice computed tomography may also provide useful insights into the responsible patho-biological mechanisms of device malfunction (93,94).

Prosthetic aortic stenosis and regurgitation. Utilizing the recent prosthetic valve echocardiography guidelines (90), the severity of prosthetic aortic valve stenosis is graded as: 1) normal; 2) possible; or 3) significant (Table 8) and prosthetic aortic valve regurgitation (central or paravalvular) as: 1) mild; 2) moderate; or 3) severe (Table 9). The clinical significance of prosthetic valve dysfunction is further supported by the presence of clinical signs, symptoms, and/or events (e.g., re-hospitalization for worsening symptoms, re-operation or death).

Table 8 Prosthetic Aortic Valve Stenosis Criteria*

Parameter	Normal	Possible Stenosis	Significant Stenosis
Peak velocity (m/s)†	<3	3–4	0.4
Mean gradient (mm Hg)†	<20	20–35	0.35
Doppler velocity index	≥0.30	0.29–0.25	<0.25
Effective orifice area (cm^2)	>1.2	1.2–0.8	<0.80
Contour of the jet velocity through the prosthetic valve	Triangular, early peaking	Triangular to intermediate	Rounded, symmetrical contour
Acceleration time (ms)	<80	80–100	>100

*In conditions of normal or near normal stroke volume (50–70 ml). †These parameters are more affected by flow, including concomitant aortic regurgitation.

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Table 9 Prosthetic Aortic Valve Regurgitation Criteria (Central and Paravalvular)

Parameter	Mild	Moderate	Severe
Valve structure and motion			
Mechanical or bioprosthetic	Usually normal	Usually abnormal	Usually abnormal
Structural parameters			
Left ventricular size	Normal	Normal/mildly dilated	Dilated
Doppler parameters (qualitative or semiquantitative)			
Jet width in central jets (% LVO diameter): color*	Narrow (≤25%)	Intermediate (26%–64%)	Large (≥65%)
Jet density: CW Doppler	Incomplete or faint	Dense	Dense
Jet deceleration rate (PHT, ms): CW Doppler†	Slow (>500)	Variable (200–500)	Steep (<200)
LV outflow vs. pulmonary flow: PW Doppler	Slightly increased	Intermediate	Greatly increased
Diastolic flow reversal in the descending aorta			
PW Doppler	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of paraprosthetic AR (%)‡	<10	10–20	>20
Doppler parameters (quantitative)			
Regurgitant volume (ml/beat)	<30	30–59	>60
Regurgitant fraction (%)	<30	30–50	>50

*Parameter applicable to central jets and is less accurate in eccentric jets. †Influenced by left ventricular compliance. ‡For paravalvular aortic regurgitation.
AR = aortic regurgitation; CW = continuous wave; LVO = left ventricular outflow; PW = pulsed wave.

Transcatheter aortic valve implantation devices are associated with a higher frequency of mild and moderate paravalvular aortic regurgitation (AR) than surgical AVR (95–107). There is a need to develop improved definitions and to better understand the long-term clinical implications of paravalvular prosthetic AR. Unfortunately, the precise grading of paravalvular AR remains controversial and many echocardiography experts believe that grading schemes for prosthetic central and paravalvular AR should be different (90,108–111). Recently, in the setting of TAVI, criteria for assessing paravalvular AR severity have emphasized a 'jet anatomy' classification, stressing the location, circumferential extent, and width of the AR jet (90). Hemodynamic factors can also be useful to assess the AR severity immediately after valve implantation (e.g., loss of aortic dicrotic notch, equalization of end-diastolic aortic and left ventricular pressures). Since there is lack of clarity concerning the long-term clinical implications of mild and moderate paravalvular AR after TAVI, echocardiography core laboratories are useful to ensure consistent evaluation methods. Echocardiograms should be performed annually in those patients known to have post-procedural paravalvular AR.

Prosthetic aortic valve thrombosis and endocarditis. Although prosthetic valve thrombosis and prosthetic valve endocarditis have been included as potential failure modes for prosthetic valve dysfunction (Table 7), they require reporting as individual endpoints. Valve thrombosis is any thrombus attached to or near an implanted valve that occludes part of the blood flow path, interferes with valve function, or is sufficiently large to warrant treatment (12). Furthermore, valve thrombus found at autopsy in a patient whose cause of death was not valve related or found at operation for an unrelated indication should also be reported as valve thrombosis. The diagnosis of prosthetic valve thrombosis is best discerned during an echocardiographical examination or during surgical exploration. There have already been case reports and anecdotes (112) of transcatheter prosthetic valve thrombosis with and without important clinical consequences.

The diagnosis of prosthetic valve endocarditis is based on one of the following criteria (12):

- reoperation with evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies;
- autopsy findings of abscess, pus, or vegetation involving a repaired or replaced valve;
- in the absence of reoperation or autopsy, fulfilling the Duke Criteria for endocarditis (113).

Isolated case reports of transcatheter aortic valve endocarditis have already been published (114,115). Owing to the variability in transcatheter valve designs and positioning within the aortic root, meticulous reporting of the pattern of endocarditis is mandatory (116).

Prosthetic Valve 'Associated' Complications

Depending on the design characteristics and final implant position, prosthetic aortic valves may come in close contact with the anterior mitral valve leaflet, the intervalvular fibrosa, the aortic annulus, the ventricular septum, the aortic sinuses and root, the coronary arteries, and the cardiac conduction system. Collectively, these anatomic structures, which are contiguous with the prosthetic aortic valve, are referred to as the *aortic valvar complex* (Fig. 2). As such, prosthetic aortic valve procedures, and in particular TAVI, may have untoward effects on any of these structures which may result in important clinical consequences. Therefore, VARC proposes to group these complications as a separate endpoint category. However, it must be noted, that some of these adverse events may not be directly related to the valve prosthesis itself, but may occur before or after valve implan-

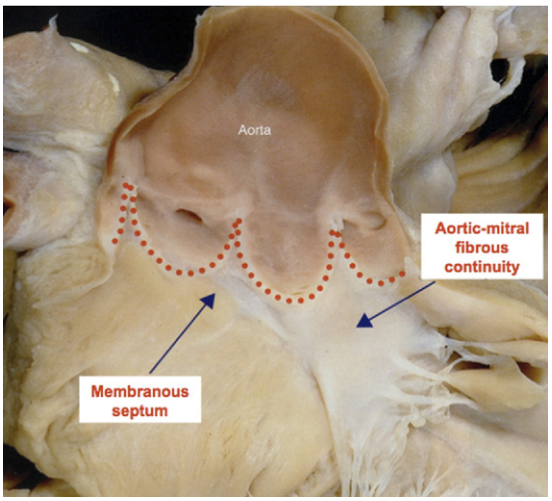

Figure 2 The Aortic Valvular Complex, Including the Aortic Valve, Annulus, Sinuses, Aorta, Coronary Arteries, Membranous Septum, and the Mitral Valve

tation (e.g., conduction disturbances after pre-implant balloon aortic valvuloplasty).

Conduction disturbances and cardiac arrhythmias. The close anatomical relationship between the aortic valvar complex and the branching atrioventricular bundle explains the possible development of conduction abnormalities following prosthetic aortic valve procedures (117,118). Following surgical AVR, new-onset bundle branch block has been reported in 16% to 32% of patients and the need for permanent pacemakers in 3% to 8% of patients (119–123). In early experiences with TAVI, new-onset bundle branch block has occurred in up to 45% of patients and the need for permanent pacemakers has varied from as low as 4% to as high as 33% (95–98,124–128). Differences among devices and heterogeneity in physician and country-based healthcare thresholds may explain the significant inter-hospital variability in new permanent pacemaker requirements after TAVI.

Although the implications of persistent left bundle branch block (LBBB) after TAVI are currently unknown, the presence of new bundle branch block after surgical AVR has been associated with increased risk of subsequent arrhythmic events during follow-up (specifically, syncope, AV dissociation, and sudden death) (119,120). Owing to this association between conduction system abnormalities and adverse patient outcomes following surgical AVR and several anecdotal reports after TAVI of either early post-discharge severe bradyarrhythmic events or sudden cardiac death (15), VARC recommends to carefully document the occurrence of new conduction system abnormalities (left bundle branch block and third degree atrioventricular block), as well as the requirements and indications for new permanent pacemakers within 30 days after the procedure. The timing (days) and location (intra-procedural, in-hospital, or post-discharge) of the event should also be recorded. To accurately capture such events, daily ECGs and continuous telemetry ECG monitoring should be considered while the patients are in-hospital, and should be required in patients with any evidence of new conduction abnormalities or arrhythmias.

Although conduction abnormalities associated with TAVI have been a recent concern, it bears noting that new onset atrial fibrillation and ventricular arrhythmias have also been observed after both TAVI and surgical AVR procedures (128). In particular, new onset atrial fibrillation occurs in as many as 20% to 30% of patients after conventional surgical AVR (129,130) and any valid comparison of transcatheter vs. surgical aortic valve treatment strategies should include a careful analysis of post-therapy supra-ventricular and ventricular arrhythmias.

Coronary obstruction. Mechanical coronary artery obstruction following TAVI or surgical AVR is rare and occurs in 1% of patients (96,97). The obstruction typically occurs during the index procedure. Importantly, clinical signs and symptoms may be subtle and not appreciated until after the procedure. Possible mechanisms for mechanical coronary obstruction include: 1) impingement of the coronary ostia by the valve support structure in the setting of suboptimal valve positioning and/or 'small aortic root' anatomy; 2) embolization from calcium, thrombus, air, or endocarditis displacement of native aortic valve leaflets towards the coronary ostia during TAVI (131,132); and 3) suture-related kinking or obstruction or cannulation-related obstruction of the coronary ostia associated with surgical AVR.

The diagnosis of TAVI-associated coronary obstruction can be determined by imaging studies (coronary angiography, intravascular ultrasound, multi-slice CT angiography, or echocardiography), surgical exploration, or autopsy findings. Cardiac biomarker elevations and ECG changes indicating new ischaemia provide corroborative evidence.

Other prosthesis-related adverse events. The short- and long-term consequences of contact, trauma, or impingement on the anterior mitral valve leaflet by the ventricular end of a transcatheter aortic valve are currently unknown. Nevertheless, any new mitral valve dysfunction (e.g., worsening mitral regurgitation or stenosis) or disruption (e.g., chordal rupture, leaflet perforation, anterior mitral valve leaflet aneurysm) related to contact with the transcatheter valve implant or mitral valve endocarditis (114–116) should be carefully documented. Other infrequent complications following TAVI include new ventricular septal defects and aortic root rupture/perforation/dissection, occurring either during the pre-implant balloon aortic valvuloplasty, or during the transcatheter valve implant (133,134).

Clinical Benefit Endpoints

In addition to the avoidance of mortality, specific endpoints to establish the clinical benefit after TAVI are important. Objective benefit parameters derived from the heart failure

literature can be adapted in valve-related clinical trials (135). Several choices are available, including exercise performance (136), assessment of New York Heart Association (NYHA) functional status (137), and various quality of life (138) and frailty questionnaires (139). Each of these symptom evaluation tools has strengths and weaknesses in the TAVI patient population, which is disproportionately represented by elderly, frail, individuals with multiple co-morbidities. For instance, exercise test performance is an appealing endpoint, but as aortic valve therapy studies are unblinded, they may be biased and they can be difficult to perform in high-risk TAVI patients.

Valve Academic Research Consortium has also considered a categorical endpoint of clinical benefit which captures failure of current AS therapy; *hospitalization for symptoms of cardiac or valve-related decompensation*, at least 30 days after the index procedure (surgical AVR or TAVI). This endpoint mandates careful adjudication by a clinical events committee and is defined as hospitalization for symptoms of valve or cardiac deterioration (e.g. new or worsening heart failure, angina, or syncope) requiring either a valve procedure (surgery or interventional treatment) or intensification of medical management (new or increased use of inotropes, vasopressors, diuretics, and/or vasodilators).

Quality-of-life and healthcare economic instruments can be useful to assess disability and impairment due to congestive heart failure (e.g., Kansas City Cardiomyopathy Questionnaire) (140) and for mapping health status compared with population-level utility weights (e.g., EuroQOL questionnaire) (141–143). However, quality-of-life questionnaires are also prone to bias and must be uniformly administered. The time points for assessment of the aforementioned clinical benefit endpoints should be at 30 days, at 6 months, and at 1 year after initiating therapy. Valve Academic Research Consortium recommends that if any measure of clinical benefit is utilized in clinical trials, there must be careful oversight and adjudication by experienced clinical events committees.

The assessment of 'frailty' in patients with advanced valvular heart disease has become increasingly important and is usually not included in surgical-risk algorithms. Frailty is loosely defined as a biological syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiological systems, and causing vulnerability to adverse outcomes (139). Various frailty indices have been developed and have been correlated with worsening clinical outcomes in geriatric patients in intensive care units and after surgery (144–146). In general, the evaluation of frailty demands a composite analysis of several categorical and continuous variables including mobility, strength, endurance, activities of daily living, cognitive impairment, and nutritional status (as discerned by body mass index and biomarkers such as serum albumin) (147,148). Although there is no standard frailty index which has been applied and validated in high-risk AS patients, multiple preliminary efforts are ongoing and VARC proposes to include measures of frailty in future clinical trials as a component of clinical benefit endpoints.

Therapy-Specific Endpoints

Given the complex nature of TAVI procedures and the rapid evolution of devices and procedural techniques, VARC proposes to record in case report forms (but not as formal endpoints) an open category of therapy-specific endpoints which may be relevant to clinical outcomes or device performance. Examples of such events include the following: 1) the unplanned use of cardio-pulmonary bypass to manage hemodynamic compromise or to reverse procedural complications; 2) conversion from a 'failed' percutaneous transcatheter procedure to an 'open' surgical AVR or to a surgical-access TAVI (149,150); 3) ventricular perforation (for any reason) with and without cardiac tamponade (151); 4) prosthetic valve migration or dislocation from the native aortic valve landing zone (152,153); 5) frequency, reasons, and results of post-TAVI balloon dilation; 6) frequency, reasons, and results after placement of a second valve over the original valve, so-called TAVI 'valve-in-valve' (154,155); 7) integrity of the support structure, including strut fractures, compression or other evidence of geometry distortion (requires careful serial imaging modalities including cine-fluoroscopic analyses and echocardiography) (90,156–158); 8) instances of device recapture (with or without repositioning), or retrieval (removal from the body) which occur during the index procedure; 9) and re-intervention (either percutaneous or surgical) for any reason after the index procedure (159). As appropriate, the timing of these events (during the index procedure, in-hospital, or post-discharge) should be carefully recorded. This category is intended to be a dynamic platform and should be added to the case report forms.

Clinically Relevant Composite Endpoints

Although VARC discourages the overuse of composite endpoints, to achieve overall impressions of safety and effectiveness may require the incorporation of more than single endpoints. These strategic assessments of TAVI as an alternative therapy should ideally include device, procedure, and patient-oriented factors. Valve Academic Research Consortium proposes three composite endpoints (Table 10): device success (intra-procedure), a combined safety endpoint (at 30 days), and a combined efficacy endpoint (at 1 year or longer).

Device success is a 'technical' composite endpoint meant to characterize the acute device and procedural factors which underlie vascular access, delivery, and performance of the TAVI system. Echocardiography should be routinely utilized as the standard for measuring prosthetic valve stenosis and regurgitation immediately after TAVI, and should always be performed in a resting state, either within 24 to 48 h after the index procedure or before hospital discharge.

Table 10 Composite End Points

Device success
Successful vascular access, delivery and deployment of the device and successful retrieval of the delivery system
Correct position of the device in the proper anatomical location
Intended performance of the prosthetic heart valve (aortic valve area >1.2 cm^2 and mean aortic valve gradient <20 mm Hg or peak velocity <3 m/s, without moderate or severe prosthetic valve AR)
Only one valve implanted in the proper anatomical location
Combined safety endpoint (at 30 days)
All-cause mortality
Major stroke
Life-threatening (or disabling) bleeding
Acute kidney injury—Stage 3 (including renal replacement therapy)
Peri-procedural MI
Major vascular complication
Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
Combined efficacy endpoint (at 1 yr or longer)
All-cause mortality (after 30 days)
Failure of current therapy for AS, requiring hospitalization for symptoms of valve-related or cardiac decompensation
Prosthetic heart valve dysfunction (aortic valve area <1.2 cm^2 and mean aortic valve gradient ≥20 mm Hg or peak velocity ≥3 m/s, OR moderate or severe prosthetic valve AR)

The 30-day *combined safety endpoint* is a hierarchical composite of the most relevant patient-oriented safety endpoints previously defined by VARC (Table 10). In addition, a repeat procedure in the first 30 days (either surgery or intervention) to treat valve-related dysfunction is also incorporated in this endpoint. Examples of urgent repeat procedures would include balloon aortic valvuloplasty or repeat TAVI (valve-in-valve) to treat either paravalvular or central severe AR after the TAVI. The focus on 30-day events after the index procedure is meant to isolate safety concerns largely pertaining to early device performance and the procedure. Nonetheless, overall patient safety also requires a careful examination of pertinent individual safety endpoints over the life history of the device.

The time-sensitive assessment of TAVI effectiveness requires a more delayed *combined efficacy endpoint* incorporating major clinical and valve performance factors. Valve Academic Research Consortium proposes a 1-year (or longer) time interval for the combined efficacy endpoint integrating three important endpoints: 1) all-cause mortality *after 30 days*, meant to reflect therapy effectiveness by measuring prevention of AS-related mortality over time; 2) failure of the current therapy for AS, requiring hospitalization for symptoms of valve-related or cardiac decompensation (adjudicated episodes of heart failure, angina, or syncope requiring an aortic valve procedure or intensification of medical management); 3) evidence of prosthetic valve dysfunction, defined using strict echocardiography criteria, possibly in conjunction with other signs of functional deterioration.

Discussion

The VARC was convened in response to an urgent call for standardized clinical research processes involving the emerging field of transcatheter valve therapies, and more specifically, TAVI in high-surgical-risk patients with AS. The inter-disciplinary nature of TAVI, combining aspects of both surgical and interventional therapies, presented special challenges and required an enlightened and collaborative approach to the development of clinical research recommendations and endpoint definitions (160,161). The VARC initiative is an attempt to achieve a necessary consensus among the various subspecialties and stakeholders, such that this innovative treatment strategy may be evaluated objectively and according to a set of practical endpoint definitions.

This consensus manuscript is not intended to be interpreted as a 'guidelines' or 'guidance' document and although thoroughly reviewed by individuals from 7 cardiology and cardiac surgery societies, the content has not been subjected to a formal society guidelines review process. These standardized endpoints are measureable, apply to both predicate surgical and new transcatheter therapies, can be adjudicated by clinical events committees, and can be used to compare findings from different clinical trials. By intent, this consensus manuscript was not device-specific and the definitions can be applied to next generation and iterative TAVI devices already under early stages of clinical investigation (162–165).

Given the rapid growth in transcatheter valve therapies, and the potential exposure of this technology to lower risk patient populations, it is certain that this preliminary attempt to arrive at consensus endpoint definitions for TAVI will need refinement in the future. In principle, the consensus process calls for the highest standards of clinical research, including 1) inter-disciplinary experts gathering to arrive at standardized endpoint definitions, 2) harmonized and well-structured data collection, interpretation, and reporting for specific TAVI-related clinical events, and 3) the consistent use of central core laboratories and independent, blinded endpoint adjudication.

Many of the endpoints discussed in this manuscript are sufficiently general that they can be applied to other AS populations and to other valvular heart disease clinical research scenarios, both surgical and interventional. This is particularly germane to TAVI clinical research, as new studies involving lower risk AS patients are already being considered. Importantly, recent reports and randomized trials using new catheter-based mitral valve therapies to treat mitral regurgitation (166–168) also suffer from non-standardized endpoint definitions and might well benefit from a comparable VARC consensus effort.

This consensus manuscript, which represents the 'first step' in a much longer road to help improve clinical research in valvular heart disease, has several limitations. The endpoint definitions were intended to be reasonably broad, but

nonetheless in some instances are also intentionally narrow to address the specific considerations of TAVI in high-surgical-risk patients with severe AS. Therefore, application of all of these endpoint definitions to other patient populations may be problematic. The important area of preclinical device testing, both assessments of valve and support structure properties and in vivo animal studies, is beyond the scope of this manuscript. Other aspects of clinical trial design and clinical trial methodologies are also essential to optimize clinical research, but similarly, a comprehensive treatment of these subjects could not be included in this manuscript. Finally, many global endpoints, such as stroke and bleeding and some specific endpoints, such as paravalvular regurgitation, are themselves in a state of evolution, subject to modifications by other consensus committees in the near future.

The VARC process embodied in this manuscript was an ambitious multi-disciplinary attempt to bring order through consensus, thereby providing standardization of clinical research in the burgeoning area of transcatheter aortic valve therapy. Hopefully, this template can also serve as a model to improve clinical research methodologies in the evaluation of new therapies for other cardiovascular diseases.

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Key Words: transcatheter aortic valve implantation.

APPENDIX 1: VALVE ACADEMIC RESEARCH CONSORTIUM CONTRIBUTING GROUPS

1. Academic Research Organizations
   Cardialysis (Rotterdam, the Netherlands)
   Cardiovascular Research Foundation (New York, NY, USA)
   Duke Clinical Research Institute (Durham, NC, USA)
   Harvard Clinical Research Institute (Boston, MA, USA)
2. Societies
   American Association for Thoracic Surgery
   American College of Cardiology
   American Heart Association
   European Association for CardioThoracic Surgery
   European Society of Cardiology
   Society of Cardiac Angiography and Intervention
   Society of Thoracic Surgeons.
3. U.S. Food and Drug Administration
4. Industry Representatives

APPENDIX 2: VALVE ACADEMIC RESEARCH CONSORTIUM PARTICIPANTS

1. Clinical Research Organizations
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APPENDIX 3: MINIMUM DATA COLLECTION AND ENDPOINT REQUIREMENTS AFTER TAVI

- Mortality (all cause and cardiovascular)
- Myocardial Infarction (peri-procedural and spontaneous) Stroke (major and minor)
- Bleeding (life threatening or disabling and major)
- Acute kidney injury (modified RIFLE stage 2 and 3, including RRT)
- Vascular complications (major)
- Prosthetic valve performance (requires serial echocardiography assessments)
  (a) Prosthetic valve stenosis (possible and significant) and regurgitation (moderate or severe with special reference to paravalvular regurgitation)
  (b) Prosthetic valve thrombosis
  (c) Prosthetic valve endocarditis
- Prosthetic valve-associated complications
  (a) Conduction disturbances and cardiac arrhythmias (including new LBBB, new permanent pacemaker implantation, and new supraventricular or ventricular arrhythmias) and
  (b) Coronary obstruction
- Clinical benefit endpoints
  (a) Symptom status (global assessments using NHYA classification and some measure of quality of life)
  (b) Repeat hospitalization (.30 days after the index procedure) for valve-related or cardiac decompensation)
- Therapy specific endpoints (ventricular perforation at any time resulting in cardiac tamponade, prosthetic valve embolization, and acute or delayed valve-in-valve treatment)
- Composite endpoints
  (a) Device success
  (b) Combined safety endpoint (at 30 days)
  (c) Combined efficacy endpoint (at 1 year or longer)