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Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document[#]

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[#] 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 (FDA), and several independent experts. However, it is not a society document. Neither the societies nor the FDA have been asked to endorse the document.

This paper also includes accompanying supplementary data published at the following website: www.eurointervention.org

Abstract

Objectives: The aim of the current Valvular Academic Research Consortium (VARC)-2 initiative was to revisit the selection and definitions of transcatheter aortic valve implantation (TAVI)- clinical endpoints to make them more suitable to the present and future needs of clinical trials. In addition, this document is intended to expand understanding of patient risk stratification and case selection.

Background: A recent study confirmed that VARC definitions have already been incorporated into clinical and research practice and represent a new standard for consistency in reporting clinical outcomes of patients with symptomatic severe aortic stenosis (AS) undergoing TAVI. However, as the clinical experience with this technology has matured and expanded, certain definitions have become unsuitable or ambiguous.

Methods and results: Two in-person meetings (held in September 2011 in Washington, DC, USA, and in February 2012 in Rotterdam, The Netherlands) involving VARC study group members, independent experts (including surgeons, interventional and non-interventional cardiologists, imaging specialists, neurologists, geriatric specialists, and clinical trialists), the United States Food and Drug Administration (FDA), and industry representatives, provided much of the substantive discussion from which this VARC-2 consensus manuscript was derived. This document also provides an overview of risk assessment and patient stratification that needed to be considered for accurate patient inclusion in studies. Working groups were assigned to define the following clinical endpoints: mortality, stroke, myocardial infarction, bleeding, acute kidney injury, vascular complications, conduction disturbances & arrhythmias, and a miscellaneous category including relevant complications not previously categorized. Furthermore, comprehensive echocardiographic recommendations are provided for evaluation of prosthetic valve (dys)function. Definitions for quality of life assessments are also reported. These endpoints formed the basis for several recommended composite endpoints.

Conclusions: This VARC-2 document has provided further standardization of endpoint definitions for studies evaluating the use of TAVI, which will lead to improved comparability and interpretability of study results, supplying an increasingly growing body of evidence with respect to transcatheter aortic valve implantation and/or surgical aortic valve replacement. This initiative and document can furthermore be used as a model during current endeavors of applying definitions to other transcatheter valve therapies (for example, mitral valve repair).

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Introduction

The first Valve Academic Research Consortium (VARC) consensus manuscript was published in January 2011 with the goal of achieving 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, for transcatheter aortic valve implantation (TAVI) clinical trials[1,2]. A recent pooled analysis, which included 3,519 patients from 16 unique studies, confirms that VARC definitions have already been incorporated into clinical and research practice and represent a new standard for consistency in reporting clinical outcomes of patients with symptomatic severe aortic stenosis (AS) undergoing TAVI[3]. However, as the clinical experience with this technology has matured and expanded, certain definitions have become unsuitable or ambiguous[3-7]. The aim of the current VARC was therefore to revisit the selection and definitions of TAVI-related clinical endpoints to make them more suitable to the present and future needs of clinical trials. In addition, this document is intended to expand understanding of patient risk stratification and case selection.

Similar to the VARC-1 process, two in-person meetings (held in September 2011 in Washington, DC, USA, and in February 2012 in Rotterdam, The Netherlands) involving VARC study group members, independent experts (including surgeons, interventional and non-interventional cardiologists, imaging specialists, neurologists, geriatric specialists, and clinical trialists), the United States Food and Drug Administration (FDA), and industry representatives, provided much of the substantive discussion from which this VARC-2 consensus manuscript was derived **(See Appendix)**.

Risk scores and comorbidities

Risk stratification of patients is crucial to identify appropriate candidates for specific cardiac procedures. The EuroSCORE and Society of Thoracic Surgeons (STS) score are the most widely used risk scores to predict operative mortality in cardiac surgery. These models were developed and validated in a standard surgical risk population. The predictive power of both models is therefore suboptimal in high-risk patients with valvular disease, although the STS score has shown to outperform the Logistic EuroSCORE[8]. These models are even more limited in application to patients who are considered prohibitive risk for cardiac surgery, a cohort of great relevance for TAVI. Current models could be improved by the addition of specific clinical and anatomical variables that affect mortality[9]. As an example, the presence of a porcelain aorta and frailty are important factors not included in either risk model but are routinely considered during patient evaluation (**Figure 1** and **Table 1**).

Perhaps the most important patient characteristic not included in current risk models is "frailty"[10]. Frailty is frequently assessed subjectively based upon an informal "eyeball test". However, physical performance assessments such as gait speed and grip strength are more objective performance measures that may capture an individual's overall functional status[11]. These continuous measures are reproducible and can be re-assessed at various time points. In addition, they require no language translation. Assessments of cognition, weight (loss), activity level, and independence in activities of daily living provide additional information on the overall health state of the individual[11]. These limitations are more often found in patients with high comorbidity burden and may coexist with certain laboratory findings (e.g., low serum albumin, elevated inflammatory markers, anaemia) that further reflect the health state and physiologic reserve of the frail patient.

Baseline evaluation of the presence of cognitive dysfunction (mild cognitive impairment or dementia) has also emerged as an essential part of the initial risk stratification, especially in older populations, where risk, benefit, and cost-effectiveness of invasive procedures must be weighed judiciously. Pre-procedural cognitive assessment may also help avoid attributing post-procedural mental status changes to stroke categories. Among the several clinically established rating scales (e.g. mini-mental state examination (MMSE), modified Telephone Interview of Cognitive Status (TICS-M), Clinical Dementia Rating Scale)[12], there is no particular standard for TAVI. Nevertheless, some systematic cognitive assessment by neuropsychological experts should be a part of the initial heart team evaluation.

Table 1 provides an overview of these and other risk factors (**Figure 1**, **Figure 2** and **Figure 3**) and VARC-2 recommendations on how each should be assessed. In clinical trials, it will be important to capture reasons for extreme operative risk and to standardize the evaluation criteria and process. This will help to determine which subsets of patients are likely to benefit from TAVI treatment.

Patient stratification - The heart team approach

Valve Academic Research Consortium-2 recommends the use of a heart team for patient evaluation. The heart team should consist of at least (interventional) cardiologists, cardiovascular surgeons, and imaging specialists, but its composition is dynamic and can also include anaesthesiologists, geriatricians, neurologists, etc. This multi-disciplinary team should convene as a group on a regular basis to review and interpret clinical data to arrive at a consensus on the optimal treatment strategy for each patient. The heart team approach also allows for adjustment of the decision-making process according to local experience and circumstances.

The heart team should agree on an estimated 30-day mortality risk for each patient based upon integrating a careful clinical assessment and utilizing appropriate risk prediction scoring systems, preferably the STS score. Surgical mortality risk strata are difficult to precisely assign, but an estimated 30-day-mortality of <4% is considered low risk, 4-10% is intermediate risk, >10% is high risk, and >15% is very high risk. A patient is considered extreme risk if at least 2 cardiovascular surgeons from a tertiary centre of excellence deny surgery because of prohibitive operative risks, estimated to be a combined >50% risk of irreversible morbidity or mortality[13]. In addition to the specific risk factors that can prohibit patients from undergoing TAVI or surgical aortic valve replacement (SAVR) **(Table 1)**, operative risk assessment is also important to identify patients who are likely not to benefit from either TAVI or SAVR

Table 1. Risk factors not captured by traditional risk scores.

Co-morbidities	Definition/Criteria	Diagnostic modalities
Porcelain aorta or severely atherosclerotic aorta	Heavy circumferential calcification or severe atheromatous plaques of the entire ascending aorta extending to the arch such that aortic cross-clamping is not feasible	Non-contrast axial CT at levels: Sinotubular junction Tubular ascending aorta between sinotubular junction and innominate Innominate artery Entire transverse arch
Frailty	Slowness, weakness, exhaustion, wasting and malnutrition, poor endurance and inactivity, loss of independence Criteria: 5 meter walking time* Grip strength* BMI <20 kg/m^2 and/or weight loss 5 kg/yr Serum albumin <3.5 g/dL Cognitive impairment or dementia	Medical history Physical examination Physical performance measures Cognitive assessments Laboratory tests
Severe liver disease/cirrhosis	Any of the following: Child-Pugh class C MELD score ≥10 Portal-caval, spleno-renal, or transjugular intrahepatic portal shunt Biopsy proven cirrhosis with portal hypertension or hepatocellular dysfunction	Medical history Physical examination Laboratory tests Child-Pugh classification MELD score Liver biopsy
Hostile chest	Any of the following or other reasons that make redo operation through sternotomy or right anterior thoracotomy prohibitively hazardous: Abnormal chest wall anatomy due to severe kyphoscoliosis or other skeletal abnormalities (including thoracoplasty, Potts' disease) Complications from prior surgery Evidence of severe radiation damage (e.g. skin burns, bone destruction, muscle loss, lung fibrosis or esophageal stricture) History of multiple recurrent pleural effusions causing internal adhesions	Medical history Physical examination Chest X-Ray CT scan
IMA or other critical conduit(s) crossing midline and/or adherent to posterior table of sternum	A patent IMA graft that is adherent to the sternum such that injuring it during re-operation is likely. A patient may be considered extreme risk if any of the following are present: The conduit(s) are radiographically indistinguishable from the posterior table of the sternum. The conduit(s) are radiographically distinguishable from the posterior table of the sternum but lie within 2-3 mm of the posterior table.	Axial CT scan images illustrating graft crossing the midline so the distance from sternum to graft can be measured. Angiogram from the lateral and PA projections and/or a CPR or VR (Volume rendering) 3-D reconstructed CT scan image showing relationships between graft and sternum
Severe pulmonary hypertension Severe right ventricular dysfunction	Primary or secondary pulmonary hypertension with PA systolic pressures greater than 2/3 of systemic pressure Criteria as defined by the guidelines (e.g. TAPSE <15mm, RV end-systolic area >20 cm^2, etc)¶	Echocardiography, right-and left heart-catheterization documenting PA and systemic pressures Documentation of secondary causes of pulmonary hypertension

*Variable with respect to age and gender without validated scientific thresholds; ¶ Rudski et al.[72]; CT: computed tomography; MELD: Model for End-Stage Liver Disease; INR: international normalized ratio; IMA: internal mammary artery; PA: pulmonary artery

(the so-called "futility" category of high-risk patients). An expected improvement in quality of life may further be necessary to identify treatment responders versus non-responders. Individualized life expectancy assumptions should be incorporated by the heart team in the clinical decision-making process as a central factor in weighing the risk-benefit ratio. Prognostic indices of life expectancy may play a central role in moving beyond arbitrary age-based cutoffs[14].

The most important role of the heart team is to provide customized management decisions for common and unusual clinical scenarios in terms of patient selection, procedural performance and complication management. An example is the frequent situation of severe AS and concomitant coronary artery disease (CAD). The complexity of CAD and appropriate revascularization strategies in the setting of AS should be determined by consensus from interventional

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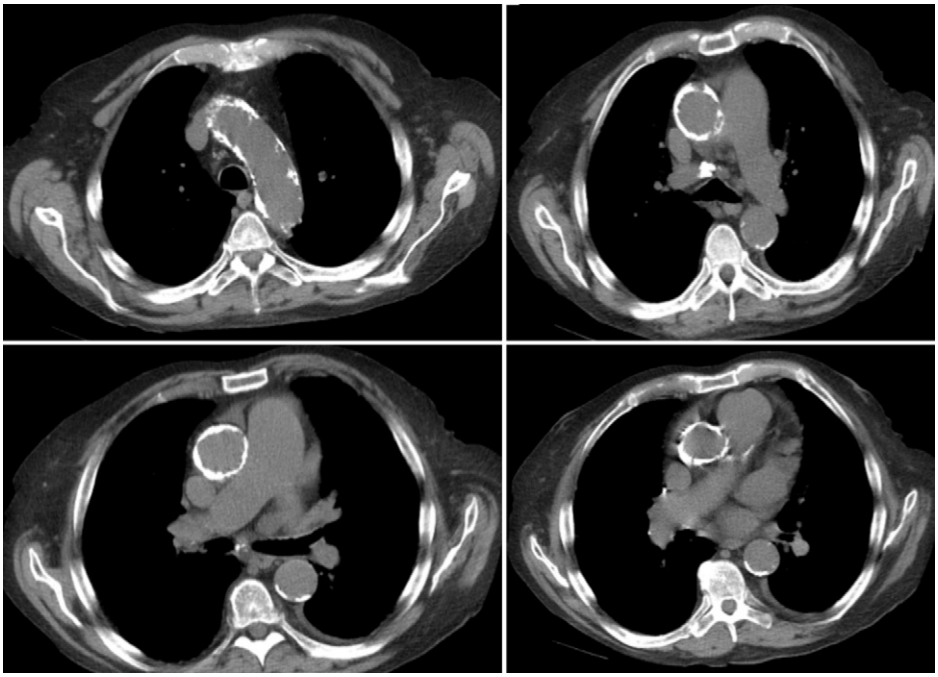

Figure 1. *Porcelain aorta (or severely atherosclerotic aorta).*

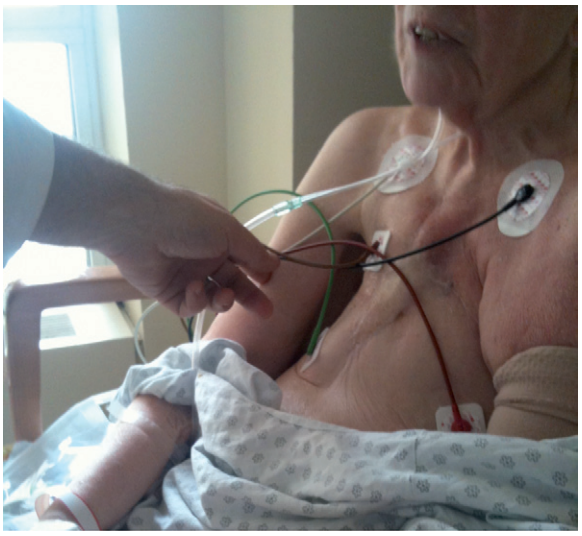

Figure 2. *Hostile chest.*

cardiologists and cardiovascular surgeons[15,16]. In new TAVI clinical trials, angiographic risk scores (e.g., SYNTAX score) may be utilized to help determine the complexity of CAD, as a basis for inclusion in the trial. Thresholds for coronary revascularization and the choice for a staged or concomitant PCI with TAVI should be guided by the complexity of the CAD and other factors as determined by the heart team[17,18]. In general, the plan to deal with other coexisting conditions (such as atrial fibrillation, other valvular lesions, and other congenital lesions) should be prespecified and all complications encountered in the treatment of associated conditions (including treatment after the TAVI procedure) should be captured. Such thorough pre-procedural assessment is also valuable in discriminating new post-procedural complications from simple exacerbations of pre-existing conditions.

Clinical endpoints

MORTALITY

In addition to the original VARC definitions, VARC-2 recommends collection of immediate procedural mortality to capture intra-procedural events that result in immediate or consequent death ≤72 h post-procedure. Taking into account the surgical literature, procedural mortality consist of all-cause mortality within 30 days or during index procedure hospitalization – if the postoperative length of stay is longer than 30 days.

The cause of death should be captured, based on a careful review of narrative summaries and source materials. All-cause, cardiovascular, and non-cardiovascular mortality should be reported after 30 days during follow-up **(Table 2)**. In determining the cause of death, the adjudication committee should consider the clinical context at the time of the index procedure and during the time interval leading up to death. All efforts (including use of national death registries) should be made to identify, precisely characterize, and appropriately classify any death.

MYOCARDIAL INFARCTION

Myocardial injury as determined by a significant rise in cardiac biomarkers occurs frequently following TAVI, and a significant magnitude of myocardial injury has been associated with worse outcomes[19].

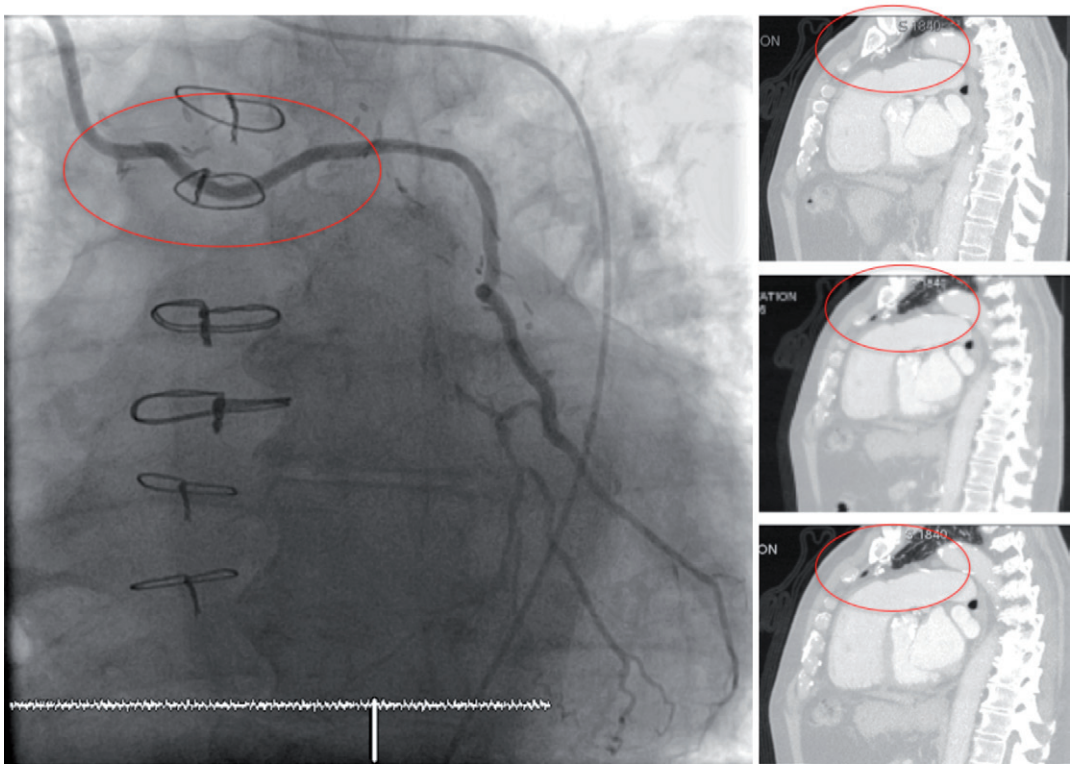

Figure 3. *Patent IMA graft crossing midline and/or adherent to posterior table of sternum.*

Table 2. Mortality.

All-cause mortality
Cardiovascular mortality
Any of the following criteria:
Death due to proximate cardiac cause (e.g. myocardial infarction, cardiac tamponade, worsening heart failure)
Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease
All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
All valve-related deaths including structural or nonstructural valve dysfunction or other valve-related adverse events
Sudden or unwitnessed death
Death of unknown cause
Non-cardiovascular mortality
Any death in which the primary cause of death is clearly related to another condition (e.g. trauma, cancer, suicide)

Valve Academic Research Consortium-2 recommends systematic collection of biomarkers of myocardial injury prior to the procedure, within 12-24 h after the procedure, at 24 h thereafter, at 72 h or at discharge, and if still elevated daily until values are declining. Similar to the previous VARC recommendations, the definition of peri-procedural (≤72 h following TAVI) MI will be based on a combination of clinical criteria and cardiac biomarkers. However, the threshold values have been adjusted **(Table 3)**. Acute ischaemic events occurring after 72 h should be considered spontaneous myocardial infarctions and defined in accordance with the universal MI guidelines[20].

STROKE

With increasing attention to stroke as an important peri-procedural complication of TAVI[21], the FDA has increasingly emphasized the need for accurate assessment of stroke and has participated actively in recommending specific details of the VARC-2 definitions. In an attempt to further align with the fundamental definitions now endorsed by the FDA[22], consensus was reached at VARC-2 to further refine the definition of stroke and recommend the use of these definitions in future TAVI clinical trials **(Table 4)**. The definitions endorsed by the FDA are intended to apply to a wide range of clinical trials and to enable those trials to assess the clinically relevant consequences of vascular brain injury for determining the safety or effectiveness of an intervention.

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Stroke may be classified as ischemic or hemorrhagic with appropriate sub-definitions. Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. Hemorrhagic stroke is defined as an acute episode of

Table 3. 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, new pathological Q waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND
Elevated cardiac biomarkers (preferable CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15x upper reference limit (troponin) or 5x for CK-MB.* If cardiac biomarkers are increased at baseline (>99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.
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 ischaemia with at least one of the following:
Symptoms of ischaemia
ECG changes indicative of new ischaemia [new ST-T changes or new left bundle branch block (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 ischaemia, and accompanied by presumably new ST 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.
*Previously in the original VARC it was 10x and 5x for troponin and CK-MB, respectively.

Table 4. Stroke and TIA.

Diagnostic criteria
Acute episode 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
Stroke – Duration of a focal or global neurological deficit ≥24 h; OR <24 h if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death
TIA – Duration of a focal or global neurological deficit <24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct
No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist*
Confirmation of the diagnosis by at least one of the following:
Neurologist or neurosurgical specialist
Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone
Stroke classification
Ischemic – An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue
Hemorrhagic – An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage
A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic
Stroke definitions¶
Disabling stroke – a mRS score of 2 or more at 90 days and an increase of at least one mRS category from an individual's pre-stroke baseline
Non-disabling stroke – a mRS score of less than 2 at 90 days or one that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline
*Patients with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction based upon neuroimaging studies (CT scan or Brain MRI). mRS: modified Rankin Scale; ¶ Modified Rankin Scale assessments should be made by qualified individuals according to a certification process[23-25].

focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. A stroke may be classified as "undetermined" if there is insufficient information to allow categorization as ischemic or hemorrhagic.

An entity closely related to ischemic stroke that should be assessed is transient ischemic attack (TIA). TIA is defined as a transient episode of focal neurological dysfunction caused by brain, spinal cord, or retinal ischemia, without acute infarction. The difference between TIA and ischemic stroke is the presence of tissue damage on neuroimaging studies or new sensory-motor deficit persisting >24 hours. By definition, TIA does not produce lasting disability.

Valve Academic Research Consortium-2 recognizes that an assessment of stroke is incomplete without an appropriate measurement of the disability resulting from the stroke. VARC-2 recommends the use of the modified Rankin Scale (mRS) to assess this clinical disability[23-25]. Assessment of the mRS should occur at all scheduled visits in a trial and at 90 days after the onset of any stroke. This approach will maximize the detection of new or recurrent strokes, assist in ongoing evaluation of events previously determined as TIA, and provide an accepted and reliable indicator of the long-term impact of a given stroke.

Previously, Valve Academic Research Consortium-2 recommended categorizing strokes as "major" and "minor" based upon mRS scores. In order to enhance accuracy in the description of a given stroke and to provide accurate categorization of strokes within a given trial, Valve Academic Research Consortium-2 now recommends the use of the terms "disabling" and "non-disabling". A disabling stroke is one that results (at 90 days after stroke onset) in a mRS score of 2 or more and an increase of at least one mRS category from an individual's pre-stroke baseline. A non-disabling stroke is one that results (at 90 days after stroke onset) in a mRS score of less than 2 or that does not result in an increase of at least one mRS category from an individual's pre-stroke baseline. In addition to this categorization in disabling and non-disabling stroke, the endpoint of all stroke should be reported.

Although brain imaging (typically, MRI for acute and chronic ischemia and hemorrhage, and CT for acute and chronic hemorrhage and chronic ischemia) is often used to supplement the clinical diagnosis of stroke[26], a diagnosis of stroke may be made on clinical grounds alone. Valve Academic Research Consortium-2 recognizes that stroke symptoms are protean and not well-suited to a pre-specified itemized listing. Accordingly, Valve Academic Research Consortium-2 recommends that a vascular neurologist experienced in clinical trials involving stroke be included in all phases of trial planning, execution, and monitoring, including involvement in the Clinical Events Committee and the Data and Safety Monitoring Board.

New insights into the timing of events show delayed or late occurrence of strokes, beyond the early post-implantation phase[27]. This may suggest that the cause of stroke is additionally related to other factors or patient susceptibilities and should generate active investigation of devices and adjunctive pharmacotherapy to reduce the frequency and severity of strokes after TAVI, including precise documentation of the use and dosage of antithrombotic and antiplatelet medication. Patient baseline characteristics (e.g., carotid stenosis) and postoperative complications (e.g., atrial fibrillation) need to be carefully documented to be able to identify contributing causes of stroke.

Invasive stroke management (catheter-based intracranial intervention) is gaining an increasingly important role and may impact morbidity and mortality. Valve Academic Research Consortium-2 therefore recommends ascertainment of any acute stroke management strategies (e.g., aspiration, thrombolysis, or conservative management).

BLEEDING COMPLICATIONS

Valve Academic Research Consortium-2 acknowledges the fact that the Bleeding Academic Research Consortium (BARC) recently convened and established standardized bleeding definitions for patients receiving antithrombotic therapy and undergoing coronary revascularization (PCI or CABG)[28,29]. However, because the current definitions have been well adopted and shown to be accurate in predicting adverse events[30], Valve Academic Research Consortium-2 has chosen to maintain the original VARC definitions **(Table 5)**, recognizing that future validation of BARC criteria in this population may warrant revision of the current recommendations.

With respect to blood transfusions, it is critical to acknowledge that a bleeding complication has to be the result of overt bleeding and cannot be adjudicated based on blood transfusions alone.

ACUTE KIDNEY INJURY (AKI)

The original VARC definitions recommended use of a modified version of the RIFLE classification. However, we now recommend using the AKIN system **(Table 6)**, which is a modified version of RIFLE that has been adopted by many in the nephrology community, including the KDIGO initiative[31,32]. As a result, AKI can also be diagnosed according to urine output measures **(Table 6)**.

In comparison with the original VARC, the timing for diagnosis of AKI is extended from 72 h to 7 days. Patients that experience AKI should have follow-up renal function assessments after 7 days until stabilization.

Table 5. Bleeding.

Life-threatening or disabling bleeding
Fatal bleeding (BARC type 5) OR
Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR
Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR
Overt source of bleeding with drop in haemoglobin of ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* (BARC type 3b)
Major bleeding (BARC type 3a)
Overt bleeding either associated with a drop in the haemoglobin level of at least 3.0 g/dL or requiring transfusion of 2 or 3 units of whole blood/RBC, or causing hospitalization or permanent injury, or requiring surgery AND
Does not meet criteria of life-threatening or disabling bleeding
Minor bleeding (BARC type 2 or 3a, depending on the severity)
Any bleeding worthy of clinical mention (e.g. access site haematoma) that does not qualify as life-threatening, disabling, or major

*Given one unit of packed RBC typically will raise haemoglobin concentration by 1 g/dL, an estimated decrease in haemoglobin will be calculated; BARC: Bleeding Academic Research Consortium[29]; RBC: red blood cell

VASCULAR COMPLICATIONS

Table 7 lists VARC-2 definitions for major and minor vascular complications. Further clarifications of these definitions to supplement the original VARC document are as follows. Pre-planned surgical access or a planned endovascular approach to vascular closure (e.g., "pre-closure")[33,34] should be considered as part of the TAVI procedure and not as a complication, unless untoward clinical consequences are documented (e.g., bleeding complications, limb ischaemia, distal embolization, or neurological impairment). Unplanned endovascular stenting or surgical repair for any vascular complications during the index procedure without other clinical sequellae should be considered as a minor vascular complication, except if associated with qualifying consequences **(Table 7)**. Complications related to alternative

Table 6. Acute kidney injury (AKIN classification*)

Stage 1
Increase in serum creatinine to 150-199% (1.5-1.99 × increase compared with baseline) OR increase of ≥0.3 mg/dL (≥26.4 mmol/L) OR
Urine output <0.5 ml/kg per hour for >6 but <12 hours
Stage 2
Increase in serum creatinine to 200-299% (2.0-2.99 × increase compared with baseline) OR
Urine output <0.5 ml/kg per hour for >12 but <24 hours
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) OR
Urine output <0.3 ml/kg per hour for ≥24 hours OR
Anuria for ≥12 hours

The increase in creatinine must occur within 48 hours; *Mehta et al.[31] ¶ Patients receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria

access sites, including the left-ventricular apex, subclavian artery, or aorta should be systematically recorded. In order to ensure accurate capture of these elements, VARC strongly recommends that detailed information regarding the access site and pre-planned vascular closure technique be recorded as well as the use of any additional unplanned access or closure techniques (surgical repair, endovascular stenting or endovascular balloon therapy). Since many vascular complications will also result in a bleeding complication, events that meet VARC-2 definitions for both categories should be reported in both categories. Finally, VARC-2 recommends that all vascular complications be recorded as either access (e.g., iliac rupture) or non-access site related (e.g., ascending aorta dissection or rupture unless aortic access is used and the event originates from cannulation site).

CONDUCTION DISTURBANCES AND ARRHYTHMIAS

Valve Academic Research Consortium-2 proposes systematic collection of data on the frequency of implant-related new and/or worsened conduction disturbances and the incidence and indication for permanent pacemaker implantation **(Table 8)**. In addition, the frequency of specific arrhythmias following TAVI should be recorded as they may result in prolonged hospitalization and impaired clinical outcomes. New-onset atrial fibrillation (or flutter) is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of atrial fibrillation (AF) and lasts sufficiently long to be recorded on a 12-lead ECG, or for at least 30 seconds on a rhythm strip[35]. The therapeutic approach to new-onset AF (spontaneous conversion, electrical or medical cardioversion, initiation of oral anticoagulation, and rate or rhythm control medications) and any clinical consequences should be thoroughly documented in the case report form.

OTHER TAVI-RELATED COMPLICATIONS

The original VARC document recommended collection of a number of TAVI-related complications, but did not provide specific endpoint definitions for several endpoints. Valve Academic Research Consortium-2 recommends reporting any other complications related to the TAVI procedure, even those occurring less frequently, and provides formal Valve Academic Research Consortium-2 definitions **(Table 9)**[36-38].

ADDITIONAL CONSIDERATIONS

For studies or trials where the occurrence, prevention or treatment of cerebral infarction is a fundamental feature (e.g., embolic protection devices) additional appropriate imaging in all or a subset of patients may be necessary to allow determination of effectiveness.

Table 7. Vascular access site and access-related complications.

Major vascular complications
Any aortic dissection, aortic rupture, annulus rupture, left ventricle perforation, or new apical aneurysm/pseudo-aneurysm OR
Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, compartment syndrome, percutaneous closure device failure) leading to death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment OR
Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage OR
The use of unplanned endovascular or surgical intervention associated with death, major bleeding, visceral ischaemia or neurological impairment OR
Any new ipsilateral lower extremity ischemia documented by patient symptoms, physical exam, and/or decreased or absent blood flow on lower extremity angiogram OR
Surgery for access site-related nerve injury OR
Permanent access site-related nerve injury
Minor vascular complications
Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneuysms, hematomas, percutaneous closure device failure) not leading to death, life-threatening or major bleeding*, visceral ischaemia or neurological impairment OR
Distal embolization treated with embolectomy and/or thrombectomy and not resulting in amputation or irreversible end-organ damage OR
Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication OR
Vascular repair or the need for vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft)
Percutaneous closure device failure
Failure of a closure device to achieve hemostasis at the arteriotomy site leading to alternative treatment (other than manual compression or adjunctive endovascular ballooning)
*Refers to VARC bleeding definitions

Table 8. Conduction disturbances and arrhythmias.

Up to 72 h, continuous rhythm monitoring is recommended in order to maximize detection of arrhythmias
Data elements to be collected should include:
Baseline conduction abnormalities, paroxysmal or permanent atrial fibrillation (or flutter), and presence of permanent pacemaker*
Implant-related new or worsened cardiac conduction disturbance (new or worsened first degree atrioventricular (AV) block, second degree AV block (Mobitz I or Mobitz II), third degree AV block, incomplete right bundle branch block, right bundle branch block, intraventricular conduction delay, left bundle branch block, left anterior fascicular block, or left posterior fascicular block, including block requiring permanent pacemaker implant
Persistent or transient high degree AV block. High grade AV block is persistent if it is present every time the underlying rhythm is checked
New permanent pacemaker implantation, with precision of the indication and number of days post-implant of placement of new permanent pacemaker
New-onset atrial fibrillation (or flutter)¶
Any new arrhythmia resulting in hemodynamic instability or requiring therapy‡
* Type of permanent pacemaker should be recorded (e.g. defibrillator, single versus dual chamber, biventricular); ¶ New-onset atrial fibrillation (or flutter)* is diagnosed as any arrhythmia within hospitalization that has the ECG characteristics of atrial fibrillation (or flutter) and lasts sufficiently long to be recorded on a 12-lead ECG, or at least 30 seconds on a rhythm strip; ‡ Therapy includes electrical/medical cardioversion or initiation of a new medication (oral anticoagulation, rhythm or rate controlling therapy)

Table 9. Other TAVI-related complications.

Conversion to open surgery Conversion to open sternotomy during the TAVI procedure secondary to any procedure-related complications
Unplanned use of cardiopulmonary bypass (CPB) Unplanned use of CPB for hemodynamic support at any time during the TAVI procedure
Coronary obstruction Angiographic or echocardiographic evidence of a new, partial or complete, obstruction of a coronary ostium, either by the valve prosthesis itself, the native leaflets, calcifications, or dissection, occurring during or after the TAVI procedure
Ventricular septal perforation Angiographic or echocardiographic evidence of a new septal perforation during or after the TAVI procedure
Mitral valve apparatus damage or dysfunction Angiographic or echocardiographic evidence of new damage (chordae papillary muscle, or to the leaflet) to the mitral valve apparatus or dysfunction (e.g. restrictions due to the THV) of the mitral valve during or after the TAVI procedure
Cardiac tamponade Evidence of a new pericardial effusion associated with hemodynamic instability and clearly related to the TAVI procedure
Endocarditis Any one of the following: Fulfillment of the Duke endocarditis criteria* Evidence of abscess, paravalvular leak, pus, or vegetation confirmed as secondary to infection by histological or bacteriological studies during a re-operation Findings of abscess, pus, or vegetation involving a repaired or replaced valve during an autopsy
Valve thrombosis 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. Note that valve-associated thrombus identified at autopsy in a patient whose cause of death was not valve-related should not be reported as valve thrombosis
Valve malpositioning Valve migration After initial correct positioning, the valve prosthesis moves upward or downward, within the aortic annulus from its initial position, with or without consequences Valve embolization The valve prosthesis moves during or after deployment such that it loses contact with the aortic annulus Ectopic valve deployment Permanent deployment of the valve prosthesis in a location other than the aortic root
TAV-in-TAV deployment An additional valve prosthesis is implanted within a previously implanted prosthesis because of suboptimal device position and/or function, during or after the index procedure

* Durack et al.[73]; TAVI: transcatheter aortic valve implantation; THV: transcatheter heart valve

Valvular function

VARC-2 maintains the original recommendations to use echocardiography as the primary imaging modality for assessment of prosthetic valve function[39]. This should include valve position, morphology, function, and evaluation of LV and RV size and function. The suggested time-points for routine follow-up transthoracic echocardiography (TTE) following valve implantation are: immediately (before discharge) following implantation for transarterial approaches or within 30 days for transapical or transaortic approaches, 6 months following implantation, 1 year following implantation, and yearly thereafter. At these endpoints, prosthetic aortic valve stenosis and regurgitation should be reported.

TRANSCATHETER VALVE STENOSIS

The assessment of prosthetic valve stenosis should be an integrative process utilizing multiple parameters of valve function. **Table 10** outlines the primary parameters used for assessing prosthetic valve function based on published guidelines[40]. Divergence from the guidelines is based on a number of studies[41,42] as well as methods used in large randomized control trials of TAVI[43,44]. In addition, VARC-2 does not recommend using acceleration time, which is dependent on ventricular function and heart rate[42]. The limitation of flow-dependent parameters such as peak jet velocity or mean transprosthetic gradient is obvious, however, even flow-independent parameters such as effective orifice area (EOA) and Doppler velocity index (DVI) have limitations: i) the absolute EOA does not account for the cardiac output requirements in relation to patient's body size thus lower criteria should be used to define prosthetic valve stenosis in patients with BSA<1.6 m^2 **(Table 10)**, ii) the indexed EOA may overestimate the valve-related hemodynamic burden in obesity, hence, lower criteria may be more appropriate in patients with body mass index ≥30 kg/m^2, iii) DVI severity criteria are dependent on left ventricular outflow tract (LVOT) size, thus a lower threshold may be more appropriate in patients with LVOT diameters of >25 mm. The EOA should generally be calculated with the use of the LVOT diameter and velocity measured just underneath the apical margin of the valve stent[45,46]. In cases where the landing zone of the stent is low in the LVOT, the diameter and velocity may both be measured in the proximal portion of the stent. Unlike the surgically-implanted valve, the transcatheter prosthetic valve EOA is defined not only by the size of the valve but also by the patient's aortic valve/annular anatomy and procedural variables. Thus, well-established normal transcatheter valve gradients and EOAs based on pre-implant aortic annular dimensions do not currently exist. Clinicians should be aware of this variability when assessing a patients for transcatheter valve function and VARC-2 strongly recommends that the patient's own initial post-implant study be used as a reference for serial comparisons.

Assessment of transcatheter valve dysfunction includes the immediate post-TAVI hemodynamics and the follow-up evaluation. The immediate post-TAVI evaluation documents initial valve appearance (position and circularity of the stent, and leaflet morphology and motion) and a comprehensive hemodynamic evaluation. VARC-2 advocates using the integrative approach outlined in the algorithm shown in **Figure 4** as part of a comprehensive hemodynamic evaluation by initially using one flow dependent (e.g., mean gradient) and one flow independent criterion (e.g., EOA) for

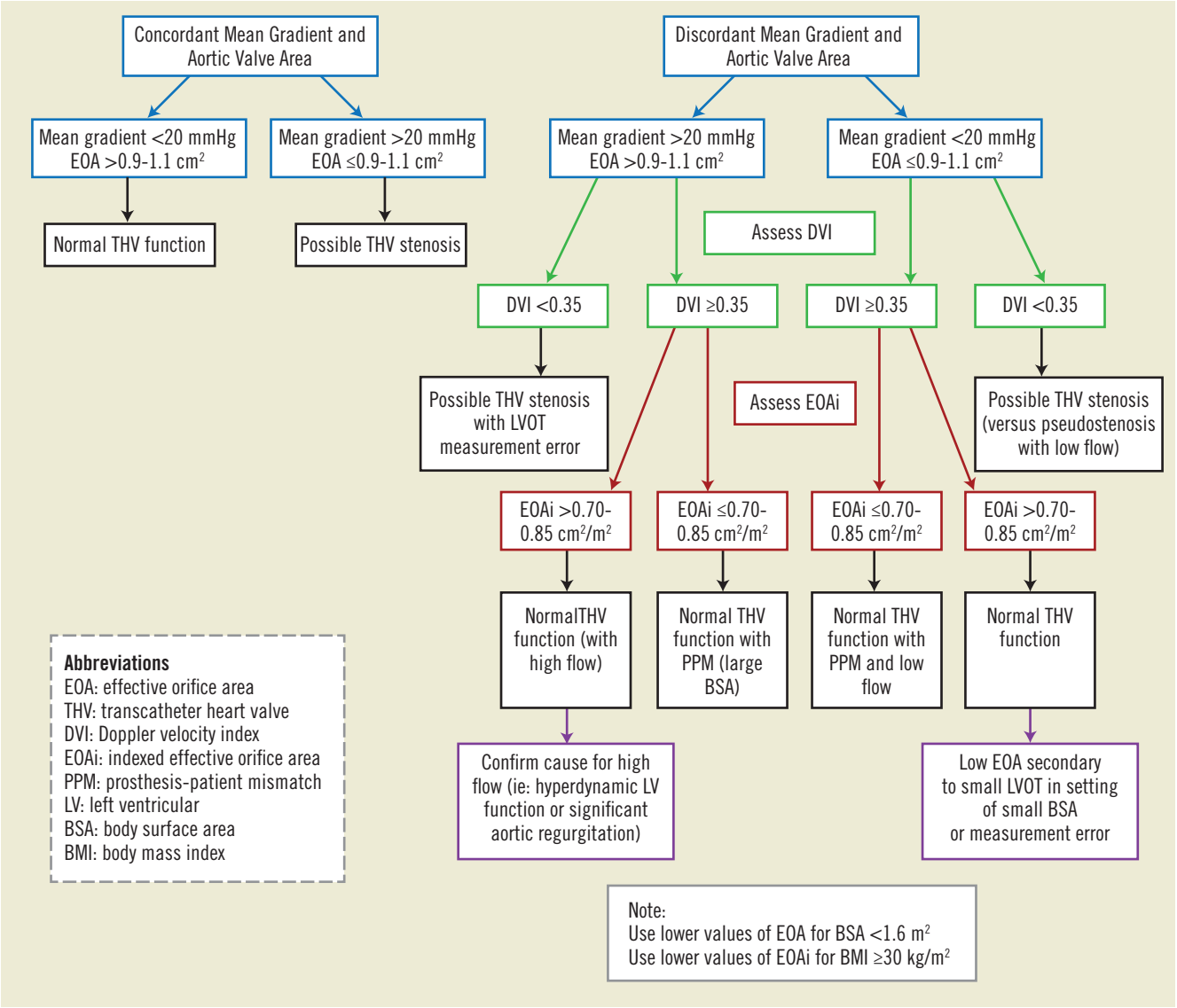

Figure 4. *Transcatheter heart valve hemodynamic evaluation algorithm.*

the initial hemodynamic evaluation. If there is discordance between these measurements, then the DVI should be calculated. An abnormal DVI indicates possible prosthetic valve dysfunction. A normal DVI indicates intrinsically normal prosthetic valve function, and the indexed EOA can then be used to determine the reason for initial measurement discordance. When the indexed EOA is low in the setting of normal DVI, the patient probably has prosthesis-patient mismatch (PPM), an indicator of the intrinsic relationship of the implanted valve to the cardiac output requirements of the patient[47]. PPM occurs in the setting of a morphologically-normal valve and is considered to be hemodynamically insignificant if the indexed EOA is >0.85 cm^2/m^2, moderate if between 0.65 and 0.85 cm^2/m^2, and severe if <0.65 cm^2/m^2. However, for obese patients (body mass index ≥30 kg/m^2) lower criteria may be more appropriate **(Table 10)**.

TRANSCATHETER VALVE REGURGITATION

There is growing evidence suggesting a significant association of post-procedural paravalvular regurgitation with short- and long-term mortality[48,49]. As the duration of implanted transcatheter heart valves increases, valve durability and dysfunction becomes more crucial. Evaluating the presence and severity of regurgitation should include an assessment of both central and paravalvular components, with a combined measurement of 'total' aortic regurgitation (AR) reflecting the summed volume load imposed on the LV **(Table 10)**. Quantitative and semi-quantitative hemodynamic assessment of AR severity should be performed with Doppler echocardiography according to the guidelines[39,50,51]. Color Doppler evaluation should be performed just below the valve stent for paravalvular jets, and at the coaptation point of the leaflets for central regurgitation. Although all imaging windows should be used,

the parasternal short-axis view is critical in assessing the number and severity of paravalvular jets. Whenever possible, quantification of prosthetic regurgitant volume, effective regurgitant orifice area and regurgitant fraction **(Table 10)** should be performed[40,51,52]. The regurgitant volume may be calculated as the difference between the stroke volume across any non-regurgitant orifice (RVOT or mitral valve) and the stroke volume across the LVOT.

It is important to realize that at this time the body of evidence supporting the numerical criteria used in **Table 10** as well as **Figure 4** may be limited. These criteria should be used as guidelines for clinical decision-making and require further validation as our experience continues to expand.

FOLLOW-UP ASSESSMENTS

The follow-up assessment should also begin with valve imaging and documentation of changes in morphology. When determining whether a patient has developed hemodynamically significant structural valve failure the patient's own baseline echocardiographic parameters should be used as a reference. An increase in mean gradient >10 mmHg, a decrease in EOA >0.3-0.4 cm^2 or a reduction in DVI >0.1-0.13 probably indicates a change in valve function and should trigger a comprehensive hemodynamic evaluation. Whenever valve dysfunction is suspected, careful evaluation of valve morphology should confirm a structurally abnormal valve. In addition, measurement error must be excluded; use of a consistent LVOT diameter for more accurate follow-up study comparisons is recommended. Finally, changes in ventricular morphology would be expected in the setting of long-standing significant valvular dysfunction and this parameter may support the clinical assessment of severity.

Although the rate of moderate or severe regurgitation may appear to be less at follow-up, this may be the result of attrition of the sickest patients. To assess such time-trends it is recommended to report individual patients' progression of regurgitation, in a table that provides changes between short-term and long-term regurgitation, including mortality[48].

Quality of life

QUALITY OF LIFE EVALUATION IN AORTIC STENOSIS

New York Heart Association (NYHA) classification is limited by the discrete nature of the scale, which provides only modest resolution to detect clinically relevant changes. Moreover, since NYHA class is assessed by an external body rather than the patient, it does not reflect the patient's perspective. Thus, NYHA class is more properly considered a measure of functional status than quality of life (QOL).

Table 10. Prosthetic valve dysfunction.

Prosthetic aortic valve stenosis*			
	Normal	Mild stenosis	Moderate/Severe stenosis
Quantitative parameters (flow-dependent)¶			
Peak velocity	<3 m/s	3-4 m/s	>4 m/s
Mean gradient	<20 mmHg	20-40 mmHg	>40 mmHg
Quantitative parameters (flow-independent)			
Doppler velocity index‡	>0.35	0.35-0.25	<0.25
Effective orifice area¶	>1.1 cm^2	1.1-0.8 cm^2	<0.8 cm^2
Effective orifice area§	>0.9 cm^2	0.9-0.6 cm^2	<0.6 cm^2
Prosthesis-patient mismatch (PPM)			
	Insignificant	Moderate	Severe
Indexed effective orifice area**	>0.85 cm^2/m^2	0.85-0.65 cm^2/m^2	<0.65 cm^2/m^2
Indexed effective orifice area¶¶	>0.70 cm^2/m^2	0.90-0.60 cm^2/m^2	<0.60 cm^2/m^2
Prosthetic aortic valve regurgitation			
	Mild	Moderate	Severe
Semi-quantitative parameters			
Diastolic flow reversal in the descending aorta – PW	Absent or brief early diastolic	Intermediate	Prominent, holodiastolic
Circumferential extent of prosthetic valve paravalvular regurgitation (%)¶¶	<10%	10-29%	≥30%
Quantitative parameters‡			
Regurgitant volume (ml/beat)	<30 ml	30-59 ml	≥60 ml
Regurgitant fraction (%)	<30%	30-49%	≥50%
EROA (cm^2)	0.10 cm^2	0.10-0.29 cm^2	≥0.30 cm^2

*In conditions of normal or near normal stroke volume (50-70 mL); ¶ These parameters are more affected by flow, including concomitant aortic regurgitation; ‡ For LVOT >2.5 cm, significant stenosis criteria is <0.20; ¶ Use in setting of BSA ≥1.6 cm^2 (note: dependent on the size of the valve and the size of the native annulus); § Use in setting of BSA <1.6 cm^2; **Use in setting of BMI <30 kg/cm^2; ¶¶ Use in setting of BMI ≥30 kg/cm^2; ¶¶ Not well-validated and may overestimate severity compared to quantitative Doppler; PW: pulsed wave; EROA: effective regurgitant orifice area

The Minnesota Living with Heart Failure Questionnaire (MLHF)[53] and the Kansas City Cardiomyopathy Questionnaire (KCCQ)[54,55] have a number of desirable properties for the evaluation of health-related QOL (HRQOL) in the setting of AS. Both instruments produce outcomes on a continuous scale, which improves responsiveness and sensitivity. Although only the MLHF has been specifically validated in patients with aortic valve disease[56], preliminary experience with the KCCQ in patients undergoing TAVI has also demonstrated a high degree of responsiveness and internal consistency[57].

RECOMMENDED ENDPOINTS AND TIMING OF ASSESSMENT

VARC-2 recommends that a comprehensive assessment of HRQOL for patients undergoing TAVI incorporate both a heart-failure specific measure (such as the KCCQ or MLHF) as well as one or more generic measures (such as the Medical Outcomes Study Short-Form 36 (SF-36), the Short-Form 12 (SF-12), or the EuroQOL (EQ-5D)[58-60]. The disease-specific measures offer improved sensitivity/responsiveness as well as clinical interpretability, whereas the inclusion of a generic health status measure is useful because it captures some additional domains. Furthermore, generic measures can enhance comparability across different diseases and populations and can be used to compare patients with population-level benchmarks.

For comparison of TAVI versus SAVR (or for comparison of alternative access sites for TAVI), we recommend that early QOL assessment be performed at 2 weeks, 1 month, and 3 months using a combination of generic instruments and pain scales (e.g. visual analog scale) to assess the early recovery process. Evaluation of QOL at an intermediate time point (e.g., 6 months) could also be considered in order to confirm that QOL recovery is complete by this stage. At later time-points (1-5 years), use of heart-failure specific instruments to identify the consequences of long-term valve performance may be more useful. Finally, the assessment of cognitive function at later time-points (1-5 years) may be valuable for comparison of surgical vs. catheter-based techniques, although these endpoints generally require highly-specialized and demanding neuropsychiatric testing[61]. In contrast, for comparison of alternative TAVI systems (as may be expected in the near future), HRQOL assessment should focus mainly on heart-failure specific endpoints at intermediate and later time-points (1-5 years), wherein between-device differences in hemodynamic performance or structural valve deterioration may emerge. Inclusion of disease-specific QOL measures in these studies can also provide insight into the consequences of valve-related complications such as the need for pacemaker insertion.

ADDITIONAL CONSIDERATIONS

It is essential to ensure complete ascertainment of HRQOL at each time-point, as missing data cannot be retrieved retrospectively and statistical adjustment techniques (e.g., multiple imputation) that assume that data are "missing at random" may not be adequate. Differential mortality between 2 treatments may complicate the interpretation of QOL results since QOL may appear to "improve" over time even with an ineffective therapy simply because of attrition of the sickest patients. The use of categorical endpoints that characterize outcomes as favorable (e.g. survival AND improvement of QOL endpoints)[57,62] or endpoints that integrate survival and QOL (e.g., quality-adjusted life expectancy), may provide more interpretable results. In such cases, reporting the outcomes in both ways (i.e., among the entire study cohort and separately among only the surviving patients) will provide the most complete description of the results.

Composite endpoints

RATIONALE AND CAVEATS

Comparisons of success, safety, and effectiveness with achievable study cohort sample sizes may at times require use of composite endpoints. However, it is important that composites contain components that have roughly similar impacts on the patient. A family of single endpoints tending in the same direction may, as a family of hypotheses, be statistically significant when individual endpoints are not.

Each post-procedural event has a different temporal risk profile (hazard function) modulated by different risk factors. Therefore, traditionally, evaluation of safety and efficacy of procedures has focused on in-hospital events (complications and morbidity), events within 30 days of the procedure, and "late" events.

SPECIFIC COMPOSITE ENDPOINTS

Assessment of TAVI, SAVR, and their alternatives or new devices should include device, procedure, and patient-oriented endpoints. These endpoints have been devised to be applicable to both TAVI and SAVR. Previous clinical trials have used all-cause mortality at one year as the primary clinical endpoint. Due to the emergence of stroke as an important clinical event, future trials should also require the composite of all-cause mortality and disabling stroke as a primary or secondary endpoint.

The first VARC document proposed three composite endpoints: device success, early safety, and clinical efficacy. VARC-2 goes beyond the early and intermediate experience of TAVI, drawing upon prior surgical AVR guidelines to include time-related safety endpoints[63]. Therefore, VARC-2 recommends a new composite endpoint, time-related valve safety, which combines valve dysfunction, endocarditis, and thrombotic complications of the prosthesis **(Table 11)**.

Discussion

While the original VARC standardized endpoint definitions were fundamentally useful and have been widely adopted, growing experience with TAVI studies has identified some definitions as ambiguous, of limited clinical utility, or in need of updating or extension[5,6,64,65]. This need provided the rationale for a VARC-2 document with such improvements and additions. As was the case with the original VARC process, it should be emphasized that this consensus manuscript is not intended to be a guidelines document, but rather a practical tool to facilitate and inform clinical research in TAVI.

Current clinical trials are focusing more on intermediate risk patients, and more studies are comparing TAVI with surgical AVR. Therefore, it becomes increasingly important to identify those

Table 11. Composite endpoints.

Device success
Absence of procedural mortality AND
Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch* and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, AND no moderate or severe prosthetic valve regurgitation*)
Early safety (at 30 days)
All-cause mortality
All stroke (disabling and non-disabling)
Life-threatening bleeding
Acute kidney injury – Stage 2 or 3 (including renal replacement therapy)
Coronary artery obstruction requiring intervention
Major vascular complication
Valve-related dysfunction requiring repeat procedure (BAV, TAVI, or SAVR)
Clinical efficacy (after 30 days)
All-cause mortality
All stroke (disabling and non-disabling)
Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure¶
NYHA class III or IV
Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 $cm^{2‡}$ and/or DVI<0.35 m/s, AND/OR moderate or severe prosthetic valve regurgitation*)
Time-related valve safety
Structural valve deterioration:
Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 $cm^{2‡}$ and/or DVI <0.35 m/s, AND/OR moderate or severe prosthetic valve regurgitation*)
Requiring repeat procedure (TAVI or SAVR)
Prosthetic valve endocarditis
Prosthetic valve thrombosis
Thromboembolic events (e.g. stroke)
VARC bleeding, unless clearly unrelated to valve therapy (e.g. trauma)

*Refers to VARC definitions; ¶As basis for calculation of "days alive outside the hospital" endpoint. Supplementary appendix of Leon et al.[74] Includes heart failure, angina or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms of CHF with objective signs including pulmonary edema, hypoperfusion or documented volume overload AND administration of IV diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (IABP or ventilation for pulmonary edema) or hemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to CAD or ACS; documented loss of consciousness not related to seizure or tachyarrhythmia; ‡Depending on body surface area; BAV: balloon aortic valvuloplasty; TAVI: transcatheter aortic valve implantation; SAVR: surgical aortic valve replacement

patients that benefit from either treatment. Specific risk categories have been defined to allow universal clinical study designs and outcome comparisons.

Changes and additions that have been applied to improve interpretation of clinical endpoint definitions and provide further insights on TAVI-related outcomes are: 1) Risk stratification should be done by a dedicated "heart team" and include other factors (e.g. frailty, porcelain aorta) beyond the traditional risk scores, and should take into account coexisting conditions; 2) immediate procedural death has been added to capture intra-procedural events that result in immediate or consequent death; 3) stroke ascertainment requires the use of precise definitions, standardized assessments, close collaboration with neurology experts including consideration of acute stroke management, and has been re-categorized as non-disabling or disabling; 4) detailed documentation of the etiology of strokes and concomitant therapies is needed to provide insights into the multi-factorial nature of acute, early, and late strokes; 5) closure device failure is now a separate category within vascular complications, and if unplanned percutaneous or surgical intervention does not lead to adverse outcomes, these are not considered as a major vascular complication, *per se*; 6) timing for AKI diagnosis has been extended from 72 h to 7 days; 7) AKI is diagnosed according to AKIN guidelines, which include classification by urine output to detect a wider range of etiologies; 8) peri-procedural myocardial infarction is defined by troponin or CK-MB elevation and has changed the troponin threshold from 10x ULN to 15X ULN based on recent data[19]; 9) assessment of conduction disturbances and arrhythmias has been reinforced[66-69]; 10) new definitions for several TAVI-related complications and valve malpositioning are reported; 11) echocardiography parameters of prosthetic valve stenosis and regurgitation have been updated and now include assessment of prosthesis-patient mismatch; 12) for quality of life assessment, VARC-2 recommends the use of both heart-failure specific and generic measures between 30 days and 5 years follow-up to fully assess the impact of the procedure and the durability of clinical benefit. These definitions can be used in studies comparing TAVI to surgical AVR, as well as in future trials comparing first generation to next generation TAVI devices.

The composite endpoint of device success has specifically been criticized for being too strict with regard to valve performance; for example, an AVA of >1.2 cm^2 seems unachievable in patients with smaller body habitus[5]. The current VARC-2 definition therefore corrects for body surface area so that valve performance is now assessed through the indexed effective orifice area. It is notable that valve-in-valve procedures for failing bioprostheses will frequently have a low device success, even with this modified definition[70]. Considering that stroke in AS patients undergoing surgical or transcatheter AVR has emerged as an important concern, the composite of all-cause mortality and stroke should be considered as a primary or secondary endpoint in future trials. Two ongoing large randomized trials (PARTNER II [NCT01314313] and SURTAVI [NCT01586910]) are already incorporating these composite endpoints.

With longer follow-up duration, it becomes more critical to include time-related valve safety composite endpoints. This will eventually provide linearized rates of complications with transcatheter valves, known as 'objective performance criteria', as has been used to evaluate surgical valves[71].

With this VARC-2 document we have provided further standardization of endpoint definitions and hope that adoption of these criteria will continue to increase, ultimately leading to improved comparability and interpretability of study results.

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Conflict of interest statement

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References

The references can be found in the online version of this article.