Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research

Genereux, P.; Piazza, N.; Alu, M.C.; Nazif, T.; Hahn, R.T.; Pibarot, P.; ... ; Leon, M.B.

Citation
Genereux, P., Piazza, N., Alu, M. C., Nazif, T., Hahn, R. T., Pibarot, P., ... Leon, M. B. (2021). Valve Academic Research Consortium 3: updated endpoint definitions for aortic valve clinical research. *Journal Of The American College Of Cardiology*, *77*(21), 2717-2746. doi:10.1016/j.jacc.2021.02.038

Version:	Publisher's Version
License:	Leiden University Non-exclusive license
Downloaded from:	https://hdl.handle.net/1887/3279740

Note: To cite this publication please use the final published version (if applicable).

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 77, NO. 21, 2021
© PUBLISHED ON BEHALF OF THE EUROPEAN SOCIETY OF CARDIOLOGY. ALL RIGHTS RESERVED. © THE AUTHOR(S) 2021.

SPECIAL ARTICLE

VALVULAR HEART DISEASE

Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research

VARC-3 WRITING COMMITTEE: Philippe Généreux,[a] Nicolo Piazza,[b] Maria C. Alu,[c] Tamim Nazif,[c] Rebecca T. Hahn,[c] Philippe Pibarot,[d] Jeroen J. Bax,[e] Jonathon A. Leipsic,[f] Philipp Blanke,[f] Eugene H. Blackstone,[g] Matthew T. Finn,[c] Samir Kapadia,[h] Axel Linke,[i] Michael J. Mack,[j] Raj Makkar,[k] Roxana Mehran,[l] Jeffrey J. Popma,[m] Michael Reardon,[n] Josep Rodes-Cabau,[d] Nicolas M. Van Mieghem,[o] John G. Webb,[p] David J. Cohen,[q] Martin B. Leon[c]

ABSTRACT

AIMS The Valve Academic Research Consortium (VARC), founded in 2010, was intended to (i) identify appropriate clinical endpoints and (ii) standardize definitions of these endpoints for transcatheter and surgical aortic valve clinical trials. Rapid evolution of the field, including the emergence of new complications, expanding clinical indications, and novel therapy strategies have mandated further refinement and expansion of these definitions to ensure clinical relevance. This document provides an update of the most appropriate clinical endpoint definitions to be used in the conduct of transcatheter and surgical aortic valve clinical research.

METHODS AND RESULTS Several years after the publication of the VARC-2 manuscript, an in-person meeting was held involving over 50 independent clinical experts representing several professional societies, academic research organizations, the US Food and Drug Administration (FDA), and industry representatives to (i) evaluate utilization of VARC endpoint definitions in clinical research, (ii) discuss the scope of this focused update, and (iii) review and revise specific clinical endpoint definitions. A writing committee of independent experts was convened and subsequently met to further address outstanding issues. There were ongoing discussions with FDA and many experts to develop a new classification schema for bioprosthetic valve dysfunction and failure. Overall, this multi-disciplinary process has resulted in important recommendations for data reporting, clinical research methods, and updated endpoint definitions. New definitions or modifications of existing

From the [a]Gagnon Cardiovascular Institute, Morristown Medical Center, Morristown, New Jersey, USA; [b]McGill University Health Centre, Montreal, Quebec, Canada; [c]Columbia University Irving Medical Center/NewYork-Presbyterian Hospital and Cardiovascular Research Foundation, New York, New York, USA; [d]Quebec Heart & Lung Institute, Laval University, Quebec, Quebec, Canada; [e]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; [f]Department of Radiology, St. Paul's Hospital and University of British Columbia, Vancouver, British Columbia, Canada; [g]Department of Thoracic and Cardiovascular Surgery, Cleveland Clinic and Department of Quantitative Health Sciences, Research Institute, Cleveland Clinic, Cleveland, Ohio, USA; [h]Department of Cardiovascular Medicine, Cleveland Clinic, Cleveland, Ohio, USA; [i]Herzzentrum Dresden, Dresden, Germany; [j]Baylor Scott & White Heart Hospital Plano, Plano, Texas, USA; [k]Smidt Heart Institute, Cedars-Sinai Medical Center, Los Angeles, California, USA; [l]The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA; [m]Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA; [n]Methodist DeBakey Heart & Vascular Center, Houston, Texas, USA; [o]Thoraxcenter, Erasmus University Medical Center, Rotterdam, The Netherlands; [p]Department of Cardiology, St. Paul's Hospital and University of British Columbia, Vancouver, British Columbia, Canada; [q]University of Missouri-Kansas City School of Medicine, Kansas City, Missouri, USA.

This article has been copublished in the *European Heart Journal*.

Address for correspondence: Dr. Martin B. Leon. E-mail: ml2398@columbia.edu.

Manuscript received April 12, 2020; revised manuscript received June 22, 2020, accepted September 24, 2020.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2021.02.038

definitions are being proposed for repeat hospitalizations, access site-related complications, bleeding events, conduction disturbances, cardiac structural complications, and bioprosthetic valve dysfunction and failure (including valve leaflet thickening and thrombosis). A more granular 5-class grading scheme for paravalvular regurgitation (PVR) is being proposed to help refine the assessment of PVR. Finally, more specific recommendations on quality-of-life assessments have been included, which have been targeted to specific clinical study designs.

CONCLUSIONS Acknowledging the dynamic and evolving nature of less-invasive aortic valve therapies, further refinements of clinical research processes are required. The adoption of these updated and newly proposed VARC-3 endpoints and definitions will ensure homogenous event reporting, accurate adjudication, and appropriate comparisons of clinical research studies involving devices and new therapeutic strategies.

INTRODUCTION

The Valve Academic Research Consortium (VARC) was organized and founded in 2010 in the spirit of the Academic Research Consortium mission (1-3) and included a diverse group of stakeholders from international societies, academic research organizations, the US Food and Drug Administration, medical device manufacturers, and independent clinician experts from interventional cardiology, cardiac imaging, cardiac surgery, heart failure, and targeted subspecialties (e.g. neurology) for the purpose of improving the processes, scientific rigour, and standardization of definitions related to clinical research in valvular heart disease. The VARC initiative has been driven by the rapid emergence of less-invasive transcatheter aortic valve replacement (TAVR) therapies for severe aortic stenosis (AS), although this process has recently expanded to also include important transcatheter mitral and tricuspid valve therapies (4-7). The first VARC consensus manuscript in January 2011 focused on selecting appropriate clinical endpoints and standardizing endpoint definitions for use in TAVR clinical trials (4). The VARC definitions for clinical endpoints were rapidly accepted and frequently utilized by the global TAVR clinical research community (8). However, <2 years later, evolution of TAVR and the ambiguous nature of certain endpoint definitions required a VARC-2 follow-up manuscript (5,9), which clarified specific definitions and expanded the understanding of patient risk stratification and case selection.

Worldwide, over 800 000 TAVR procedures have been performed in more than 65 countries. Concurrently, TAVR clinical research has matured and clinical research needs have changed through the incorporation of findings from key clinical trials, the rapid development of new clinical indications, and the introduction of new and iterative medical device technologies. In addition, new advances in surgical aortic valve replacement (SAVR), and the growing overlap between interventional and surgical procedures, have mandated a similar approach to clinical research for both fields. The improvement in clinical outcomes after TAVR (10-14) combined with an emphasis on lower surgical risk patients in the future will direct greater attention to important secondary endpoints such as all strokes, repeat hospitalization, paravalvular regurgitation (PVR), and conduction disturbances. Similarly, new clinical trials will also rely heavily on carefully constructed composite safety and composite efficacy endpoints, many of which will be tailored to the device being studied and the anticipated risks and benefits (e.g. cerebral protection devices or large bore vascular closure devices). In the future, device safety assessments will be facilitated by the more rigorous use of objective performance criteria derived from contemporary clinical trials and/or validated national databases, like the ACC/STS Transcatheter Valve Therapy registry (15,16). Routinely, composite *efficacy* endpoints will combine both 'hard' clinical outcomes (like death and stroke) with other 'softer' therapy benefit assessments (like a quality-of-life matrix or a functional assessment, e.g. 6-min walking distance). Finally, as clinical trials include younger patients (e.g. asymptomatic, 'all-comer', or bicuspid aortic valve studies), there is greater sensitivity to both early safety concerns and longer-term prosthetic valve function.

The main goal of this VARC-3 consensus manuscript is to provide an update of these emerging clinical research issues in aortic valve therapy. A clarification of existing endpoint definitions and a redirection of endpoint selection for future clinical trials, registries or other studies can enable clinicians, research scientists, and clinical event committees to optimally conduct clinical research in the field of aortic valve disease. A detailed summary of important additions and changes compared with VARC-2 definitions is presented in the Supplementary material online, Appendix.

Clinical endpoints

VARC-3 recommends the use of clinically relevant endpoints with consistent definitions, appropriate to the size

TABLE 1 Valve Academic Research Consortium proposed clinical endpoints

Mortality
Neurologic events
Hospitalization (or re-hospitalization)
Bleeding and transfusions
Vascular and access-related complications
Cardiac structural complications
Other procedural or valve-related complications
New conduction disturbances and arrhythmias
Acute kidney injury
Myocardial infarction
Bioprosthetic valve dysfunction
Leaflet thickening and reduced motion
Clinically significant valve thrombosis
Patient-reported outcomes and health status
Composite endpoints

and type of clinical studies. Endpoints that VARC-3 considers to be essential to collect, adjudicate, and report when performing large, randomized trials or rigorous observational studies are listed in **Table 1**. Clinical event committees for large randomized trials or single-arm registry studies should include at least one cardiologist and one cardiovascular surgeon (both knowledgeable in TAVR and SAVR), and when required, additional subspecialty physicians (especially a neurologist for studies in which stroke is part of the primary endpoint). It is crucial to assign device or procedure-relatedness to the clinical endpoints and to catalogue event timing relative to the index procedure. Under most circumstances, early events (especially in the first 30 days) should be attributed to the device or procedure, unless there is definitive evidence to the contrary.

Mortality

Death is the most objective and unbiased endpoint. All efforts should be made to accurately determine the status (dead or alive) of all patients at all time points during study follow-up, including complementary interrogation of national registry and administrative databases. Establishing the exact cause of death may be difficult (17,18), so all-cause mortality should remain the preferred primary endpoint measure. Nevertheless, death should furthermore be classified as cardiovascular or non-cardiovascular when possible and adjudicated by a clinical events committee based on narrative summaries and source documents (**Table 2**). Any deaths occurring during the procedure should be considered cardiovascular. Death should be considered non-cardiovascular only if clearly related to another cause. When doubt exists regarding the exact cause of death (i.e. sudden death, unexpected death), it should be considered cardiovascular.

TABLE 2 Mortality*

Causes of mortality
All-cause mortality
Cardiovascular mortality
Death meeting one of the following criteria: ■ Related to heart failure, cardiogenic shock, bioprosthetic valve dysfunction, myocardial infarction, stroke, thromboembolism, bleeding, tamponade, vascular complication, arrhythmia or conduction system disturbances, cardiovascular infection (e.g. mediastinitis, endocarditis), or other clear cardiovascular cause ■ Intraprocedural death ■ Sudden death ■ Death of unknown cause
Valve-related mortality
Death presumed to be related to bioprosthetic valve dysfunction†
Non-cardiovascular mortality
Death clearly related to a non-cardiovascular cause: such as respiratory failure *not* related to heart failure (e.g. pneumonia), renal failure, liver failure, infection (e.g. urosepsis), cancer, trauma, and suicide
Timing of mortality
Periprocedural mortality
Death meeting one of the following criteria: ■ Occurring ≤30 days after the index procedure ■ Occurring >30 days but during the index hospitalization‡
Early mortality
Death occurring >30 days but ≤1 year after the index hospitalization
Late mortality
Death occurring >1 year after the index hospitalization

*Mortality should be reported using Kaplan–Meier methods.
†As defined in **Table 12 and Central Illustration**.
‡Includes transfer to another hospital or rehabilitation facility for continuity of acute care, but excludes chronic treatment at a rehabilitation facility or nursing home.

Death is further classified by the time of occurrence. While VARC-2 introduced immediate procedural mortality to evaluate dramatic complications that occur within the first 72 h post-procedure (5), this endpoint occurs with a low incidence and has not been adopted in the TAVR literature. Moreover, with patients now being discharged earlier post-procedure (19–24), the usefulness of this measure has become questionable. Therefore, VARC-3 no longer recommends the use of immediate procedural mortality and recommends instead the use of periprocedural, early, and late mortality. Death should be classified as periprocedural if it occurs within 30 days of the index procedure or beyond 30 days if the patient is still hospitalized (including transfer to another hospital for continuity of acute care, but excluding a rehabilitation facility or nursing home). Of particular importance, the relationship between death and any potential major periprocedural complication, device failure, malfunction, or misuse should be determined (**Table 2**). Besides periprocedural mortality, collection of early mortality, defined as mortality occurring between 30 days and 1 year after the index procedure, and late mortality (1 year and beyond after the

TABLE 3 Neurologic events

Categories of neurologic events
Overt CNS injury (NeuroARC Type 1)
All stroke*
■ *Ischaemic stroke*†
Acute onset of focal neurological signs or symptoms conforming to a focal or multifocal vascular territory within the brain, spinal cord, or retina (NeuroARC Type 1a or 1aH) and fulfilling one of the following criteria:
■ Signs or symptoms lasting ≥24 h or until death, with pathology or neuroimaging evidence of CNS infarction, or absence of other apparent causes
■ Symptoms lasting <24 h, with pathology or neuroimaging confirmation of CNS infarction in the corresponding vascular territory‡
■ *Haemorrhagic stroke*
Acute onset of neurological signs or symptoms due to intracranial bleeding from intracerebral or subarachnoid haemorrhage not due to trauma (NeuroARC Types 1b or 1c)
■ *Stroke, not otherwise specified*
Acute onset of neurological signs or symptoms persisting ≥24 h or until death but without sufficient neuroimaging or pathology evidence to be classified (NeuroARC Type 1d)
Symptomatic hypoxic-ischaemic injury
Non-focal (global) neurological signs or symptoms with diffuse brain, spinal cord, or retinal cell death confirmed by pathology or neuroimaging and attributable to hypotension or hypoxia (NeuroARC Type 1e)
Covert CNS injury (NeuroARC Type 2)
Covert CNS infarction‡ or haemorrhage
Neuroimaging or pathological evidence of CNS focal or multifocal ischaemia (NeuroARC Type 2a or 2aH) or haemorrhage (NeuroARC 2b) *without* acute neurological symptoms consistent with the lesion or bleeding location
Neurologic dysfunction (acutely symptomatic) without CNS injury (NeuroARC Type 3)
TIA
Transient focal neurological signs or symptoms lasting <24 h presumed to be due to focal brain, spinal cord, or retinal ischaemia, but *without* evidence of acute infarction by neuroimaging or pathology, or with no imaging performed (NeuroARC Type 3a or Type 3aH)
Delirium without CNS injury
Transient non-focal neurological signs or symptoms, typically of variable duration, *without* evidence of infarction on neuroimaging or pathology, or with no imaging performed (NeuroARC Type 3b)
Stroke grading*
Acute stroke severity§
■ *Mild neurological dysfunction*: NIHSS 0-5
■ *Moderate neurological dysfunction*: NIHSS 6-14
■ *Severe neurological dysfunction*: NIHSS ≥15
Stroke disability‖
■ *Fatal Stroke:* death resulting from a stroke
■ *Stroke with disability:* mRS score of ≥2 at 90 days‖ *and* increase of ≥1 from pre-stroke baseline
■ *Stroke without disability:* mRS score of 0 (no symptoms) or 1 (able to carry out all usual duties and activities) at 90 days‖ or *no* increase in mRS category from pre-stroke baseline
Neurological events timing
■ *Periprocedural:* Occurring ≤30 days after the index procedure
■ Acute: Occurring ≤24 h after the index procedure
■ Sub-acute: Occurring >24 h and ≤30 days after the index procedure
■ *Early:* Occurring >30 days and ≤1 year after the index procedure
■ *Late:* Occurring >1 year after the index procedure

*In general, all studies should report at a minimum all stroke and stroke disability.
†Includes haemorrhagic conversions when ischaemic infarction is the primary mechanism.
‡When CNS infarction location does not match transient (<24 h) symptoms, the event should be classified as covert CNS infarction (NeuroARC Type 2a) and TIA (NeuroARC Type 3a), not as an ischaemic stroke.
§Severity assessment should be performed at the time of stroke diagnosis using the NIHSS.
‖Disability assessment using the mRS should be performed between 30 and 90 days with 90 days being optimal.
CNS, central nervous system; mRS, modified Rankin Scale; NIHSS, National Institute of Health Stroke Scale; TIA, transient ischaemic attack.

index procedure) will help to determine safety and efficacy and to appropriately compare the impact of competing treatment strategies (25,26). Transcatheter aortic valve replacement is now being considered as an alternative therapy in low-risk patients, many of whom are relatively younger than those at a higher surgical risk, placing a premium on the assessment of long-term outcomes >5 years after the index procedure. Longer-time intervals from the procedure are associated with increased difficulty to accurately determine cardiovascular cause of death. Therefore, all-cause mortality is a more reliable endpoint for late clinical assessments. However, to accommodate the need to quantify valve durability in low-risk patients, VARC-3 also introduces the endpoint of 'valve-related' mortality, defined as cardiovascular mortality adjudicated to be associated with bioprosthetic valve dysfunction (BVD; see below bioprosthetic valve dysfunction).

Mortality should be reported as Kaplan-Meier cumulative failure rates to account for differential follow-up

time. Corresponding survival should be reported as Kaplan-Meier estimates and not as proportions.

Neurologic events

The occurrence of stroke is considered by patients, physicians, and device regulators to be one of the most important adverse events following cardiovascular procedures. Periprocedural stroke in this context occurs primarily due to procedure-related central nervous system (CNS) embolization, while late events may be either device-related or spontaneous. Despite the substantial decrease in the reported rate of stroke after TAVR in recent trials (11,13,27–32), stroke clearly remains an important clinical outcome, and the prevention of stroke and CNS injury has emerged as an important therapeutic target with the introduction of cerebral embolic protection devices (CEPD) (33–36). Recent studies have demonstrated that the detection of overt and covert CNS injury is highly dependent on the intensity of surveillance, with systematic examination by neurologists and routine CNS imaging yielding substantially higher event rates (37). This underscores the importance of accurate ascertainment and standardized adjudication of neurological endpoints in cardiovascular trials.

VARC-3, like the Neurologic Academic Research Consortium (NeuroARC) (38), recommends combining appropriate assessment of neurologic symptoms with tissue-based criteria [pathology or neuroimaging, ideally diffusion-weighted magnetic resonance imaging (DW-MRI)] for defining stroke and other CNS injury. **Table 3** outlines VARC-3 definitions for stroke and other overt CNS injury, covert CNS injury, and neurologic dysfunction without CNS injury (transient ischaemic attack and delirium) in harmonization with recent consensus definitions (38–40). It also includes recommendations for reporting acute stroke severity and associated disability. Similar to mortality, neurological events should be defined as being periprocedural if they occur within 30 days or during the index hospitalization, early if they occur within 1 year of the index procedure, or late if they occur beyond 1 year. Periprocedural neurological events could be further sub-classified as acute (occurring within 24 h of the index procedure) or sub-acute (occurring between 24 h and 30 days following the index procedure). It is important to recognize that the occurrence of neurologic events is also influenced by patient co-morbidities and other factors that should be clearly reported (baseline or new-onset atrial fibrillation, oral anticoagulation or antiplatelet therapy, left atrial appendage or left ventricle thrombus, carotid artery disease, etc.).

Stroke can be described both in terms of acute severity and subsequent disability (40). Acute stroke severity, as assessed by the National Institutes of Health Stroke Scale (NIHSS), may be reported in clinical trials, with an NIHSS of 0–5 considered to be a mild stroke, 6–14 moderate, and ≥15 severe (41). However, stroke-related disability, measured using the modified Rankin scale (mRS) continues to be the preferred classification of stroke within clinical trials (40) and should be collected routinely. Importantly, and conforming to the original mRS (42), VARC-2, and NeuroARC, stroke should be classified as being fatal, stroke with disability (mRS ≥2 and increase of at least 1 from baseline) or stroke without disability (mRS <2 or without increase from baseline). Although neurologic disability is best assessed at 90 days post-event, such follow-up may not be included in some trials or routinely performed in clinical practice. VARC-3 acknowledges these practical challenges and considers an assessment performed 30–90 days after a neurologic event acceptable, although this may lead to an overestimation of the disability associated with stroke and thus represent a 'worst-case scenario'. In low surgical risk and younger patients, since activity, return-to-work, and longevity expectations are greater, there has been a tendency to reduce the stroke disability threshold and include all strokes (with and without disability) as a component of the primary endpoint (11,13).

Valve Academic Research Consortium 3 has attempted to harmonize the above definitions and classifications with Neuro-ARC, while recognizing that Neuro-ARC definitions may be too detailed for application in daily practice or within studies not primarily focused on neurological events. Similarly, the routine use of DW-MRI is both logistically challenging and expensive, and thus, should be reserved for dedicated studies related to neuroembolic protection. While the assessment of neurologic deficits will ideally be performed by a neurologist, assessment by a non-neurologist clinician may be acceptable, particularly when accompanied by brain imaging to confirm the clinical diagnosis (38,43). However, for CEPD trials, the assessment of neurologic deficits should be performed by a neurologist.

Despite the growing interest in periprocedural, clinically silent brain infarction (39) and neurocognitive impairment (detected by extensive neurocognitive testing) (44,45), routine inclusion of these endpoints in clinical trials remains challenging for several reasons: (i) uncertainty related to their association with hard clinical endpoints (e.g. mortality) and quality of life (QOL); (ii) current lack of standardization of definitions and assessment; (iii) variability in the cognitive domain ascertained by different neuropsychological tests; and (iv) important heterogeneity related to test execution (44). Indeed, abnormalities in neurocognitive testing used in SAVR and TAVR trials have not been consistently associated with the presence or severity of lesions detected by MRI (46–53). Nevertheless, given the weight of evidence suggesting a potential association between silent infarct and

TABLE 4 Hospitalization (or re-hospitalization)

Definition
Any admission after the index hospitalization or study enrolment to an inpatient unit or hospital ward for ≥24 h, including an emergency department stay. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition. Visits to urgent care centres or emergency departments <24 h may also be included if substantive intensification of therapy changes (e.g. heart failure episodes) are enacted (e.g. intravenous diuretics, significant increases in drug therapy dosages or addition of new pharmacotherapy agents)
Categories of hospitalization
Cardiovascular hospitalization
Procedure-related or valve-related hospitalization ■ ***Hospitalization for new complications*** such as stroke, bleeding (e.g. haemothorax, retroperitoneal haematoma), pericardial effusion, vascular or access-site complication (e.g. limb ischaemia, wound infection), new conduction disturbance or arrhythmia (e.g. atrioventricular block, atrial fibrillation), acute kidney injury, or any other procedure-related new complication, including periprocedural valve-related heart failure (e.g. paravalvular leak, worsening LV function, worsening sub-valvular obstruction) ■ ***Exacerbation or deterioration of previous in-hospital periprocedural complication*** (e.g. ventilator-induced pneumonia, recurrent pericardial or pleural effusion, recurrent haemothorax, valve-related heart failure) ■ ***Bioprosthetic valve dysfunction**** such as valve thrombosis, endocarditis, structural valve deterioration, or non-structural valve dysfunction ■ ***Untreated diseased native aortic valve†*** or its related consequences such as heart failure, syncope, angina, new-onset arrhythmia, endocarditis, or any other symptoms or consequences related to the untreated native aortic valve ■ ***Bleeding complications related to oral anticoagulation or antiplatelet therapy*** for valve-related thromboembolic prevention or atrial fibrillation ■ ***Heart failure-related hospitalizations‡*** requiring that new or worsening heart failure be the predominant reason for a hospital stay ≥24 h on the basis of symptoms and signs of heart failure with confirmation by diagnostic tests and necessitating treatment using intravenous or mechanical heart failure therapies. Includes primary (cardiac related) and secondary (non-cardiac related)
Other cardiovascular hospitalization ■ ***Cardiovascular hospitalization not directly related to the index procedure or the untreated native aortic valve***
Including: acute myocardial infarction or chronic coronary artery disease, hypertension, arrhythmia (not related to the procedure or aortic valve), heart failure from other specific and proven aetiologies (e.g. cardiomyopathies, concomitant untreated non-aortic valvular disease, severe right ventricular dysfunction), peripheral vascular disease
Non-cardiovascular hospitalization ■ ***Hospitalization not due to cardiovascular causes as defined above***
Including: non-cardiovascular infection and sepsis (e.g. urosepsis), respiratory failure that is not related to heart failure (e.g. pneumonia), renal failure, liver failure, delirium or dementia, cancer, trauma, or psychiatric illness

*As defined in Table 12 and Central Illustration.
†Untreated diseased native aortic valve in the context of a strategy trial comparing transcatheter or surgical aortic valve replacement to clinical surveillance with medical therapy, as appropriate.
‡Some trials may choose to focus on an endpoint of heart failure-related hospitalization.

cognitive impairment on longer-term follow-up (54-58), it may be reasonable for dedicated trials investigating different neuroprotection strategies to consider including diffusion-weighted MRI and comprehensive neurocognitive testing, among the neurologic endpoints collected (34,35,59).

Hospitalization or re-hospitalization

Hospitalization or multiple re-hospitalizations after an index procedure are clinically and economically meaningful endpoints for patients, third-party payers, and health care systems in general. Recently, hospitalizations as an endpoint in cardiovascular clinical trials have been elevated in importance, especially when hospitalizations for worsening heart failure are a consequence of myocardial or valvular heart disease (6,60-63). Hospitalizations due to worsening heart failure have been associated with increased early mortality and frequent repeat hospitalizations (64-66). Using Mitral VARC (MVARC) as a starting platform (6), VARC-3 defines hospitalization (or re-hospitalization) as any admission to an inpatient unit or hospital ward for ≥24 h, including an emergency department stay (Table 4). Visits to urgent care facilities or emergency departments for <24 h should also be noted (including reasons and therapies) and they can be included in this endpoint, only if substantive intensification of therapy changes are enacted (e.g. intravenous diuretics, ≥50% increase in drug therapy dosages, or addition of new pharmacotherapy agents). In recent heart failure trials, the association of intensification of medical therapy with all-cause and cardiovascular mortality was similar to heart failure hospitalizations and emergency department visits (62). Valve Academic Research Consortium 3 places emphasis on hospitalizations which are either procedure-related or valve-related (Table 4). Such hospitalizations may be due to (i) new complications such as strokes or conduction disturbances, (ii) exacerbation or deterioration of previous in-hospital periprocedural complications (e.g. recurrent pleural effusion, worsening heart failure), (iii) BVD [e.g. PVR, valve thrombosis, endocarditis, or structural valve deterioration (SVD)], and (iv) bleeding complications related to oral anticoagulation or antiplatelet therapy for valve-related thromboembolic prevention or atrial fibrillation. In specific clinical trials comparing a strategy of either TAVR or SAVR vs. clinical surveillance of the diseased native aortic valve (e.g. early AVR vs. clinical surveillance for asymptomatic severe AS), the progression of native aortic valve disease resulting in hospitalizations (due to heart failure,

angina, syncope, or other valve-related reasons) can also be used as a worthwhile clinical endpoint.

Heart failure-related hospitalizations are of special interest and may be considered as a powered primary endpoint or powered/hypothesis-driven secondary endpoint in some clinical trials. Valve Academic Research Consortium 3 requires that new or worsening heart failure as the predominant reason for a hospital stay ≥24 h is based on symptoms and signs of heart failure with confirmation by diagnostic tests and necessitating treatment using intravenous or mechanical heart failure therapies. Heart failure hospitalizations may be associated with primary (cardiac related) causes or secondary (non-cardiac related) aetiologies, such as heart failure due to sepsis or fluid overload in renal failure patients.

Valve Academic Research Consortium 3 recommends dividing cardiovascular hospitalizations into those that are procedure-related or valve-related and a separate category of 'other' cardiovascular hospitalizations (**Table 4**). Examples of 'other' cardiovascular hospitalizations would include hospitalizations associated with acute myocardial infarction (MI) or hypertensive emergencies, which are clearly unrelated to the valve therapies under investigation. Finally, there should be a category of non-cardiovascular hospitalizations (examples in **Table 4**), which may be common in aortic valve clinical trials wherein patients are frequently elderly or have multiple co-morbidities.

To account for multiple re-hospitalizations, it is possible to also consider the total number of hospitalizations rather than the time-to-first event, as demonstrated in the recent Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial (63). All hospitalizations and re-hospitalizations must be carefully adjudicated by a clinical events committee with available source documents.

Bleeding complications and blood transfusions

Bleeding complications are frequent after TAVR and SAVR and are associated with increased short- and long-term mortality (67–73). Besides the procedure, many other factors, including patient co-morbidities (e.g. renal insufficiency), associated conditions (e.g. angiodysplasia), and concomitant therapies (e.g. oral anticoagulation, anti-platelet agents), predispose patients to bleeding (74,75). Therefore, it is essential to report periprocedural and long-term bleeding events and to identify relevant contributing factors.

Prior VARC consensus documents used the terms 'minor', 'major', and 'life-threatening' to characterize the severity of bleeding events (5,76). While this classification offers an intuitively appealing general grading system for bleeding severity (77), the nomenclature may not appropriately describe the true magnitude and clinical impact of bleeding which occurs during surgical procedures. For example, significant bleeding occurring during an open SAVR that would have been classified as 'life-threatening' by VARC-2 criteria may be anticipated and inherent to the SAVR procedure. Therefore, the former subjective classifications have been modified into a more descriptive classification scheme, similar to the Bleeding Academic Research Consortium (BARC) bleeding classification (3): Type 1 (minor), Type 2 (major), Type 3 (life-threatening), and Type 4 (leading to death) bleeding (**Table 5**).

'Overt' bleeding is defined as any bleeding with a clinically obvious source (e.g. neurologic, gastrointestinal, haemothorax, access-site related, any procedural-related bleeding) or with a source identified after appropriate clinical investigation and diagnostic testing (mainly imaging). Importantly, any procedural blood loss should be considered overt bleeding.

TABLE 5 Bleeding and transfusions*

Overt bleeding† that fulfils one of the following criteria:

Type 1
- Overt bleeding that does not require surgical or percutaneous intervention, but does require medical intervention by a health care professional, leading to hospitalization, an increased level of care, or medical evaluation (BARC 2)
- Overt bleeding that requires a transfusion of 1 unit of whole blood/red blood cells‡ (BARC 3a)

Type 2
- Overt bleeding that requires a transfusion of 2–4 units of whole blood/red blood cells‡ (BARC 3a)
- Overt bleeding associated with a haemoglobin drop of >3 g/dL (>1.86 mmol/L) but <5 g/d (<3.1 mmol/L) (BARC 3a)

Type 3
- Overt bleeding in a critical organ, such as intracranial, intraspinal, intraocular, pericardial (associated with haemodynamic compromise/tamponade and necessitating intervention), or intramuscular with compartment syndrome (BARC 3b, BARC 3c)
- Overt bleeding causing hypovolemic shock or severe hypotension (systolic blood pressure <90 mmHg lasting >30 min and not responding to volume resuscitation) or requiring vasopressors or surgery (BARC 3b)
- Overt bleeding requiring reoperation, surgical exploration, or re-intervention for the purpose of controlling bleeding (BARC 3b, BARC 4)
- Post-thoracotomy chest tube output ≥2 L within a 24-h period (BARC 4)
- Overt bleeding requiring a transfusion of ≥5 units of whole blood/red blood cells (BARC 3a) ‡
- Overt bleeding associated with a haemoglobin drop ≥5 g/dL (≥3.1 mmol/L) (BARC 3b).

Type 4
- Overt bleeding leading to death. Should be classified as:
  - ***Probable:*** Clinical suspicion (BARC 5a)
  - ***Definite:*** Confirmed by autopsy or imaging (BARC 5b)

*The timing, indication, and number of transfused blood products should be collected and reported specifically during the index procedure, during the entire index hospitalization, and during follow-up after discharge, whether or not overt bleeding is identified. †Overt bleeding is defined as any clinically obvious source of bleeding or bleeding source identified after appropriate investigation and diagnostic testing (e.g. imaging). Any procedural blood loss should be considered overt bleeding. ‡Total number of transfusions should be reported separately for (i) within 48 h of the index procedure, (ii) the total duration of the index procedure hospitalization, and (iii) during any subsequent repeat hospitalization.

TABLE 6 Vascular and access-related complications*

Vascular complications†
Major
One of the following: ■ Aortic dissection or aortic rupture ■ Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia, arterial or venous thrombosis including pulmonary embolism, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, infection) or compartment syndrome resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment ■ Distal embolization (non-cerebral) from a vascular source resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage ■ Unplanned endovascular or surgical intervention resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment ■ Closure device failure‡ resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
Minor
One of the following: ■ Vascular (arterial or venous) injury (perforation, rupture, dissection, stenosis, ischaemia, arterial or venous thrombosis including pulmonary embolism, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, infection) *not* resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment ■ Distal embolization treated with embolectomy and/or thrombectomy, *not* resulting in death, amputation, limb or visceral ischaemia, or irreversible end-organ damage ■ Any unplanned endovascular or surgical intervention, ultra-sound guided compression, or thrombin injection, *not* resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment ■ Closure device failure‡ *not* resulting in death, VARC type ≥2 bleeding, limb or visceral ischaemia, or irreversible neurologic impairment
Access-related non-vascular complications
Major
One of the following: ■ Non-vascular structure, non-cardiac structure§ perforation, injury, or infection resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention ■ Non-vascular access site (e.g. trans-apical left ventricular) perforation, injury, or infection resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention
Minor
One of the following: ■ Non-vascular structure, non-cardiac structure§ perforation, injury, or infection *not* resulting in death, VARC type ≥2, irreversible nerve injury, or requiring unplanned surgery or percutaneous intervention ■ Non-vascular access site (e.g. trans-apical left ventricular) perforation, injury, or infection *not* resulting in death, VARC type ≥2 bleeding, irreversible nerve injury or requiring unplanned surgery or percutaneous intervention

*Any complication related to the device insertion, delivery, and complete removal of all its components (delivery catheter, sheath, guide wire), excluding the actual implantation in the heart.
†Any device-related vascular access site and any other accessory access sites (venous or arterial) used during procedure.
‡A failure to achieve haemostasis at the access site, resulting in alternative treatment (other than manual compression or planned adjunctive endovascular balloon inflation).
§Including, but not limited to, the lung (e.g. pneumothorax), direct nerve injury, access site or wound infection, mediastinitis, sternal instability, wound dehiscence, and inability to close the chest.

Given the adverse prognostic implications of blood transfusions (67,72,78), the exact volume, time relative to the index procedure, and specific indication for each blood transfusion should be reported, whether or not it was associated with overt bleeding. The total number of transfusions should be reported for the index procedure hospitalization and for any subsequent repeat hospitalization. Additionally, in order to better reflect the severity and acuity of periprocedural bleeding events, the number of transfusions received within 48 h of the index procedure should be reported separately. Finally, VARC-3 acknowledges that many bleeding scales have been developed, validated, and used in clinical trials (79–83). Given the uncertainty regarding which scale is the most optimal, the BARC bleeding classification should also be prospectively recorded to complement the VARC-3 bleeding scale, especially for non-periprocedural and late (>1 year) bleeding events (3).

Vascular and access-related complications

While the frequency of vascular complications has decreased significantly with iterative improvements in TAVR device delivery system profile (84), the use of multiple alternative access approaches (subclavian, axillary, transcaval, transcarotid, direct aortic, suprasternal aortic, etc.) and novel percutaneous vascular closure device systems reinforce the need to appropriately capture and report access site-related complications (85–95). VARC-3 now expands the classic definitions of major and minor vascular complications to better capture and classify vascular complications related to these emerging approaches (**Table 6**). Valve Academic Research Consortium 3 also introduces a new sub-category of complications related to access but not directly vascular in nature (access-related non-vascular complications). These complications include injuries involving structures surrounding the access site [e.g. lung (pneumothorax),

nerves], non-vascular infection of access sites, and also any complication related to trans-apical approach. Surgical complications related to opening or closing the chest wall or sternum (e.g. sternum instability, wound dehiscence, mediastinitis) should also be classified as access-related non-vascular complications.

Vascular and access-site-related complications include any complication occurring from the actual entry site (e.g. femoral artery or vein, subclavian or axillary artery, carotid artery, aorta, left ventricle apex, sternum, etc.), the insertion or removal of the device or any of its components/accessories (including needle, wire, dilator, sheath, and catheter), and the delivery process of the device, but exclude any complication associated with the actual device implantation in the heart. Any complications involving cardiac structures per se (e.g. aortic valve annulus, left ventricle outflow tract, left or right ventricle) should be reported specifically under cardiac structural complications and are not considered vascular in nature (see Cardiac structural complications section below). The specific case of complications related to the transapical approach, where the apex of the left ventricle is used as an entry point to deliver the device, should be classified as access-related non-vascular complications. On the other hand, left ventricle perforation originating from wire perforation from a transfemoral approach should be considered as a cardiac structural complication. Vascular complications should include complications related to the primary vascular access site for a transcatheter device, as well as any accessory vascular access sites (venous or arterial) used during TAVR or SAVR (e.g. contralateral venous or arterial femoral access, radial access, surgical cannula, haemodynamic support) (96). Vascular and access-site-related complications may include those occurring acutely during the procedure or at a delayed time (e.g. pseudoaneurysm, fistula, access-site infection).

Closure device (sutures-based, collagen-based, patch-based, or membrane based) failure is an important subcategory of vascular complications that should also be captured and reported as a distinct entity (91,97,98). Closure device failure is defined as failure to achieve successful haemostasis at the access site, leading to alternative treatment (other than manual compression or planned adjunctive endovascular balloon dilation).

Complications involving surgical access, including sternal wound infection, sternal dehiscence, sternal instability, or inability to close the chest, should be reported as access-related non-vascular complications.

Cardiac structural complications

Valve Academic Research Consortium 3 introduces a new category of complications deemed to capture and classify injury of any cardiac structure occurring during the procedure (**Table 7**). These include injury involving the aortic annulus, left ventricle outflow tract, ventricular septum, left or right ventricle, left or right atrium, mitral valve apparatus, tricuspid valve apparatus, and coronary sinus (99–102). It also includes any new procedure-related pericardial effusion, which usually originates from injury of a cardiac structure, and any new unplanned intra-cardiac communication, resulting in a significant shunt (Qp/Qs ≥ 1.5:1).

Coronary obstruction represents an important complication associated with poor prognosis (103–106). Valve Academic Research Consortium 3 recommends that any coronary obstruction leading to death, haemodynamic compromise, MI, or unplanned surgical or percutaneous coronary intervention should be reported and classified as a major cardiac structural complication. Timing of occurrence should be carefully collected, acknowledging the potential for delayed coronary occlusion (107,108). Similarly, any subsequent failure to access optimally the coronary artery ostium should be reported, and those precluding the completion of a planned coronary

TABLE 7 Cardiac structural complications

Major
One of the following:
■ Cardiac structure* perforation, injury, or compromise resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
■ New pericardial effusion resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
■ Coronary obstruction† resulting in death, haemodynamic compromise, myocardial infarction, or unplanned surgical or percutaneous intervention. Coronary obstruction may be acute (during the procedure) or delayed (after completion of the procedure).
■ Coronary artery access difficulties for needed coronary angiography or intervention, resulting in death, haemodynamic compromise, myocardial infarction, coronary or aortic root injury, compromise in aortic valve prosthesis integrity, unplanned surgical or percutaneous intervention, or the inability to perform the intended procedure
Minor
One of the following:
■ Cardiac structure* perforation, injury, or compromise *not* resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
■ New pericardial effusion *not* resulting in death, VARC type ≥2 bleeding, haemodynamic compromise or tamponade, or requiring unplanned surgical or percutaneous intervention
■ Coronary obstruction *not* resulting in death, haemodynamic compromise, myocardial infarction, or unplanned surgical or percutaneous intervention
■ Coronary artery access difficulties for needed coronary angiography or intervention, *not* resulting in death, haemodynamic compromise, myocardial infarction, coronary or aortic root injury, compromise in aortic valve prosthesis integrity, unplanned surgical or percutaneous intervention, or the inability to perform the intended procedure

*Aortic annulus, left ventricular outflow tract, ventricular septum, left or right ventricle, atrial septum, left or right atrium, mitral valve apparatus, tricuspid valve apparatus, coronary artery, and coronary sinus. Also includes any new inter-cardiac cavity communication (e.g. VSD), and new left-to-right or right-to-left shunt.

†Angiographic or echocardiographic evidence of a new partial or complete obstruction of a coronary ostium or an epicardial coronary artery, either by the valve prosthesis itself, the native leaflets, embolized material (e.g. calcification, thrombus, and/or tissue), external device compression, or the consequence of coronary artery instrumentation (e.g. dissection, occlusion, embolization), occurring during or after the procedure, and with objective evidence of ischaemia (i.e. new ST-segment deviation on electrocardiogram) or symptoms. Excludes coronary complications due to a concomitant or subsequent planned percutaneous intervention for significant coronary artery disease.

TABLE 8 Other acute procedural and technical valve-related complications*

Conversion to open surgery

Conversion to open sternotomy or thoracotomy using cardiopulmonary bypass secondary to any procedure-related complication or failed intended transcatheter approach. Should be classified as:
- *Intraprocedural conversion:* during the index procedure
- *Periprocedural conversion:* ≤30 days after the index procedure
- *Delayed conversion*: >30 days after the index procedure

Unplanned use of mechanical circulatory support†

Implantation of multiple (>1) transcatheter valves during the index hospitalization

Valve malposition

Should be classified as:
- *Valve migration:* After initial correct positioning, the valve prosthesis moves upward or downward, within the aortic annulus from its initial position, without valve embolization
- *Valve embolization:* The valve prosthesis moves either upward or downward after final deployment such that it loses contact with the aortic annulus
- *Ectopic valve deployment:* Irretrievable deployment of a valve prosthesis at a site other than the intended position because of valve embolization or inability to deliver the prosthesis to the desired location

Paravalvular regurgitation (see Table 16)

*Individual events should be collected so that specific event rates can be determined.
†Mechanical circulatory support includes: cardiopulmonary bypass (CPB), extracorporeal membrane oxygenation (ECMO), transcatheter pumps (e.g. Impella) or intra-aortic balloon pump (IABP).

procedure (diagnostic or intervention) or resulting in haemodynamic compromise, MI, unplanned surgical or percutaneous intervention, or death should be classified as a major cardiac structural complication (109–111).

Other procedural valve-related complications

In addition to previously described endpoints, Table 8 provides a list of several important procedure-related endpoints that should be reported. These include the need for conversion to open surgery, the use of unplanned haemodynamic support, valve malposition, and PVR (see section on Assessment of Aortic Valve Function and Haemodynamics for a more detailed description of PVR) (8,112–114).

Conduction disorders and arrhythmias

New cardiac conduction disturbances and arrhythmias, including atrial fibrillation, left bundle branch block (LBBB), atrioventricular block, or other abnormalities requiring permanent pacemaker and/or implantable cardioverter-defibrillator implantation, are among the most frequent complications of aortic valve procedures (115–127). Studies have shown that both pre-existing and new-onset conduction disturbances and arrhythmias may impact prognosis after AVR (128–133). Baseline conduction abnormalities, including 1st-degree atrioventricular block, right bundle branch block (RBBB), and LBBB have also been shown to increase the risk of permanent pacemaker implantation after AVR (127,134). Moreover, a

TABLE 9 Conduction disturbances and arrhythmias

Pre-index procedure
- **Conduction disturbances**
  - 1st-degree AV block
  - *2nd-degree AV block*
  - Left bundle branch block
  - Right bundle branch block
  - IVCD with QRS ≥120 ms
  - Bradycardia (heart rate <60 b.p.m.) or SSS
- **Permanent pacemaker**
  - Type of permanent pacemaker should be recorded (e.g. single chamber, dual chamber, biventricular, defibrillator)
- **Atrial fibrillation (or flutter)**
  - Paroxysmal, persistent, long-standing persistent, or permanent

During or after index procedure*
- **Conduction disturbances**
  - 1st-, 2nd-, 3rd-degree AV block
  - Left bundle branch block
  - IVCD with QRS ≥120 ms
  - ***New-onset***: defined as a new conduction disturbance relative to baseline
  - ***Timing of occurrence:*** Procedural: ≤24 h after the index procedure
  Delayed: >24 h after the index procedure
  - ***Duration:*** Transient: resolved before discharge or ≤7 days after the index procedure in case of prolonged hospitalization
  Persistent: present at hospital discharge or >7 days after the index procedure in case of prolonged hospitalization
  Permanent: present >30 days after the index procedure
- **Permanent pacemaker**
  - ***Type:*** single, dual, biventricular, defibrillator, leadless
  - ***Timing:*** No. of days after the index procedure
  - ***Indication:*** including AV Block, SSS
- **Atrial fibrillation (or flutter)**
  - ***New-onset:*** defined as any arrhythmia that was not present at baseline 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 s on a rhythm strip
  - ***Timing of occurrence†***:
  Periprocedural: ≤30 days after the index procedure
  Late/spontaneous: >30 days after the index procedure
  - ***Duration†:***
  Paroxysmal: atrial fibrillation that terminates spontaneously or with intervention ≤7 days of onset.
  Persistent: Continuous atrial fibrillation that is sustained >7 days.
  Long-standing persistent: Continuous atrial fibrillation >12 months in duration.
  Permanent: Used when the patient and clinician make a joint decision to stop further attempts to restore and/or maintain sinus rhythm.

*The calculation of new pacemaker rates should exclude patients with pre-existing pacemaker. The same principle applies to reporting of rates of new conduction disturbances and arrhythmias.
†From January et al (136).
AF = atrial fibrillation or atrial flutter; AV = atrioventricular; ECG =, electrocardiogram; IVCD = intraventricular conduction delay; SSS = sick sinus syndrome.

recent expert consensus document has proposed a stratification scheme based on the presence or absence of baseline ECG findings (RBBB, PR interval) and the development of new conduction disturbances post-AVR (new LBBB, PR, or QRS prolongation, or new atrioventricular block) (135). Given these considerations, it is recommended that all studies at minimum report the baseline and post-procedure presence of the most important conduction disturbances and arrhythmias, including those that have been shown to alter prognosis or predict permanent pacemaker implantation (Table 9). Studies specifically investigating conduction disturbances and arrhythmias may wish to collect and report more granular data, collected at more frequent time-points. These

TABLE 10 Acute kidney injury*

Stage 1
AKI that fulfils at least one of the following criteria: ■ Increase in serum creatinine ≥150–200% (≥1.5–2.0× increase) within 7 days compared with baseline ■ Increase of ≥ 0.3mg/dL (≥26.4 μmol/L) within 48 h of the index procedure
Stage 2
AKI that fulfils the following criterion: ■ Increase in serum creatinine >200–300% (>2.0–3.0× increase) within 7 days compared with baseline
Stage 3
AKI that fulfils at least one of the following criteria: ■ Increase in serum creatinine >300% (>3.0× increase) within 7 days compared with baseline ■ Serum creatinine ≥4.0 mg/dL (≥354 μmol/L) with an acute increase of ≥0.5 mg/dL (≥44 μmol/L)
Stage 4
AKI requiring new temporary or permanent renal replacement therapy

Adapted from Clinical Practice Guidelines for Acute Kidney Injury 2012. https://kdigo.org/guidelines/acute-kidney-injury/.

*Given practical challenges with the use of urine output criteria in daily practice, AKI should be solely defined based on serum creatinine values. Acute kidney injury defined by urine output using the following criteria might be used in the context of a dedicated AKI study: AKI Stage 1: Urine output <0.5 mL/kg/h for ≥6 but <12 h; AKI stage 2: Urine output <0.5 mL/kg/h for ≥12 but <24 h; AKI stage 3: Urine output <0.3 mL/kg/h for ≥24 h or anuria for ≥12 h.

AKI = acute kidney injury.

studies may also collect additional information regarding therapies, including anti-arrhythmic agents, chronotropic agents, temporary pacemakers, ablation, oral anticoagulants, or left atrial appendage occlusion.

Conduction disturbances and arrhythmias, particularly LBBB, high-degree atrioventricular block, and atrial fibrillation, can be transient or persistent after AVR (121–137). Substantial variability exists across studies in the rates of these complications, which may in part be due to significant differences in the frequency of ascertainment and definitions used. Valve Academic Research Consortium 3 recommends the collection of 12-lead electrocardiograms (ECGs) at a minimum, at baseline, as early as feasible after the procedure, daily during hospitalization, and at regular follow-up intervals (at least 30 days and yearly). It is also recommended that standardized consensus definitions for conduction disturbances be adopted. Specifically, the diagnosis of LBBB should follow the American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society recommendation (138). Given the substantial resolution of new LBBB within the first 30 days after AVR (139), VARC-3 now proposes the following definition to better characterize LBBB occurrence: transient LBBB (resolved before discharge or within 7 days post-AVR in case of prolonged hospitalization), persistent LBBB (present at hospital discharge or until Day 7 post-AVR in case of prolonged hospitalization), or permanent LBBB (present at 30 days and beyond). Similarly, VARC-3 proposes to categorize the timing of occurrence of important conduction disorders as procedural (occurring ≤24 h after the index procedure) or delayed (occurring >24 h after the index procedure).

New-onset atrial fibrillation (or flutter) is defined as any arrhythmia during the index 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 s on a rhythm strip. Its duration (both pre- and post-index procedure) is characterized as being paroxysmal, persistent, long-standing persistent, or permanent (**Table 9**). Valve Academic Research Consortium 3 endorses the definitions provided by AHA/ACCF/HRS guidelines and recommendations for standardization and interpretation of ECGs (138,140,141), but proposes a further classification regarding the timing of occurrence of new-onset atrial fibrillation: periprocedural if it occurs within 30 days of the index procedure and late/spontaneous, if it occurs beyond 30 days of the index procedure.

Finally, it is problematic that many studies have reported the rate of new permanent pacemaker requirement as a percentage of the entire study population (142). Valve Academic Research Consortium 3 now explicitly recommends that the calculation of the rate of new permanent pacemaker implantation exclude from the denominator patients with prior permanent pacemaker, who are not at risk for the outcome. This, in addition to reporting of the timing and indication for permanent pacemaker implantation, should help to facilitate comparisons across studies. The same principle applies to the reporting of the rates of other conduction disturbances (LBBB) and arrhythmias (atrial fibrillation) that may pre-date the aortic valve procedure.

Acute kidney injury

Acute kidney injury after TAVR or SAVR is a complication associated with poor prognosis (143–147). Valve Academic Research Consortium 3 recommends using the widely recognized Kidney Disease: Improving Global Outcomes (KDIGO) definition of acute kidney injury (148) (**Table 10**). Acknowledging the challenges related to the use of urine output as a criterion in daily practice (149,150), serum creatinine criteria should be the default criteria, and the urine output definition can be considered in the setting of dedicated acute kidney injury studies (91,151). The need for new renal replacement therapy (temporary or permanent) should now be reported as a separate entity (acute kidney injury stage 4). As described in the above section, the denominator for dialysis should exclude patients already on chronic dialysis prior to the aortic valve procedure.

While VARC-3 recognizes that eGFR is widely used clinically to classify severity of renal dysfunction, the KDIGo guidelines have not adopted changes in eGFR for

AKI classification, and as such, VARC-3 will follow the same classification. Valve Academic Research Consortium 3 also acknowledges the challenges in following creatinine levels beyond 48 h, especially in the context of early discharge. Creatinine levels should be measured at a minimum, at baseline and within 24 h post-procedure, and ideally daily up to 48 h post-procedure. If post-procedure values are increased compared with baseline, an additional value should be drawn, and serial measures should be assessed until the creatinine declines from its peak value.

Myocardial infarction

Characterizing myocardial injury after SAVR or TAVR is important and should be reported appropriately (152–157). Despite a growing body of evidence related to the potential clinical impact of different degrees of myocardial injury post-valve replacement (158), many challenges remain regarding the diagnosis, adjudication, and comparison of MI post-AVR procedures: (i) the different degrees of myocardial injury inherent to different techniques and approaches (e.g. SAVR vs. alternative access TAVR vs. transfemoral TAVR), (ii) the use of different biomarkers (creatine kinase-MB, standard troponin, high-sensitivity troponin) with variable sensitivities and availability, (iii) the arbitrary (and evolving) nature of MI definitions used in cardiovascular trials, and (iv) the lack of strong and conclusive evidence of association with hard clinical outcomes, especially among patients undergoing AVR. In the absence of definitive data, and given the high incidence of concomitant coronary disease (159–162) and potential need for coronary revascularization (111,163–165), VARC-3 endorses the general classification of the Fourth Universal Myocardial Definition in regards to spontaneous MI (Type 1), imbalance between oxygen supply and demand (Type 2), MI leading to death (Type 3), and MI related to coronary stent thrombosis (Type 4B) and coronary restenosis (Type 4C) (166). However, for periprocedural MI post-percutaneous coronary intervention (Type 4A) and post-coronary artery bypass graft (Type 5), VARC-3 endorses the modified SCAI (167) and ARC-2 (168) definition, which provide a common biomarker (troponin or CK-MB) threshold for both PCI and CABG, and proposes to use the same definition for periprocedural MI post-SAVR and TAVR. Given that most current and future studies related to AVR strategies will involve long-term follow-up, with patients frequently suffering from coronary artery disease, VARC-3 believes that these definitions will allow the most appropriate characterization and classification of types of MI occurring in this population (6,166). Periprocedural biomarker elevations not meeting the criteria for MI should be categorized as 'myocardial injury not meeting MI criteria', and the implications of these lower levels of myonecrosis should be carefully examined. Importantly, biomarker elevations in the context of valve-related complications such as acute or delayed coronary occlusion, or failure to appropriately engage the coronary ostium, with subsequent complications during a coronary procedure, should also be classified as cardiac structural complications (**Table 11**).

Biomarkers of myocardial injury should be collected prior to the procedure and be performed twice within the first 24 h post-procedure. If the biomarker level at either time point is elevated by ≥50% compared with baseline, serial measures should be drawn until the peak has been reached and the levels begin to decline. All patients should also have a baseline 12-lead ECG, and this should be repeated as soon as feasible after the AVR procedure and daily until hospital discharge.

Mechanical aortic valve and autograft root replacement

European and American guidelines currently recommend the use of bioprosthetic valves in patients above the age of 65 and 70 years old, respectively (170,171). Both guidelines also support the use of mechanical valves for patients below the age of 60 years old. Mechanical aortic prostheses have the advantage of prolonged durability, although they require systemic oral anticoagulation and are thus associated with increased bleeding risks over time (172,173). The decision-making process in the selection of prosthesis type includes factors such as: (i) life expectancy and potential need for re-intervention, (ii) bleeding risk, (iii) patient lifestyle, (iv) concomitant comorbidities requiring lifetime oral anticoagulation or affecting bioprosthetic valve durability, and (v) patient preferences (174). Some mechanical heart valves require a lower level of systemic anticoagulation, which is expected to lower the risk of long-term bleeding (175,176). Recently, a novel biopolymer-based leaflet material has been developed, raising hopes for a heart valve implant with prolonged durability and no need for oral anticoagulation (177). Finally, in younger and middle-aged adults, autograft implantation (Ross Procedure) represents a viable option (178,179). While the VARC-3 criteria for valve degeneration and failure presented below mainly focus on bioprosthetic valves, the modes of failure are similar for mechanical implants and autograft replacements as well (structural failure, non-structural failure, endocarditis, thrombosis), though they also include re-intervention for recurrent/life-threatening bleeding or pulmonary valve insufficiency. The VARC-3 classification characterizing mode of valve failure could also be applied to other types of aortic valve implants, and the reasons for associated re-intervention should be appropriately captured.

TABLE 11 Myocardial infarction (adapted from 4th Universal, SCAI and ARC-2 definitions)

Type 1 (Spontaneous MI) (>48 h after the index procedure)*
- Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL with at least one of the following:
  - Symptoms of acute ischaemia
  - New ischaemic ECG changes (new ST-segment or T-wave changes or new LBBB)
  - New pathologic Q-waves in ≥2 contiguous leads
  - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality in a pattern consistent with an ischaemic aetiology
  - Identification of a coronary thrombus by angiography or autopsy
- Post-mortem demonstration of an atherothrombus in the artery supplying the infarcted myocardium, or a macroscopically large circumscribed area of necrosis with or without intramyocardial haemorrhage, meets the type 1 MI criteria regardless of cTn values

Type 2 (Imbalance between myocardial oxygen supply and demand)*
- Detection of a rise and/or fall of cTn values with at least one value above the 99th percentile URL, and evidence of an imbalance between myocardial oxygen supply and demand unrelated to coronary thrombosis, requiring at least one of the following:
  - Symptoms of ischaemia
  - ECG changes indicative of new ischaemia (new ST-segment or T-wave changes or new LBBB)
  - New pathologic Q-waves in ≥2 contiguous leads
  - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality

Type 3 (MI associated with sudden cardiac death)*
- Patients who suffer cardiac death, with symptoms suggestive of myocardial ischaemia accompanied by presumed new ischaemic ECG changes or ventricular fibrillation but die before blood samples for biomarkers can be obtained, or before increases in cardiac biomarkers can be identified, or MI is detected by autopsy examination.

Type 4A (Criteria for PCI-related MI ≤48 h after the index procedure)†
- ***In patients with normal baseline CK-MB:*** The peak CK-MB measured within 48 h of the procedure ≥10× the local laboratory ULN or CK-MB ≥5× ULN with one or more of the following:
  - New pathologic Q-waves in ≥2 contiguous leads
  - New persistent LBBB‡
  - Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
  - Substantial new loss of viable myocardium on imaging related to the procedure
- In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥70× the local laboratory ULN or ≥35× ULN with one or more of the following:
  - New pathologic Q-waves in ≥2 contiguous leads
  - New persistent LBBB‡
  - Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
  - Substantial new loss of viable myocardium on imaging related to the procedure
- ***In patients with elevated baseline CK-MB (or cTn):*** The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described.

Type 4B (Stent thrombosis)*
- Stent thrombosis as documented by angiography or autopsy using the same criteria utilized for type 1 MI.
  - Acute: 0 to 24 h
- Subacute: >24 h to 30 days
- Late: >30 days to 1 year
- Very late: >1 year after stent implantation

Type 4C (Coronary stent restenosis)*
- Focal or diffuse restenosis, or a complex lesion associated with a rise and/or fall of cTn values above the 99th percentile URL applying, the same criteria utilized for type 1 MI

Type 5 Periprocedural (post-SAVR, TAVR or CABG) MI (≤48 h after the index procedure)†
- ***In patients with normal baseline CK-MB:*** The peak CK-MB measured within 48 h of the procedure ≥10× the local laboratory ULN or CK-MB ≥5× ULN with one or more of the following:
  - New pathologic Q-waves in ≥2 contiguous leads
- New persistent LBBB‡
- Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
- Substantial new loss of viable myocardium on imaging related to the procedure
- In the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the procedure rises to ≥70× the local laboratory ULN or ≥35× ULN with one or more of the following:
  - New pathologic Q-waves in ≥2 contiguous leads
- New persistent LBBB‡
- Flow-limiting angiographic complications in a major epicardial vessel or >1.5 mm diameter branch
- Substantial new loss of viable myocardium on imaging related to the procedure
- ***In patients with elevated baseline CK-MB (or cTn):*** The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus new ECG changes as described.

The use of high-sensitivity (hs)-troponins is recommended for diagnosis of spontaneous MI, but has not been studied for assessment of periprocedural MI. Standard troponin assays are therefore recommended for evaluation of periprocedural MI. Periprocedural biomarker elevation >ULN not meeting the criteria for MI should be categorized as 'myocardial injury not meeting MI criteria'.

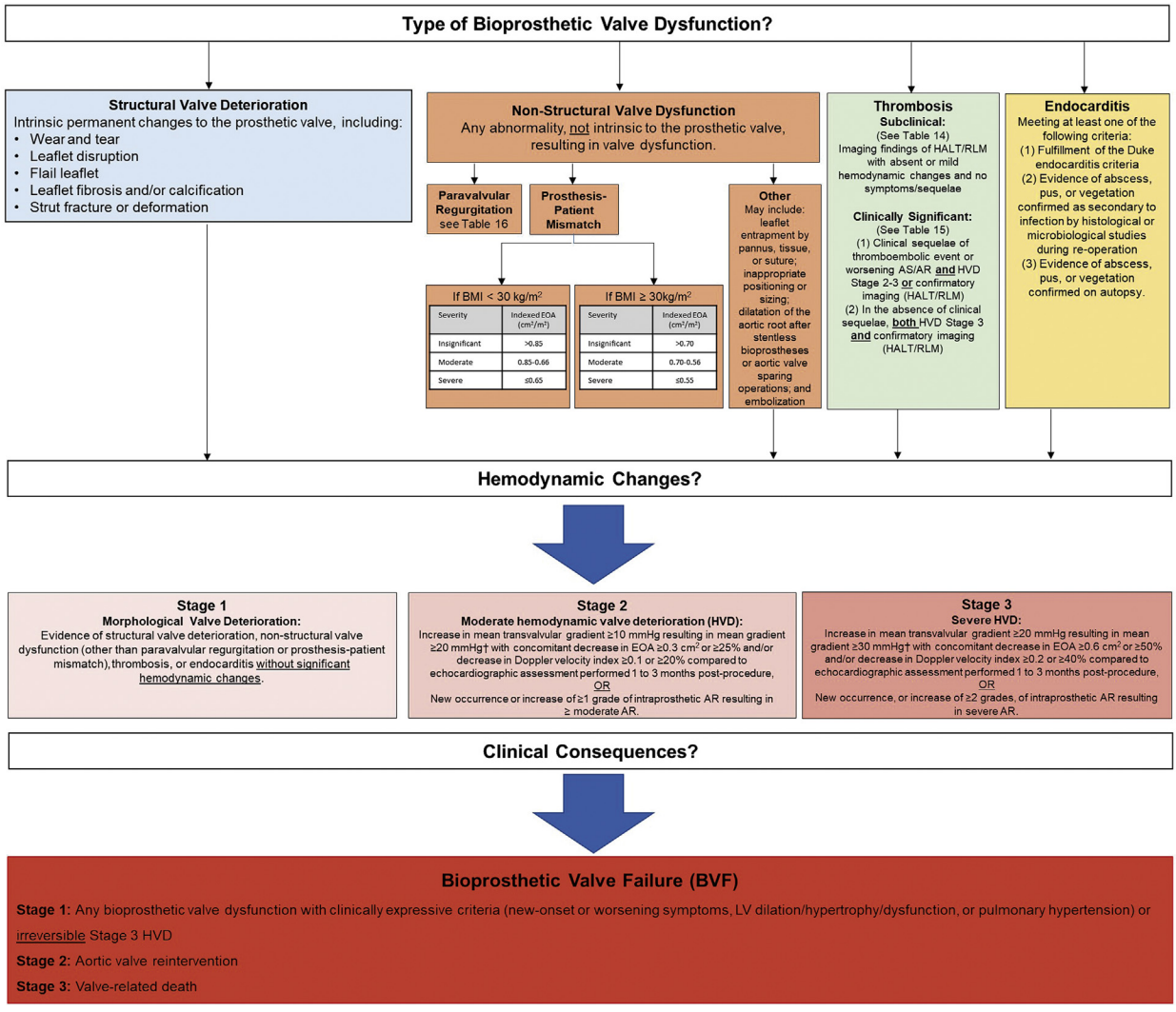
*Adapted from Thygesen *et al.* (169).

†Adapted from Moussa *et al.* (167) and Garcia-Garcia *et al.* (168).

‡LBBB criteria to be used with caution after TAVR or SAVR given the relatively high rate of new LBBB after these procedures.

CK-MB = creatine kinase-MB; cTn, cardiac troponin; ECG = electrocardiogram; LBBB = left bundle branch block; MI, myocardial infarction; SAVR = surgical aortic valve replacement; TAVR = transcatheter aortic valve replacement; ULN = upper limit of normal; URL = upper reference limit.

CENTRAL ILLUSTRATION **Bioprosthetic Valve Dysfunction and Bioprosthetic Valve Failure**



Généreux, P. et al. J Am Coll Cardiol. 2021;77(21):2717–46.

BMI = body mass index; BVD = bioprosthetic valve dysfunction; BVF = bioprosthetic valve failure; HALT = hypo-attenuated leaflet thickening; RLM = reduced leaflet motion.

Bioprosthetic valve dysfunction

Central Illustration summarizes endpoints for both structural and non-structural bioprosthetic valve dysfunction (BVD) and depicts the recommended decision tree for classification of aetiology and severity of BVD, consistent with recently published consensus documents (180–183). In most instances, BVD is a progressive process that requires serial longitudinal assessments of clinical status, as well as valve morphology, function, and haemodynamics. Classification of BVD is further detailed in **Table 12** and haemodynamic criteria for assessment of BVD severity in **Table 13**. Of note, due to the inherent variability of echocardiographic imaging and assessment, as well as fluctuations in blood flow which can result in changes to Doppler measurements, a definite diagnosis of SVD should not rely on the measurement of a single haemodynamic parameter, and preferably should incorporate evidence from at least two serial echocardiograms. This is in contrast to prior definitions which considered only absolute threshold values of aortic valve area and gradient. A baseline post-procedural echocardiogram is essential to ensure adequate comparison during

TABLE 12 Aortic bioprosthetic valve dysfunction

Categories of BVD

Structural valve deterioration (SVD)
- Intrinsic permanent changes to the prosthetic valve, including wear and tear, leaflet disruption, flail leaflet, leaflet fibrosis and/or calcification, or strut fracture or deformation
- See Table 13 for grading severity

Non-structural valve dysfunction (NSVD)
- Any abnormality, not intrinsic to the prosthetic valve, resulting in valve dysfunction. Examples include residual intra- or para-prosthetic aortic regurgitation; leaflet entrapment by pannus, tissue, or suture; inappropriate positioning or sizing; dilatation of the aortic root after stentless prostheses or aortic valve sparing operations; prosthesis-patient mismatch; and embolization

Thrombosis
- See Tables 13–15

Endocarditis
- Meeting at least one of the following criteria: (i) Fulfilment of the Duke endocarditis criteria (ii) Evidence of abscess, pus, or vegetation confirmed as secondary to infection by histological or microbiological studies during re-operation; and (iii) Evidence of abscess, pus, or vegetation confirmed on autopsy.

Clinical presentation
- ***Subclinical:*** Any bioprosthetic valve dysfunction associated with absent or mild haemodynamic changes, AND absent symptoms or sequelae
- ***Bioprosthetic valve failure (BVF):***
  - ***Stage 1:*** Any bioprosthetic valve dysfunction associated with clinically expressive criteria (new-onset or worsening symptoms, LV dilation/hypertrophy/dysfunction, or pulmonary hypertension) or irreversible Stage 3 haemodynamic valve deterioration (HVD)
  - ***Stage 2:*** Aortic valve reoperation or re-intervention
  - ***Stage 3:*** Valve-related death*

*Valve-related death defined as in Table 2: cardiovascular mortality presumed to be associated with bioprosthetic valve dysfunction.

BVD = bioprosthetic valve dysfunction.

TABLE 13 Stages of bioprosthetic valve deterioration*†

Stage 1: Morphological valve deterioration
- Evidence of structural valve deterioration, non-structural valve dysfunction (other than paravalvular regurgitation or prosthesis-patient mismatch), thrombosis, or endocarditis *without significant haemodynamic changes.*

Stage 2: Moderate haemodynamic valve deterioration
- Increase in mean transvalvular gradient ≥10 mmHg resulting in mean gradient ≥20 mmHg‡ with concomitant decrease in EOA ≥0.3 cm^2 or ≥25% and/or decrease in Doppler velocity index ≥0.1 or ≥20% compared with echocardiographic assessment performed 1–3 months post-procedure, *OR* new occurrence or increase of ≥1 grade§ of intra-prosthetic AR resulting in ≥ moderate AR.

Stage 3: Severe haemodynamic valve deterioration
- Increase in mean transvalvular gradient ≥20 mmHg resulting in mean gradient ≥30 mmHg‡ with concomitant decrease in EOA ≥0.6 cm^2 or ≥50% and/or decrease in Doppler velocity index ≥0.2 or ≥40% compared with echocardiographic assessment performed 1–3 months post-procedure, *OR* new occurrence, or increase of ≥2 grades,§ of intraprosthetic AR resulting in severe AR.

*Adapted from Capodanno *et al.* (180), Lancellotti *et al.* (184), and Dvir *et al.* (185). †When assessing the presence and severity of haemodynamic valve deterioration, it is important to differentiate true-haemodynamic changes vs. inter-echo variability in the measurement of gradient, EOA, DVI, or AR. In particular, one should use the same window for continuous-wave Doppler interrogation when comparing gradients in early (1–3 months) post-AVR echo vs. follow-up echo. Each case with potential haemodynamic valve deterioration should be individually adjudicated to confirm presence, stage, and aetiology. Haemodynamic valve deterioration may be caused by structural valve deterioration but also by non-structural dysfunction including valve thrombosis and endocarditis. The assessment of valve leaflet morphology and structure is key to make differential diagnosis between the different aetiologies of haemodynamic valve deterioration. ‡This criterion for haemodynamic dysfunction assumes normal flow. §This criteria is assessed with the 3-class grading scheme (See Table 16).

AR = aortic regurgitation; EOA = effective orifice area; DVI = Doppler velocity index.

follow-up, especially if prosthesis-patient mismatch is present after valve implantation. Although echocardiography is a cornerstone for the evaluation of valve function and haemodynamics, cardiac computed tomography (CT) is becoming increasingly used to better understand the pathology and mechanisms underlying BVD. In particular, CT has become central to the diagnosis of leaflet and valve thrombosis, described in more detail below and summarized in Tables 14 and 15. Bioprosthetic valve dysfunction may be related to several aetiologies (Central Illustration): (i) SVD, which implies irreversible intrinsic changes to structural elements of the valve itself; (ii) non-structural valve dysfunction, which includes PVR and prosthesis-patient mismatch; (iii) endocarditis; or (iv) thrombosis. The stages of SVD are described in Table 13: Stage 1: morphological valve deterioration; Stage 2: moderate haemodynamic valve deterioration; and Stage 3: severe haemodynamic valve deterioration. When assessing the presence and severity of haemodynamic valve deterioration, it is important to differentiate true-haemodynamic changes vs. inter-echo variability in the measurement of gradient, effective orifice area, Doppler velocity index, or AR. Each case with potential haemodynamic valve deterioration should be individually adjudicated to confirm presence, stage, and aetiology. Haemodynamic valve deterioration may be caused by SVD but also by valve thrombosis or endocarditis. The assessment of valve leaflet morphology and structure is key to make a differential diagnosis between the different aetiologies of haemodynamic valve deterioration. The definitions of SVD presented in Table 13 allow one to differentiate haemodynamic deterioration that is related to SVD vs., for example, from high residual transprosthetic gradients related to prosthesis-patient mismatch.

An important addition to VARC-3 is the incorporation of the definition for bioprosthetic valve failure (BVF). Bioprosthetic valve failure is a patient-oriented clinical endpoint that takes into account relevant and clinically meaningful consequences of BVD such as SVD-related Stage 3 haemodynamic valve deterioration and irreversible changes in haemodynamics, as well as clinical symptoms or sequelae, including valve-related death and re-intervention (either surgical or transcatheter; Central Illustration). Thrombosis or endocarditis may also lead to irreversible Stage 3 haemodynamic valve deterioration and thus BVF. Bioprosthetic valve failure should be reported separately from subclinical BVD detected solely by haemodynamic findings. Given the competing risks

TABLE 14 Diagnosis and criteria for leaflet thickening and reduced leaflet motion*†‡

Hypo-attenuated leaflet thickening (HALT)
- Hypo-attenuating thickening in typically meniscal configuration on one or more leaflets visually identified on computed tomography (2D multiplanar reconstructions or 3D volume-rendering), with or without reduced leaflet motion (RLM)§
- The extent of HALT should be described per leaflet, using a 4-tier grading scale in regard to leaflet involvement along the curvilinear contour, assuming maximum involvement at the base of the leaflet:
  - ≤*25%* (limited to the base)
  - >*25% and* ≤*50%*
  - >*50% and* ≤*75%*
  - >*75%*
- *Inconclusive for HALT*: imaging with insufficient image quality or presence of artifact

Reduced leaflet motion (RLM)
- Reduced leaflet excursion in the presence of HALT identified on computed tomography (2D multiplanar reconstructions or 3D volume rendering) and/or trans-oesophageal echocardiography
- The extent of RLM should be described per leaflet, using a 4-tier grading scale
  - *None:* no reduction in leaflet excursion
  - <50% reduction in leaflet excursion
  - ≥50% reduction in leaflet excursion
  - *Immobile:* immobile leaflet
  - *Inconclusive for RLM:* imaging with insufficient image quality or presence of artefact

Presentation
- *Subclinical:* Absent or mild haemodynamic changes and absent symptoms or sequela compatible with valve thrombosis or thromboembolism.
- *Clinically significant:* See **Table 15**

Timing
- *Acute:* Within 0–24 h of the index procedure
- *Subacute:* >24 h and ≤30 days after the index procedure
- *Late:* >30 days and ≤1 year after the index procedure
- *Very late:* >1 year after the index procedure

*Adapted from Blanke *et al.* (193).
†CT with high spatial and temporal resolution is required to accurately assess leaflet thickness and motion. Typical CT acquisition parameters include: Intravenous contrast-enhancement, sub-millimetre slice thickness, ECG-gating with full cardiac cycle coverage and without dose modulation, target heart rate ≤70 b.p.m. If computed tomography is of either low quality, contra-indicated or inconclusive, trans-oesophageal echocardiography (TEE) may be used for the evaluation of leaflet thickness and motion.
‡Causes of leaflet thickening and reduced leaflet motion included phenomenon such as leaflet thrombosis, endocarditis, leaflet deterioration, and valve frame expansion issues.
§Additional leaflet assessments may include: (i) diastolic measurements of maximal affected leaflet thickness and area on longitudinal and axial projections of the aortic valve, respectively; (ii) affected prosthetic leaflet(s) should be identified relative to the positions of the native commissures; Additional stent/frame assessments includes: (i) implant depth, (ii) stent expansion and eccentricity at multiple levels, and (iii) stent strut-separation at the inflow level.

TABLE 15 Clinically significant valve thrombosis

Clinical sequelae of a thromboembolic event (e.g. stroke, TIA, retinal occlusion, other evidence of systemic thromboembolism) or worsening valve stenosis/regurgitation (e.g. signs of heart failure, syncope) *and*
- Haemodynamic valve deterioration Stage 2 or 3* *or*
- Confirmatory imaging (CT evidence of HALT† or TEE findings)
- In the absence of clinical sequelae, *both*
- Haemodynamic valve deterioration Stage 3* *and*
- Confirmatory imaging (CT evidence of HALT† or TEE findings)

Timing
- ***Acute:*** Within 0–24 h of the index procedure
- ***Subacute:*** >24 h and ≤30 days after the index procedure
- ***Late:*** >30 days and ≤1 year after the index procedure
- ***Very late:*** >1 year after the index procedure

Response to anticoagulant therapy (≥3 months)
- ***Resolved:*** Partial or complete resolution of symptoms, imaging findings, and HVD
- ***Persistent:*** No improvement in symptoms, imaging findings, or HVD
- ***Recurrent:*** Recurrence of symptoms, imaging findings, or HVD

Certainty of diagnosis
- ***Definite:*** Histopathological confirmation
- ***Probable:*** Haemodynamic changes and imaging findings compatible with valve thrombosis, with resolution of haemodynamic changes and imaging findings following anticoagulation therapy
- ***Possible:*** Imaging demonstrated findings compatible with leaflet thrombosis formation, but either haemodynamic changes or imaging findings persist following anticoagulation therapy or anticoagulation therapy is not (yet) administered

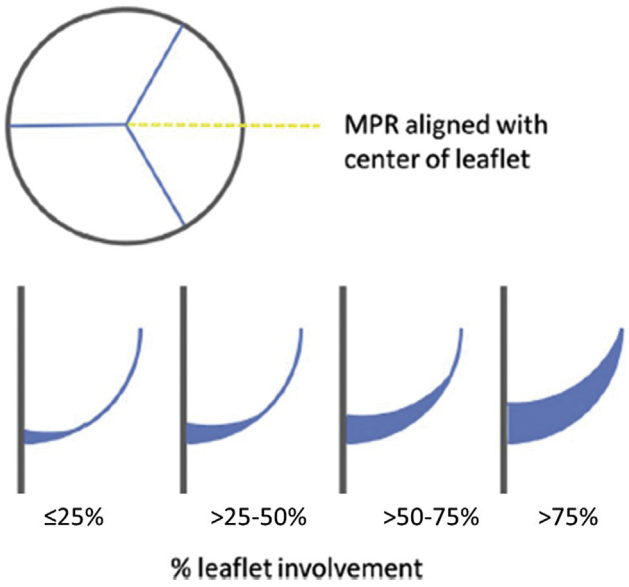
*As defined in **Table 13**.
†As defined in **Table 14**.
CT = computed tomography; TEE = trans-oesophageal echocardiogram; HALT = hypo-attenuated leaflet thickening; HVD = haemodynamic valve deterioration.

between BVF and death, conventional Kaplan-Meier estimates (i.e. actuarial analysis) may overestimate the risk of BVF by assuming that patients without BVF, whether currently alive or dead, will have BVF in the future. This overestimation can have important implications for clinical trials involving elderly patients who will likely die before experiencing BVF. To correctly understand the probability of BVF during the course of a patient's lifetime, competing risks (cumulative probability) methods should be used (186,187). For mortality calculations alone, actuarial and competing risks methods would provide identical curves. However, in estimating durability of a bioprosthesis (the device rather than the patient), death introduces informative censoring that results in overestimating device durability; the competing risk function known as conditional probability gives a more accurate depiction of device durability than the Kaplan-Meier method. The exposure adjusted incidence rates of BVD, SVD, and BVF can also be reported as exposure adjusted cumulative rate, which is defined as the number of subjects exposed to the bioprosthesis and experiencing an event (BVD, SVD, or BVF) divided by the total exposure time of all patients who are at risk of event, and it is expressed per 100 patient-years (188).

Hypo-attenuated leaflet thickening and reduced leaflet motion

Hypo-attenuated leaflet thickening (HALT) is visually identified increased thickness of the bioprosthetic leaflet on contrast-enhanced cardiac CT. Hypo-attenuated leaflet thickening typically exhibits a meniscal-shaped configuration, starting and thickest at the insertion of the bioprosthetic leaflet at the stent frame or valve scaffold, and gradually tapering towards the free edge of the leaflets. While the occurrence of HALT has been described across all transcatheter aortic valve platforms and surgical bioprostheses (189,190), its effect on patient outcome and long-term valve function remains unclear (191,192). When assessing the extent of HALT within a clinical study, a semi-quantitative grading scale should be used per leaflet

FIGURE 1 Multiplanar Reconstruction Alignment and Semi-Quantitative Grading of Hypo-Attenuated Leaflet Thickening By Computed Tomography Imaging



The **dashed yellow line** indicates the orientation of the long-axis views in the lower row, aligned with the centre of the cusps. The extent of leaflet thickening can be graded on a subjective 4-tier grading scale along the curvilinear orientation of the leaflet. Typically, hypo-attenuated leaflet thickening appears meniscal-shaped on long-axis reformats, with greater thickness at the base than towards the centre of the leaflet. Reprinted with permission from Blanke *et al.* (193). Note—percentage ranges modified from source to eliminate ambiguity.

as presented in **Table 14 and Figure 1**, describing the percentage leaflet involvement starting at its basal insertion (193). The evaluation of HALT is performed using multiplanar reformats with optional volume-rendered reconstructions. The strength of cardiac CT is its high spatial resolution. However, evaluation for the presence of HALT may be impaired by streak artefacts caused by the stent frame, motion artefact or suboptimal contrast attenuation, rendering CT studies at times inconclusive for HALT. Leaflet restriction caused by HALT can be described as reduced leaflet motion (RLM). However, given the limited temporal resolution of cardiac CT, the strength of cardiac CT is in the diagnosis of HALT and findings of restricted leaflet motion should only be pursued in the setting of HALT. Assessing leaflet motion in the absence of HALT increases the likelihood of false-positive diagnosis of RLM, in particular in the presence of image arteact and limited image frames. Causes of leaflet thickening and reduced leaflet motion include phenomena such as leaflet thrombosis, endocarditis, leaflet deterioration and valve frame expansion issues. However, the terms HALT and RLM have been used mainly as a synonym of subclinical leaflet thrombosis in most of the early literature.

Clinical data

The presence of HALT and RLM has been described in 5% to as many as 40% of patients who undergo MDCT scan assessment post-AVR (189,190,194-196). The RESOLVE and SAVORY registries initially reported subclinical leaflet thrombosis in 12% of patients undergoing systematic 4D MDCT scans (mean time ~3 months) post-AVR, with TAVR patients having approximately three-fold higher rates of leaflet thrombosis than SAVR patients (13% vs. 4%, $P = 0.001$) (189). Leaflet thrombosis was associated with higher rates of transient ischaemic attacks (TIA) (2.9 vs. 0.7%, $P = 0.03$) and the composites of strokes or TIA (4.1 vs. 1.3%, $P = 0.04$). However, a temporal separation between the clinical event and the CT findings was observed, and due to the natural history of subclinical leaflet thrombosis, which may regress or progress spontaneously (197), no definitive conclusions on clinical impact of the phenomenon could be drawn from this study.

In an attempt to better understand the natural history and haemodynamic impact of subclinical leaflet thrombosis, the FDA mandated CT sub-studies from two large randomized trials, with analyses performed by the same blinded and independent CT core laboratory (191,198). In the PARTNER 3 and Evolut Low Risk randomized trials, CT sub-studies were performed with serial imaging in patients treated with TAVR or surgery at 30 days and 1 year. In the two studies, the frequency of HALT and RLM varied from 10% to 16% at 30 days and increased to 24–30% at 1 year. The natural history of subclinical leaflet thrombosis derived from serial CTs in the absence of anticoagulation was characterized by spontaneous resolution in approximately half the patients and a significant number of new cases occurring between 30 days and 1 year. The association of HALT and RLM and increasing aortic valve gradients was small and varied among the studies. These trials were not powered to determine the impact of CT findings on subsequent clinical events.

Whether more aggressive antithrombotic strategies could potentially mitigate the occurrence of subclinical leaflet thrombosis is a matter of active investigation. In the CT sub-study of the GALILEo trial, patients who had undergone successful TAVR and who did not have an indication for long-term anticoagulation were randomized to a rivaroxaban-based antithrombotic strategy or an antiplatelet-based strategy. Patients underwent evaluation by 4D MDCT at 90 days after randomization. While both HALT (12.4% vs. 32.4%) and high grade RLM (2.1% vs. 10.9%; $P = 0.01$) were reduced in the rivaroxaban group, the risk of death or thromboembolic events and the risk of life-threatening, disabling, or major bleeding were higher with rivaroxaban (hazard ratios of 1.35 and 1.50, respectively) (192,199). In light of these findings, further studies are needed to better understand the clinical and valve-related consequences of subclinical leaflet thrombosis and the consequences of systematic anticoagulation regimens.

Clinically significant valve thrombosis

The frequent, but commonly subclinical, occurrence of HALT, at times described as subclinical leaflet thrombosis should be distinguished from valve thrombosis with clinical manifestations. In transcatheter heart valves in the aortic position, clinically significant valve thrombosis occurs in <1% of implants within 2 years of the index procedure, and is typically associated with rapid increases in transvalvular gradients (mean AV gradient >40 mmHg) (181,200–203). Patients with valve thrombosis often present with worsening dyspnoea and heart failure symptoms, occasionally associated with thromboembolic complications. Valve thrombosis must be distinguished from rapidly progressive SVD and endocarditis, and typically responds to treatment with oral anticoagulation (vitamin K antagonists) for 2–4 months, with reduced gradients and improved symptoms.

Valve Academic Research Consortium 3 is updating the previously vague definition of *valve thrombosis* proposed in 2011 (**Table 15**). Clinically significant prosthetic valve thrombosis requires (i) clinical sequelae of (a) a thromboembolic event (stroke, TIA, retinal occlusion, or other evidence of systemic thromboembolism) or (b) worsening valve stenosis/regurgitation (increasing dyspnoea or signs of heart failure) AND either imaging evidence of valve-related thrombus (CT or trans-oesophageal echocardiogram) or haemodynamic valve deterioration stage 2 or 3, OR (ii) no clinical sequelae but imaging evidence of both valve-related thrombus (CT or trans-oesophageal echocardiogram) and haemodynamic valve deterioration stage 3, observed during routine interval imaging assessments. Importantly, the use and response to oral anticoagulant therapy must be carefully documented and provides corroboration of the valve thrombosis diagnosis.

If valve thrombosis is suspected, either by transthoracic echocardiogram (increase in gradient or reduced leaflet motion) or because of a clinical event (e.g. thromboembolic event, heart failure), further investigation by CT or trans-oesophageal echocardiogram should be performed to confirm the diagnosis, and alternative diagnoses such as endocarditis ruled out. Analogous to the ARC definition of stent thrombosis (1), valve thrombosis can be characterized according to the timing of the event (acute, subacute, late, or very late), presentation (clinical, subclinical), and certainty (definite, probable, or possible). The method of acute and chronic antithrombotic treatment should be specified (e.g. thrombolysis, intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin, antiplatelet agent, or oral anticoagulant). If oral anticoagulant therapy is instituted, the following information should be specified: (i) specific drug used; (ii) target international normalized ratio (INR); (iii) average achieved INR; (iv) method of anticoagulation control (e.g. physician or nurse directed, patient home self-management); (v) duration of treatment; and (vi) adherence to medication. If the patient has a clinical event related to valve thrombosis, the INR temporally associated with the event should be reported together with any anticoagulant or antiplatelet therapy. The response to antithrombotic therapy should be assessed at 3 months and classified as resolved, persistent or recurrent.

Assessment of aortic valve function and haemodynamics

Echocardiography is the recommended imaging modality for the assessment of native AS as well as prosthetic valve function (204–207). The suggested time points for routine follow-up TTE following AVR within a large comparative

randomized trial or new device approval study are: baseline, within 30 days, 1 year, and yearly thereafter. A 6-month echocardiogram is recommended for research and mechanistic studies, but will be difficult to obtain routinely and can be omitted for practical reasons.

Post-procedural valve assessment should include an evaluation of structure, function, and haemodynamics of both the prosthetic valve and ventricles. General recommendations for follow-up, outlined in prior prosthetic valve guidelines (204,207–210), imaging assessment recommendations (184,210,211) and reviews (212), include the acquisition of pertinent patient information such as valve type, valve size, and implantation date, and the importance of blood pressure recording, given its potential impact on multiple parameters. Comparison with baseline or follow-up studies is particularly useful in determining valvular dysfunction. Despite the recent developments in subclinical leaflet thrombosis, VARC-3 does not recommend routine follow-up with MDCT unless clinically indicated or required in the context of a clinical study.

Paravalvular regurgitation

Despite the recent description of several angiographic, haemodynamic catheter-based, CT-based, and MRI techniques to evaluate the severity and/or the repercussions of post-TAVR AR (213–220), Doppler echocardiography remains the primary modality for assessing and comparing regurgitation after AVR. The technical difficulties in evaluating prosthetic valve regurgitation by echocardiography are fully discussed in the American Society of Echocardiography (ASE) and European Association of Cardiovascular Imaging (EACVI) guidelines and other recent studies or reviews advocating for the use of specific parameters for assessment of post-TAVR and post-SAVR patients (184,204,210,211,221,222).

Grading scheme for paravalvular regurgitation post-AVR

Most recent guidelines have used a 3-class grading scheme (mild, moderate, severe) to report the severity of PVR (5,184,204,210), whereas angiographic grading and some echocardiographic grading schemes reported in the literature employ a 4-class grading scheme (Grade 1–4) (217). In the 4-class scheme, there is often ambiguity or even frank differences in Grades 2 and 3; the Grade 2 class may be considered mild or moderate and Grade 3 may be considered moderate or moderate-severe. In fact, a 5-class scheme is frequently used clinically. This divides mild PVR into two separate grades of mild and mild-to-moderate, and divides moderate PVR into two separate grades of moderate and moderate-to-severe (211). In this scheme, no PVR and trace PVR could be combined into grade 0. Indeed, no studies have shown that no or trace PVR has any impact on mortality (211,223,224). For research purposes, it is reasonable in some situations to capture trace PVR separately from no PVR; however, trace PVR should never be combined with mild PVR, as this may dilute the impact of mild PVR on mortality. The 5-class grading scheme (mild, mild-moderate, moderate, moderate-severe, severe) can be easily collapsed and reported as the 3-class scheme (mild, moderate, severe) recommended by the ASE and European Association of Cardiovascular Imaging (EACVI) guidelines (184,204,210,225). Although more grades would initially produce greater variability, using the 5-class scheme, which assigns 'in-between' grades into a predetermined category, has already been shown to reduce variability between echocardiography core laboratories (226). An analysis of inter-core laboratory variability within the Placement of Aortic Transcatheter Valve (PARTNER) II SAPIEN 3 registry, in which 3 core laboratories were used to assess PVR, has further supported this finding with an intra-class correlation coefficient of 0.8 using the 5-grade scheme and 1.0 once collapsed into the 3-grade scheme (211).

Table 16 summarizes the unifying grading scheme with a suggested categorization of each qualitative, semi-quantitative, and quantitative parameter (211,222,224). The proposed research-grading scheme attempts to synchronize multiple grading schemes with common clinical practice. Valve Academic Research Consortium 3 believes that the granular scheme provides a mechanism for systematic study of outcomes and a means for correlating outcomes with prior grading schemes.

Patient-reported outcomes

Quality-of-life evaluation in aortic stenosis

Ideally, patient-reported health status measures such as the Minnesota Living with Heart Failure Questionnaire (MLHFQ) and the Kansas City Cardiomyopathy Questionnaire (KCCQ) should be used to assess disease-specific health status and QOL in patients with AS (227–230). The KCCQ has been used in several clinical trials of patients undergoing TAVR and SAVR (231–235) and is collected as part of the Society of Thoracic Surgeons and American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) registry (236).

Recommended endpoints and timing of assessments

As previously described (5), a comprehensive QOL assessment that includes both disease-specific health status measures (such as the KCCQ or MLHFQ) and generic health status measures [such as the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) (237), the 12-Item Short-Form Health Survey (SF-12) (238), or the EuroQoL (EQ-5D) (239)] is recommended. However, for studies with limited resources or for clinical

TABLE 16 Criteria for prosthetic aortic valve regurgitation*

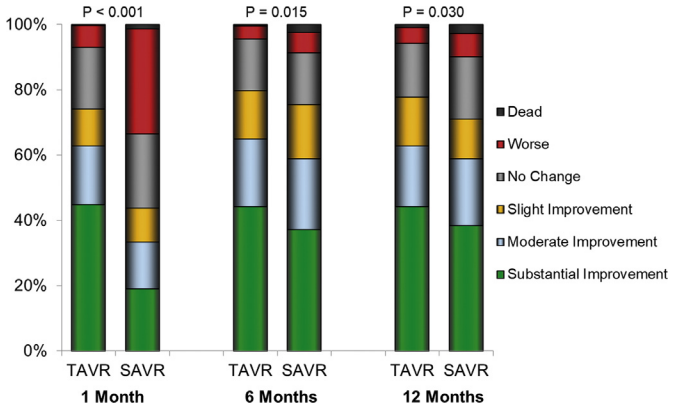
Three-class grading scheme	None/Trace	Mild		Moderate		Severe
Five-class grading scheme	**None/Trace**	**Mild**	**Mild-moderate**	**Moderate**	**Moderate-severe**	**Severe**
Doppler parameters (qualitative or semi-quantitative)						
Jet features†						
Extensive/wide jet origin	Absent	Absent	Absent	Present	Present	Present
Multiple jets	Possible	Possible	Often present	Often present	Usually present	Usually present
Jet path visible along the stent	Absent	Absent	Possible	Often present	Usually present	Present
Proximal flow convergence visible	Absent	Absent	Absent	Possible	Often present	Often present
E/A ratio‡	<1.0	<1.0	<1.0	≥1.5	≥1.5	≥1.5
Vena contracta width (mm)† (colour Doppler)	Not quantifiable	<2	2 to <4	4 to <5	5 to <6	≥6
Vena contracta area (mm^2)§ (3D colour Doppler)	Not quantifiable	<5	5 to <10	10 to <20	20 to <30	≥30
Jet width at its origin (%LVOT diameter)† (colour Doppler)	Narrow (<5)	Narrow (5 to <15)	Intermediate (15 to <30)	Intermediate (30 to <45)	Large (45 to <60)	Large (≥60)
Jet density (CW Doppler)	Incomplete or faint	Incomplete or faint	Variable	Dense	Dense	Dense
Jet deceleration rate (PHT, ms) ‡‖¶ (CW Doppler)	Slow (>500)	Slow (>500)	Variable (200 to <500)	Variable (200 to <500)	Variable (200 to <500)	Steep (<200)
Diastolic flow reversal in proximal descending aorta‖¶ (PW Doppler)	Absent	Absent or brief early diastolic	Intermediate	Intermediate	Holodiastolic (end-diastolic velocity 20 to <30 cm/s)	Holodiastolic (end-diastolic velocity ≥30 cm/s)
Circumferential extent of PVR (%) (colour Doppler)**	Not quantifiable	<5	5 to <10	10 to <20	20 to <30	≥30
Doppler parameters (quantitative)						
Regurgitant volume (mL/beat)††	<15	<15	15 to <30	30 to <45	45 to <60	≥60
Regurgitant orifice area (mm^2)††	<5	<5	5 to <10	10 to <20	20 to <30	≥30
Regurgitant fraction (%)††	<15	<15	15 to <30	30 to <40	40 to <50	≥50
CMR parameters						
Regurgitant fraction (%)††	<15	<15	15 to <30	30 to <40	40 to <50	≥50

*Adapted from Pibarot et al. (211), Ruiz et al. (222), and Zoghbi et al. (210).
†These parameters are generally assessed visually.
‡This parameter is highly influenced by both left atrial and left ventricular loading conditions and concomitant left ventricular diastolic dysfunction which is highly prevalent in this population. It may be useful to assess severity of PVR immediately after procedure by comparing with pre-procedure E/A ratio. For values between 1.0 and <1.5, the results are not interpretable.
§The vena contracta area is measured by planimetry of the vena contracta of the jet(s) on 2D or 3D colour Doppler images in the short-axis view.
‖Applies to chronic PVR but is less reliable for periprocedural or early post-procedural assessment.
¶These parameters are influenced by LV and aortic compliance. Hence, low transvalvular end-diastolic aorta to LV pressure gradient due to concomitant moderate/severe LV diastolic dysfunction may lead to false-positive results. The high dependency of aortic flow reversal on aortic compliance considerably limits the utility of this parameter in the elderly population. These parameters are also influenced by chronotropy.
**The circumferential extent of PVR is measured as the sum of the circumferential lengths of each regurgitant jet vena contracta (not including the non-regurgitant space between the separate jets) divided by the circumference of the outer edge of the transcatheter valve.
††The regurgitant fraction is calculated by dividing the regurgitant volume by the LV outflow tract stroke volume. The regurgitant volume is calculated as the difference of stroke volume measured in the LV outflow tract minus the stroke volume measured in the right ventricular outflow tract. The effective regurgitant orifice area is calculated by dividing the regurgitant volume by the time velocity integral of the AR flow by CW Doppler. The criteria for regurgitant volume and orifice area are derived from studies on chronic native AR and may not be suitable (i.e. too high) to the context or prosthetic aortic valve AR and more weight should be put on RF for quantitation of prosthetic valve AR.

CW = continuous wave; LVOT = left ventricular outflow tract; PHT = pressure half-time; PVR = paravalvular regurgitation; PW = pulsed wave.

practice, where brevity of survey tools is paramount, the KCCQ-12 may be useful. It is essential to ensure complete ascertainment of health status measures at each time point, as missing data cannot be retrieved retrospectively, and statistical adjustment techniques may not be adequate. Acknowledging the maturation of TAVR and considering the many different trial designs that are being considered depending on specific treatment goals, VARC-

FIGURE 2 **Ordinal Analysis of Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OS)**



Reprinted with permission from Baron *et al.* (243).

3 recommends that the selection of QOL measures and the timing of assessments should be customized to the particular trial design. For example, in a study involving the use of cerebral protection devices during TAVR, in addition to early and late assessments of disease-specific heath status measures (e.g. KCCQ), it may be appropriate to also collect early (<30 days) and late (through 5 years) neurocognitive testing assessments.

Interpretation and reporting of quality-of-life results

For the KCCQ Overall Summary (OS) Score, previous studies have demonstrated that a difference of 5 points corresponds with a small but clinically relevant difference, a 10-point difference represents a moderate difference, and a 20-point difference represents a large difference (240). For the SF-12 physical and mental summary scales, a difference of 2.5 points may be considered clinically relevant (241,242). However, no such reference standard is available for the EQ-5D, since its main role is to provide population-derived utility weights for the purposes of cost-effectiveness analysis. Of note, these differences apply to an individual patient; there are no similar standards for interpretation of mean differences between groups. To address this issue, investigators are encouraged to report the number (and percentage) of patients that reach the magnitude of these improvements either as categories or in the form of a cumulative response distribution curve.

An example of this distinction may be seen in the results of the QOL sub-study of the PARTNER 3 trial (243). In that study, TAVR demonstrated a small but statistically significant health status benefit over SAVR at 1-year follow-up with a mean between-group difference of 1.8 points on the KCCQ-OS score (95% CI 0.1-3.5). However, when the cumulative response to therapy was examined, there was a 5% greater likelihood of achieving a large (i.e. >20 point) improvement in the KCCQ-OS score in TAVR patients, demonstrating that this small between-group difference was clinically relevant at the individual patient level (**Figure 2**).

Differential mortality between two treatments may complicate the interpretation of QOL results, since QOL may appear to improve over time with less effective therapy owing to attrition of the sickest patients. As such, use of endpoints that integrate survival and QOL may provide more interpretable results. Definitions have been proposed to integrate these important outcomes—at least for patients at extreme, high, or intermediate risk of complications with SAVR (26,244,245) and have been adopted by VARC-3 (**Table 17**). Even more granular categorical analyses provide further perspectives on the effect of these interventions over time and are also recommended by VARC-3 (236). Ordinal categories based on previously established thresholds for clinically relevant changes in the KCCQ-OS scores have been defined as death, worsened (decrease from baseline >5 points), no change (change between −5 and <5 points), mildly improved (increase between 5 and <10 points), moderately improved (increase between 10 and <20 points), and substantially improved (increase ≥20 points). We believe that these integrated definitions better reflect the goals of treatment of patients since patients who have a reasonable QOL prior to treatment are most likely undergoing aortic valve replacement for its survival benefits; for such patients, a good outcome would be survival without worsening QOL. On the other hand, for patients who have a poor QOL, the main goal of aortic valve replacement is to improve QOL, and a good outcome would be survival with

TABLE 17 General outcome from a patient-reported perspective

Favourable outcome

At 1 year, a patient:
■ Is alive; and
  ■ Has a KCCQ Overall Summary score ≥60 (roughly equivalent to NYHA Class II or better)
  ■ Has not had a decline of >10 points in the KCCQ Overall Summary score from baseline

Acceptable outcome

At 1 year, a patient:
■ Is alive; andslr○
  ■ Has a KCCQ Overall Summary score ≥45 (roughly equivalent to NYHA Class III or better)
  ■ Has not had a decline of >10 points in the KCCQ Overall Summary score from baseline

Unfavourable outcome

At 1 year, a patient:
■ Is not alive; or
■ Is alive; and
  ■ Has a KCCQ Overall Summary score <45 (roughly equivalent to NYHA Class IV)
  ■ Has had a decline of >10 points in the KCCQ Overall Summary score from baseline

KCCQ = Kansas City Cardiomyopathy Questionnaire; NYHA = New York Heart Association.

TABLE 18 Composite endpoints

Technical success (at exit from procedure room) ■ Freedom from mortality ■ Successful access, delivery of the device, and retrieval of the delivery system ■ Correct positioning of a single prosthetic heart valve into the proper anatomical location ■ Freedom from surgery or intervention related to the device* or to a major vascular or access-related, or cardiac structural complication
Device success (at 30 days†) ■ Technical success ■ Freedom from mortality ■ Freedom from surgery or intervention related to the device* or to a major vascular or access-related or cardiac structural complication ■ Intended performance of the valve‡ (mean gradient <20 mmHg, peak velocity <3 m/s, Doppler velocity index ≥0.25, and less than moderate aortic regurgitation)
Early safety (at 30 days) ■ Freedom from all-cause mortality ■ Freedom from all stroke ■ Freedom from VARC type 2–4 bleeding (in trials where control group is surgery, it is appropriate to include only Type 3 and 4 bleeding) ■ Freedom from major vascular, access-related, or cardiac structural complication ■ Freedom from acute kidney injury stage 3 or 4 ■ Freedom from moderate or severe aortic regurgitation ■ Freedom from new permanent pacemaker due to procedure-related conduction abnormalities ■ Freedom from surgery or intervention related to the device
Clinical efficacy (at 1 year and thereafter) ■ Freedom from all-cause mortality ■ Freedom from all stroke ■ Freedom from hospitalization for procedure- or valve-related causes ■ Freedom from KCCQ Overall Summary Score <45 or decline from baseline of >10 point (i.e. Unfavourable Outcome)
Valve-related long-term clinical efficacy (at 5 years and thereafter) ■ Freedom from bioprosthetic Valve Failure (defined as: Valve-related mortality *OR* Aortic valve re-operation/re-intervention *OR* Stage 3 haemodynamic valve deterioration—See **Central Illustration**) ■ Freedom from stroke or peripheral embolism (presumably valve-related, after ruling out other non-valve aetiologies) ■ Freedom from VARC Type 2–4 bleeding secondary to or exacerbated by antiplatelet or anticoagulant agents, used specifically for valve-related concerns (e.g. clinically apparent leaflet thrombosis)

*Excluding permanent pacemaker. †In-hospital may be used if 30-day data are not available. ‡Haemodynamic valve performance standards may differ depending on the specific valve sizes implanted.

at least a reasonable QOL. These types of outcomes are particularly important to elderly patients who are considering TAVR, as survival alone is unlikely to fully encompass their goals of treatment. In cases where there is a survival difference between treatments, we recommend reporting both the composite categorical outcomes as well as QOL among survivors in order to provide the most complete description of the results.

Composite endpoints

Proposed VARC composite endpoints were originally organized as (i) device success, (ii) early patient safety, and (iii) clinical efficacy. As TAVR experience increased, time-related valve safety was added as a fourth endpoint in VARC-2. In the modern era, with considerably more TAVR experience, wherein younger and lower-risk patients will also be treated selectively with TAVR, VARC-3 recognizes the need to make adjustments in the required composite endpoints.

Similar to MVARC, an additional composite endpoint, technical success, has been introduced that captures the immediate success of a procedure, which is measured at the time of leaving the procedure room and encompasses the true technical safety of the device and its delivery (**Table 18**). Subsequently, the endpoint of device success addresses short-term procedure- or valve-related issues that occur after achieving technical success, and additionally includes the early performance of the valve. Of note, coronary obstruction requiring unplanned intervention should be captured in both these composite endpoints, while permanent pacemaker implantation or other conduction disturbances should not be considered in this endpoint.

The composite of early safety measured at 30 days (see VARC-2), as traditionally used in the surgical literature, relates to the invasiveness of the procedure and captures adverse events that significantly impact long-term prognosis. The need for a new permanent pacemaker has been added to the composite of early safety, acknowledging the growing evidence of its negative impact after aortic valve replacement (246-248). Recently, a negative long-term prognosis with a new LBBB after TAVR has been observed (118,132,133,248,249). At the present time, new LBBB was not included in the safety composite, but VARC-3

recognizes that this may become an important endpoint to consider in the future. As a result of the frequency and relative benign nature of VARC-3 type 2 bleeding in the setting of surgery and its significant impact on prognosis after TAVR, early safety should include VARC-3 type 3-4 bleeding in the setting of surgery but VARC-3 type 2-4 bleeding in the setting of TAVR.

The composite endpoint of clinical efficacy in VARC-2 included aggregated endpoints of dispar8ate importance, variable reliability, and endpoint type (time-to-event or longitudinal status data). Moreover, health-related QOL and hospitalization have emerged as important metrics to assess the value of an intervention. The VARC-3 updated composite endpoint of clinical efficacy therefore has a clearer focus on clinical endpoints, excluding echocardiographic results and subjective measures of functional status (NYHA classification).

Valve Academic Research Consortium 3 has also replaced the composite time-related valve safety endpoint with valve-related long-term clinical efficacy which more appropriately directs attention to the potential long-term clinical consequences and modes of failure of bioprosthetic heart valves. The new composite endpoint (**Table 18**) includes: (i) BVF, defined as valve-related mortality or aortic valve re-operation/re-intervention, or stage 3 haemodynamic valve deterioration (**Central Illustration**), (ii) stroke or peripheral embolism (presumably valve-related, after ruling out other non-valve aetiologies), and (iii) VARC-3 Type 2-4 bleeding secondary to or exacerbated by antiplatelet or anticoagulant agents used specifically for valve-related concerns (e.g. clinically apparent leaflet thrombosis). Importantly, this endpoint is recorded at 5 years and thereafter (annually through 10 years or longer) and is intended to compare treatment strategies with long-term surveillance of outcomes. This endpoint will help to differentiate iterative existing TAVR devices from new devices and will be particularly relevant as TAVR is expanded to younger patients who may over their lifetime require multiple valve interventions.

Valve Academic Research Consortium 3 criteria and aortic regurgitation-related research

Valve Academic Research Consortium originally was triggered by the emergence of a novel therapy and subsequent research related to the treatment of severe AS. Recently, early experiences for treatment of pure aortic regurgitation (AR) with dedicated transcatheter devices have been described (250–253), and larger feasibility and comparative studies are to be expected (e.g. NCT02732704). Valve Academic Research Consortium 3 criteria and definitions can appropriately be used during the conduct of research related to AR, whether surgical, transcatheter, or medical treatments are being studied.

Valve Academic Research Consortium 3 and the Covid-19 pandemic

Valve Academic Research Consortium 3 recommends rigorous endpoint definitions with precise timing and frequency of follow-up, attempting to achieve optimal capture, reporting, and dissemination of clinical research. Most of these endpoints imply either physical assessment of patients or the performance of testing involving patient contact. Recently, the Covid-19 pandemic resulted in major challenges to the conduct of clinical research, and has caused a re-evaluation of methods for data acquisition and greater flexibility in time windows for outcome assessments. Valve Academic Research Consortium 3 acknowledges these challenges and supports alternative and innovative ways to ensure appropriate follow-up and measurement of patient outcomes (e.g. telemedicine), without compromising the safety of patients and healthcare workers. Similarly, stringent follow-up schedules should be adapted to avoid unreasonable burdens to the clinical sites. Finally, since Covid-19 infections can have serious cardiovascular and other medical consequences, the competing risks of Covid-19-related clinical events must be recognized and considered as the causation of some clinical outcomes are adjudicated.

CONCLUSION

The striking evolution of TAVR over the past decade mandates an equally nimble and meticulous refinement in clinical research tools and reference materials. The VARC-3 update is concordant with the initial ARC initiative and the VARC mission to provide clinically meaningful and standardized definitions which would be useful across the spectrum of clinical research related to aortic valve disease therapy. Acknowledging the dynamic and evolving nature of these definitions, the adoption of these VARC updated endpoints and criteria will ensure homogenous reporting, adjudication, and comparison between devices and therapeutic strategies.

ACKNOWLEDGEMENTS The authors wish to thank the following individuals, who made significant contributions to the development of this document: Stuart J. Head, MD, PhD (Medtronic, Inc.), A. Pieter Kappetein, MD, PhD (Medtronic), Neil E. Moat, MD (Abbott), and Bahira Shahim, MD, PhD (Cardiovascular Research Foundation).

FUNDING SUPPORT AND AUTHOR DISCLOSURES

P.G. has received consultant fees from Abbott Vascular, Abiomed, Boston Scientific, Cardinal Health, Cardiovascular System Inc., Edwards Lifesciences, Medtronic, Opsens, Siemens, SoundBite Medical Solutions, Sig.Num, Saranas, Teleflex, Tryton Medical, and has equity in Pi-Cardia, Sig.Num, SoundBite Medical Solutions, Saranas, and Puzzle Medical. N.P. has received consultant fees from Medtronic, Peijia, and Microport. M.C.A.'s institution receives research funding from Edwards Lifesciences and Abbott. T.N. discloses consulting fees or honoraria from Edwards

LifeSciences, Medtronic, Boston Scientific, and Biotrace Medical and consulting fees and equity from Keystone Heart. R.T.H. reports speaker fees from Boston Scientific Corporation and Baylis Medical; consulting for Abbott Structural, Edwards Lifesciences, Medtronic, Navigate, Philips Healthcare and Siemens Healthcare; non-financial support from 3mensio; and is the Chief Scientific Officer for the Echocardiography Core Laboratory at the Cardiovascular Research Foundation for multiple industry-sponsored trials, for which she receives no direct industry compensation. P.P. received research grants from Edwards Lifesciences and Medtronic for echo corelab analyses in TAVR. J.B. reports personal fees from Abbott Vascular and Boehringer Ingelheim, and grants from Edwards, Boston Scientific, General Electric, Biotronik, and Medtronic, all outside the submitted work. J.L. reports personal fees from Circle CVI, GE Healthcare, Philips and HeartFlow, as well as grants to his institution for core lab work from Medtronic, Edwards, Abbott, and GE Healthcare. E.H.B. reports grants to his institution from Edwards Lifesciences. A.L. reports grants from Novartis and Edwards Lifesciences, personal fees from Medtronic, Abbott, Edwards, Boston Scientific, AstraZeneca, Novartis, Pfizer, Abiomed, Bayer, Boehringer, and stock options from Picardia, Transverse Medical, and Claret Medical. M.M. reports grants from Abbott, Medtronic, and Edwards. R.M. reports grants from Abbott and Edwards Lifesciences, and personal fees from Cordis and Medtronic. R.M. reports grants, personal fees, and other from Abbott Laboratories, grants from AstraZeneca, Bayer, and Beth Israel Deaconess, grants and other from Bristol-Myers Squibb, grants from CERC, Chiesi, Concept Medical, CSL Behring, DSI, Medtronic, Novartis Pharmaceuticals, and OrbusNeich, grants and other from Abiomed, other from the Medicines Company, personal fees from Boston Scientific, personal fees from Janssen Scientific Affairs, Medscape/WebMD, Roivant Services, Sanofi, Siemens Medical Solutions, and non-financial support and other from Idorsia Pharmaceuticals, non-financial support and other from Regeneron Pharmaceuticals, other from Spectranetics/Philips/Volcano Corp, personal fees from Medtelligence (Janssen Scientific Affairs), other from Watermark Research Partners, other from Claret Medical, other from Elixir Medical, personal fees from ACC, personal fees from AMA, grants from Applied Therapeutics, other from Merck, outside the submitted work. J.P.P. reports grants from Medtronic, grants and personal fees from Edwards, grants from Boston Scientific, grants from Abbott, outside the submitted work. M.R. reports consulting for Medtronic, with fees to his institution. J.R.-C. has received institutional research grants from Edwards Lifesciences, Medtronic and Boston Scientific. Nicolas Van Mieghem has received research grants from Abbott, Boston Scientific, Edwards, Medtronic and Essential Medical/Teleflex. He received advisory fees from Abbott, Boston Scientific, Ancora, Medtronic and Essential Medical/Teleflex. J.G.W. has received consulting fees from Edwards Lifesciences. D.J.C. reports institutional research grants and personal fees from Edwards Lifesciences, grants and personal fees from Medtronic, grants and personal fees from Boston Scientific, grants and personal fees from Abbott, outside the submitted work. M.B.L. reports institutional research grants from Edwards Lifesciences, Medtronic, Boston Scientific and Abbott, and advisory board/consulting fees from Medtronic, Boston Scientific, Abbott, Gore Medical and Meril Lifescience, all outside the submitted work.

REFERENCES

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

2. Krucoff MW, Mehran R, van Es GA, et al. The academic research consortium governance charter. J Am Coll Cardiol Intv. 2011;4:595–6.

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

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

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

6. Stone GW, Adams DH, Abraham WT, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. Eur Heart J. 2015;36:1878–91.

7. Taramasso M. Standardizing tricuspid assessment and outcomes: towards T-VARC. *Paper presented at: TVT 2017; June 14th 2017; Chicago, IL 199*. J Am Coll Cardiol. 2020;75:3003–15.

8. Genereux P, Head SJ, Van Mieghem NM, et al. Clinical outcomes after transcatheter aortic valve replacement using Valve Academic Research Consortium definitions: a weighted meta-analysis of 3,519 patients from 16 studies. J Am Coll Cardiol. 2012;59:2317–26.

9. Erlebach M, Head SJ, Mylotte D, et al. VARC endpoint definition compliance rates in contemporary transcatheter aortic valve implantation studies. EuroIntervention. 2016;12:375–80.

10. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet. 2016;387:2218–25.

11. Mack MJ, Leon MB, Thourani VH, et al. Transcatheter aortic-valve replacement with a balloon-expandable valve in low-risk patients. N Engl J Med. 2019;380:1695–705.

12. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2016;374:1609–20.

13. Popma JJ, Deeb GM, Yakubov SJ, et al., Evolut Low Risk Trial Investigators. Transcatheter aortic-valve replacement with a self-expanding valve in low-risk patients. N Engl J Med. 2019;380:1706–15.

14. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med. 2017;376:1321–31.

15. Head SJ, Mylotte D, Mack MJ, et al. Considerations and recommendations for the introduction of objective performance criteria for transcatheter aortic heart valve device approval. Circulation. 2016;133:2086–93.

16. Vemulapalli S, Carroll JD, Mack MJ, et al. Procedural volume and outcomes for transcatheter aortic-valve replacement. N Engl J Med. 2019;380:2541–50.

17. Svensson LG, Blackstone EH, Rajeswaran J, et al., PARTNER Trial Investigators. Comprehensive analysis of mortality among patients undergoing TAVR: results of the PARTNER trial. J Am Coll Cardiol. 2014;64:158–68.

18. Urena M, Webb JG, Eltchaninoff H, et al. Late cardiac death in patients undergoing transcatheter aortic valve replacement: incidence and predictors of advanced heart failure and sudden cardiac death. J Am Coll Cardiol. 2015;65:437–48.

19. Genereux P, Demers P, Poulin F. Same day discharge after transcatheter aortic valve replacement: are we there yet? Catheter Cardiovasc Interv. 2016;87:980–2.

20. Barbanti M, Capranzano P, Ohno Y, et al. Early discharge after transfemoral transcatheter aortic valve implantation. Heart. 2015;101:1485–90.

21. Noad RL, Johnston N, McKinley A, et al. A pathway to earlier discharge following TAVI: assessment of safety and resource utilization. Catheter Cardiovasc Interv. 2016;87:134–42.

22. Durand E, Eltchaninoff H, Canville A, et al. Feasibility and safety of early discharge after transfemoral transcatheter aortic valve implantation with the Edwards SAPIEN-XT prosthesis. Am J Cardiol. 2015;115:1116–22.

23. Kotronias RA, Teitelbaum M, Webb JG, et al. Early versus standard discharge after transcatheter aortic valve replacement: a systematic review and meta-analysis. J Am Coll Cardiol Intv. 2018;11:1759–71.

24. Wood DA, Lauck SB, Cairns JA, et al. The Vancouver 3M (multidisciplinary, multimodality, but minimalist) clinical pathway facilitates safe next-day discharge home at low-, medium-, and high-volume transfemoral transcatheter aortic valve replacement centers: the 3M TAVR study. J Am Coll Cardiol Intv. 2019;12:459–69.

25. Arnold SV, Reynolds MR, Lei Y, et al., Cohen DJPARTNER Investigators. Predictors of poor outcomes after transcatheter aortic valve replacement:

results from the PARTNER (Placement of Aortic Transcatheter Valve) trial. Circulation. 2014;129:2682–90.

26. Arnold SV, Spertus JA, Lei Y, et al. How to define a poor outcome after transcatheter aortic valve replacement: conceptual framework and empirical observations from the placement of aortic transcatheter valve (PARTNER) trial. Circ Cardiovasc Qual Outcomes. 2013;6:591–7.

27. Daneault B, Kirtane AJ, Kodali SK, et al. Stroke associated with surgical and transcatheter treatment of aortic stenosis: a comprehensive review. J Am Coll Cardiol. 2011;58:2143–50.

28. Binder RK, Rodes-Cabau J, Wood DA, et al. Transcatheter aortic valve replacement with the SAPIEN 3: a new balloon-expandable transcatheter heart valve. J Am Coll Cardiol Intv. 2013;6:293–300.

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

30. Bosmans J, Bleiziffer S, Gerckens U, et al., Linke AADVANCE Study Investigators. The incidence and predictors of early- and mid-term clinically relevant neurological events after transcatheter aortic valve replacement in real-world patients. J Am Coll Cardiol. 2015;66:209–17.

31. Herrmann HC, Thourani VH, Kodali SK, et al. One-year clinical outcomes with SAPIEN 3 transcatheter aortic valve replacement in high-risk and inoperable patients with severe aortic stenosis. Circulation. 2016;134:130–40.

32. Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. Eur Heart J. 2016;37:2252–62.

33. Kapadia SR, Kodali S, Makkar R, et al., SENTINEL Trial Investigators. Protection against cerebral embolism during transcatheter aortic valve replacement. J Am Coll Cardiol. 2017;69:367–77.

34. Lansky AJ, Schofer J, Tchetche D, et al. A prospective randomized evaluation of the TriGuard HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial. Eur Heart J. 2015;36:2070–8.

35. Rodes-Cabau J, Kahlert P, Neumann FJ, et al. Feasibility and exploratory efficacy evaluation of the Embrella Embolic Deflector system for the prevention of cerebral emboli in patients undergoing transcatheter aortic valve replacement: the PROTAVI-C pilot study. J Am Coll Cardiol Intv. 2014;7:1146–55.

36. Wendt D, Kleinbongard P, Knipp S, et al. Intraaortic protection from embolization in patients undergoing transaortic transcatheter aortic valve implantation. Ann Thorac Surg. 2015;100:686–91.

37. Messé SR, Acker MA, Kasner SE, et al. The Determining Neurologic Outcomes from Valve Operations (DeNOVO) Investigators. Stroke after aortic valve surgery: results from a prospective cohort. Circulation. 2014;129:2253–61.

38. Lansky AJ, Messe SR, Brickman AM, et al. Proposed standardized neurological endpoints for cardiovascular clinical trials: an Academic Research Consortium initiative. Eur Heart J. 2018;39:1687–97.

39. Sacco RL, Kasner SE, Broderick JP, et al. American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia, Council on Cardiovascular Radiology and Intervention, Council on Cardiovascular and Stroke Nursing, Council on Epidemiology and Prevention, Council on Peripheral Vascular Disease, Council on Nutrition, Physical Activity and Metabolism. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:2064–89.

40. Hicks KA, Mahaffey KW, Mehran R, et al. 2017 cardiovascular and stroke endpoint definitions for clinical trials. Circulation. 2018;137:961–72.

41. Brott T, Adams HP Jr., Olinger CP, et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke. 1989;20:864–70.

42. Broderick JP, Adeoye O, Elm J. Evolution of the modified rankin scale and its use in future stroke trials. Stroke. 2017;48:2007–12.

43. Wintermark M, Albers GW, Alexandrov AV, et al. Acute stroke imaging research roadmap. AJNR Am J Neuroradiol. 2008;39:e23.

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

45. Abdul-Jawad Altisent O, Ferreira-Gonzalez I, Marsal JR, et al. Neurological damage after transcatheter aortic valve implantation compared with surgical aortic valve replacement in intermediate risk patients. Clin Res Cardiol. 2016;105:508–17.

46. Knipp SC, Kahlert P, Jokisch D, et al. Cognitive function after transapical aortic valve implantation: a single-centre study with 3-month follow-up. Interact Cardiovasc Thorac Surg. 2013;16:116–22.

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

48. Rodés-Cabau J, Dumont E, Boone RH, et al. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. J Am Coll Cardiol. 2011;57:18–28.

49. Fanning JP, Wesley AJ, Platts DG, et al. The silent and apparent neurological injury in transcatheter aortic valve implantation study (SANITY): concept, design and rationale. BMC Cardiovasc Disord. 2014;14:45.

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

51. Arnold M, Schulz-Heise S, Achenbach S, et al. Embolic cerebral insults after transapical aortic valve implantation detected by magnetic resonance imaging. J Am Coll Cardiol Intv. 2010;3:1126–32.

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

53. Lazar RM, Pavol MA, Bormann T, et al. Neurocognition and cerebral lesion burden in high-risk patients before undergoing transcatheter aortic valve replacement: insights from the SENTINEL Trial. J Am Coll Cardiol Intv. 2018;11:384–92.

54. Breteler MM. Vascular risk factors for Alzheimer's disease: an epidemiologic perspective. Neurobiol Aging. 2000;21:153–60.

55. Lopez OL, Jagust WJ, Dulberg C, et al. Risk factors for mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 2. Arch Neurol. 2003;60:1394–9.

56. Vermeer SE, Prins ND, den Heijer T, et al. Silent brain infarcts and the risk of dementia and cognitive decline. N Engl J Med. 2003;348:1215–22.

57. Haglund M, Passant U, Sjobeck M, et al. Cerebral amyloid angiopathy and cortical microinfarcts as putative substrates of vascular dementia. Int J Geriatr Psychiatry. 2006;21:681–7.

58. Bernick C, Kuller L, Dulberg C, et al., Price TCardiovascular Health Study Collaborative Reseach Group. Silent MRI infarcts and the risk of future stroke: the cardiovascular health study. Neurology. 2001;57:1222–9.

59. Baumbach A, Mullen M, Brickman AM, et al. Safety and performance of a novel embolic deflection device in patients undergoing transcatheter aortic valve replacement: results from the DEFLECT I study. EuroIntervention. 2015;11:75–84.

60. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371:993–1004.

61. Pitt B, Pfeffer MA, Assmann SF, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370:1383–92.

62. Obadia JF, Messika-Zeitoun D, Leurent G, et al., Mewton NMITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med. 2018;379:2297–306.

63. Stone GW, Lindenfeld J, Abraham WT, et al., Mack MJCOAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med. 2018;379:2307–18.

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

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

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

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

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

69. Genereux P, Cohen DJ, Mack M, et al. Incidence, predictors, and prognostic impact of late bleeding complications after transcatheter aortic valve replacement. J Am Coll Cardiol. 2014;64:2605–15.

70. Pilgrim T, Stortecky S, Luterbacher F, et al. Transcatheter aortic valve implantation and bleeding: incidence, predictors and prognosis. J Thromb Thrombolysis. 2013;35:456–62.

71. Borz B, Durand E, Godin M, et al. Incidence, predictors and impact of bleeding after transcatheter aortic valve implantation using the balloon-expandable Edwards prosthesis. Heart. 2013;99:860–5.

72. Tchetche D, Van der Boon RM, Dumonteil N, et al. Adverse impact of bleeding and transfusion on the outcome post-transcatheter aortic valve implantation: insights from the Pooled-RotterdAm-Milano-Toulouse In Collaboration Plus (PRAGMATIC Plus) initiative. Am Heart J. 2012;164:402–9.

73. Piccolo R, Pilgrim T, Franzone A, et al. Frequency, timing, and impact of access-site and non-access-site bleeding on mortality among patients undergoing transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2017;10:1436–46.

74. Rodés-Cabau J, Masson J-B, Welsh RC, et al. Aspirin versus aspirin plus clopidogrel as antithrombotic treatment following transcatheter aortic valve replacement with a balloon-expandable valve: the ARTE (Aspirin Versus Aspirin + Clopidogrel Following Transcatheter Aortic Valve Implantation) randomized clinical trial. JACC Cardiovasc Interv. 2017;10:1357–65.

75. Abdul-Jawad Altisent O, Durand E, Muñoz-García AJ, et al. Warfarin and antiplatelet therapy versus warfarin alone for treating patients with atrial fibrillation undergoing transcatheter aortic valve replacement. JACC Cardiovasc Interv. 2016;9:1706–17.

76. Leon MB, Piazza N, Nikolsky E, et al. Standardized endpoint definitions for transcatheter aortic valve implantation clinical trials: a consensus report from the Valve Academic Research Consortium. Eur Heart J. 2011;32:205–17.

77. Stortecky S, Stefanini GG, Pilgrim T, et al. Validation of the Valve Academic Research Consortium bleeding definition in patients with severe aortic stenosis undergoing transcatheter aortic valve implantation. J Am Heart Assoc. 2015;4:e002135.

78. Nuis RJ, Rodes-Cabau J, Sinning JM, et al. Blood transfusion and the risk of acute kidney injury after transcatheter aortic valve implantation. Circ Cardiovasc Interv. 2012;5:680–8.

79. Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) TrialMismatchr transcatheter aortic valve implantationrtic stenosis undergoing transcatheter aortic valve implantationboration Plus (PRAGMATIC Plus) initiativeion PA, Metabolismrevention. J Am Coll Cardiol. 1988;11:1–11.

80. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med. 1993;329:673–82.

81. Yusuf S, Zhao F, Mehta SR, et al. Clopidogrel in unstable angina to prevent recurrent events trial I. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345:494–502.

82. Stone GW, McLaurin BT, Cox DA, et al., Ohman EMACUITY Investigators. Bivalirudin for patients with acute coronary syndromes. N Engl J Med. 2006;355:2203–16.

83. Stone GW, Witzenbichler B, Guagliumi G, et al., HORIZONS-AMI Trial Investigators. Bivalirudin during primary PCI in acute myocardial infarction. N Engl J Med. 2008;358:2218–30.

84. Ando T, Akintoye E, Telila T, et al. Trends in vascular complications in high-risk patients following transcatheter aortic valve replacement in the United States. Am J Cardiol. 2017;119:1433–7.

85. Thourani VH, Gunter RL, Neravetla S, et al. Use of transaortic, transapical, and transcarotid transcatheter aortic valve replacement in inoperable patients. Ann Thorac Surg. 2013;96:1349–57.

86. Guyton RA, Block PC, Thourani VH, et al. Carotid artery access for transcatheter aortic valve replacement. Catheter Cardiovasc Interv. 2013;82:E583–6.

87. Greenbaum AB, O'Neill WW, Paone G, et al. Caval-aortic access to allow transcatheter aortic valve replacement in otherwise ineligible patients: initial human experience. J Am Coll Cardiol. 2014;63 Pt A:2795–804.

88. Thourani VH, Jensen HA, Babaliaros V, et al. Transapical and transaortic transcatheter aortic valve replacement in the United States. Ann Thorac Surg. 2015;100:1718–26; discussion 1726–7.

89. Basir MB, Velez C, Fuller B, et al. Rates of vascular access use in transcatheter aortic valve replacement: a look into the next generation. Catheter Cardiovasc Interv. 2016;87:E166–71.

90. Thourani VH, Li C, Devireddy C, et al. High-risk patients with inoperative aortic stenosis: use of transapical, transaortic, and transcarotid techniques. Ann Thorac Surg. 2015;99:817–23; discussion 823–5.

91. Barbash IM, Barbanti M, Webb J, et al. Comparison of vascular closure devices for access site closure after transfemoral aortic valve implantation. Eur Heart J. 2015;36:3370–9.

92. Amat-Santos IJ, Rojas P, Gutierrez H, et al. Transubclavian approach: a competitive access for transcatheter aortic valve implantation as compared to transfemoral. Catheter Cardiovasc Interv. 2018;92:935–44.

93. Greenbaum AB, Babaliaros VC, Chen MY, et al. Transcaval access and closure for transcatheter aortic valve replacement: a prospective investigation. J Am Coll Cardiol. 2017;69:511–21.

94. Capretti G, Urena M, Himbert D, et al. Suprasternal brachiocephalic approach as an alternative route for transcatheter aortic valve implantation: a single-centre experience. EuroIntervention. 2017;12:e1849–56.

95. Philipsen TE, Collas VM, Rodrigus IE, et al. Brachiocephalic artery access in transcatheter aortic valve implantation: a valuable alternative: 3-year institutional experience. Interact Cardiovasc Thorac Surg. 2015;21:734–40.

96. Allende R, Urena M, Cordoba JG, et al. Impact of the use of transradial versus transfemoral approach as secondary access in transcatheter aortic valve implantation procedures. Am J Cardiol. 2014;114:1729–34.

97. Wood DA, Krajcer Z, Sathananthan J, et al., SAFE MANTA Study Investigators. Pivotal clinical study to evaluate the safety and effectiveness of the MANTA percutaneous vascular closure device. Circ Cardiovasc Interv. 2019;12:e007258.

98. Kambara AM, Bastos Metzger P, Ribamar Costa J Jr., et al. First-in-man assessment of the InSeal VCD, a novel closure device for large puncture accesses. EuroIntervention. 2015;10:1391–5.

99. Barbanti M, Yang TH, Rodes Cabau J, et al. Anatomical and procedural features associated with aortic root rupture during balloon-expandable transcatheter aortic valve replacement. Circulation. 2013;128:244–53.

100. Bax JJ, Delgado V, Bapat V, et al. Open issues in transcatheter aortic valve implantation. Part 2: procedural issues and outcomes after transcatheter aortic valve implantation. Eur Heart J. 2014;35:2639–54.

101. Girdauskas E, Owais T, Fey B, et al. Subannular perforation of left ventricular outflow tract associated with transcatheter valve implantation: pathophysiological background and clinical implications. Eur J Cardiothorac Surg. 2017;51:91–6.

102. Pasic M, Unbehaun A, Buz S, et al. Annular rupture during transcatheter aortic valve replacement: classification, pathophysiology, diagnostics, treatment approaches, and prevention. J Am Coll Cardiol Intv. 2015;8:1–9.

103. Dvir D, Leipsic J, Blanke P, et al. Coronary obstruction in transcatheter aortic valve-in-valve implantation: preprocedural evaluation, device selection, protection, and treatment. Circ Cardiovasc Interv. 2015;8:e002079.

104. Ribeiro HB, Nombela-Franco L, Urena M, et al. Coronary obstruction following transcatheter aortic valve implantation: a systematic review. J Am Coll Cardiol Intv. 2013;6:452–61.

105. Ribeiro HB, Rodes-Cabau J, Blanke P, et al. Incidence, predictors, and clinical outcomes of coronary obstruction following transcatheter aortic valve replacement for degenerative bioprosthetic surgical valves: insights from the VIVID registry. Eur Heart J. 2018;39:687–95.

106. Ribeiro HB, Webb JG, Makkar RR, et al. Predictive factors, management, and clinical outcomes of coronary obstruction following transcatheter aortic valve implantation: insights from a large multicenter registry. J Am Coll Cardiol. 2013;62:1552–62.

107. Jabbour RJ, Tanaka A, Finkelstein A, et al. Delayed coronary obstruction after transcatheter aortic valve replacement. J Am Coll Cardiol. 2018;71:1513–24.

108. Tang GHL, Zaid S, Ahmad H, et al. Transcatheter valve neo-commissural overlap with coronary orifices after transcatheter aortic valve replacement. Circ Cardiovasc Interv. 2018;11:e007263.

109. Harhash A, Ansari J, Mandel L, Kipperman R. STEMI after TAVR: procedural challenge and catastrophic outcome. J Am Coll Cardiol Intv. 2016;9:1412–3.

110. Htun WW, Grines C, Schreiber T. Feasibility of coronary angiography and percutaneous coronary intervention after transcatheter aortic valve replacement using a Medtronic self-expandable bioprosthetic valve. Catheter Cardiovasc Interv. 2018;91:1339–44.

111. Yudi MB, Sharma SK, Tang GHL, Kini A. Coronary angiography and percutaneous coronary intervention after transcatheter aortic valve replacement. J Am Coll Cardiol. 2018;71:1360–78.

112. Makkar RR, Jilaihawi H, Chakravarty T, et al. Determinants and outcomes of acute transcatheter valve-in-valve therapy or embolization: a study of multiple

valve implants in the U.S. PARTNER trial (Placement of AoRTic TraNscathetER Valve Trial Edwards SAPIEN Transcatheter Heart Valve). J Am Coll Cardiol. 2013;62:418–30.

113. Walther T, Hamm CW, Schuler G, et al. Perioperative results and complications in 15,964 transcatheter aortic valve replacements: prospective data from the GARY Registry. J Am Coll Cardiol. 2015;65:2173–80.

114. Goldfarb M, Drudi L, Almohammadi M, et al. Outcome reporting in cardiac surgery trials: systematic review and critical appraisal. J Am Heart Assoc. 2015;4:e002204.

115. Biviano AB, Nazif T, Dizon J, et al. Atrial fibrillation is associated with increased mortality in patients undergoing transcatheter aortic valve replacement: insights from the Placement of Aortic Transcatheter Valve (PARTNER) trial. Circ Cardiovasc Interv. 2016;9:e002766.

116. Dizon JM, Nazif TM, Hess PL, et al., PARTNER Publications Office. Chronic pacing and adverse outcomes after transcatheter aortic valve implantation. Heart. 2015;101:1665–71.

117. Nazif TM, Dizon JM, Hahn RT, et al., Kodali SKPARTNER Publications Office. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (Placement of AoRtic TraNscathetER Valves) trial and registry. J Am Coll Cardiol Intv. 2015;8 Pt A:60–9.

118. Nazif TM, Williams MR, Hahn RT, et al. Clinical implications of new-onset left bundle branch block after transcatheter aortic valve replacement: analysis of the PARTNER experience. Eur Heart J. 2014;35:1599–607.

119. Urena M, Webb JG, Cheema A, et al. Impact of new-onset persistent left bundle branch block on late clinical outcomes in patients undergoing transcatheter aortic valve implantation with a balloon-expandable valve. J Am Coll Cardiol Intv. 2014;7:128–36.

120. Mok M, Urena M, Nombela-Franco L, et al. Clinical and prognostic implications of existing and new-onset atrial fibrillation in patients undergoing transcatheter aortic valve implantation. J Thromb Thrombolysis. 2013;35:450–5.

121. Urena M, Mok M, Serra V, et al. Predictive factors and long-term clinical consequences of persistent left bundle branch block following transcatheter aortic valve implantation with a balloon-expandable valve. J Am Coll Cardiol. 2012;60:1743–52.

122. Amat-Santos IJ, Rodes-Cabau J, Urena M, et al. Incidence, predictive factors, and prognostic value of new-onset atrial fibrillation following transcatheter aortic valve implantation. J Am Coll Cardiol. 2012;59:178–88.

123. Bagur R, Rodes-Cabau J, Gurvitch R, et al. Need for permanent pacemaker as a complication of transcatheter aortic valve implantation and surgical aortic valve replacement in elderly patients with severe aortic stenosis and similar baseline electrocardiographic findings. J Am Coll Cardiol Intv. 2012;5:540–51.

124. Urena M, Hayek S, Cheema AN, et al. Arrhythmia burden in elderly patients with severe aortic stenosis as determined by continuous electrocardiographic recording: toward a better understanding of arrhythmic events after transcatheter aortic valve replacement. Circulation. 2015;131:469–77.

125. Buellesfeld L, Stortecky S, Heg D, et al. Impact of permanent pacemaker implantation on clinical outcome among patients undergoing transcatheter aortic valve implantation. J Am Coll Cardiol. 2012;60:493–501.

126. Roten L, Stortecky S, Scarcia F, et al. Atrioventricular conduction after transcatheter aortic valve implantation and surgical aortic valve replacement. J Cardiovasc Electrophysiol. 2012;23:1115–22.

127. Siontis GC, Juni P, Pilgrim T, et al. Predictors of permanent pacemaker implantation in patients with severe aortic stenosis undergoing TAVR: a meta-analysis. J Am Coll Cardiol. 2014;64:129–40.

128. Houthuizen P, van der Boon RMA, Urena M, et al. Occurrence, fate and consequences of ventricular conduction abnormalities after transcatheter aortic valve implantation. EuroIntervention. 2014;9:1142–50.

129. Houthuizen P, Van Garsse LA, Poels TT, et al. Left bundle-branch block induced by transcatheter aortic valve implantation increases risk of death. Circulation. 2012;126:720–8.

130. Prihadi EA, Leung M, Vollema EM, et al. Prevalence and prognostic relevance of ventricular conduction disturbances in patients with aortic stenosis. Am J Cardiol. 2017;120:2226–32.

131. Schymik G, Tzamalis P, Bramlage P, et al. Clinical impact of a new left bundle branch block following TAVI implantation: 1-year results of the TAVIK cohort. Clin Res Cardiol. 2015;104:351–62.

132. Regueiro A, Abdul-Jawad Altisent O, Del Trigo M, et al. Impact of new-onset left bundle branch block and periprocedural permanent pacemaker implantation on clinical outcomes in patients undergoing transcatheter aortic valve replacement: a systematic review and meta-analysis. Circ Cardiovasc Interv. 2016;9:e003635.

133. Faroux L, Chen S, Muntane-Carol G, et al. Clinical impact of conduction disturbances in transcatheter aortic valve replacement recipients: a systematic review and meta-analysis. Eur Heart J. 2020;41:2771–81.

134. van Rosendael PJ, Delgado V, Bax JJ. Pacemaker implantation rate after transcatheter aortic valve implantation with early and new-generation devices: a systematic review. Eur Heart J. 2018;39:2003–13.

135. Rodes-Cabau J, Ellenbogen KA, Krahn AD, et al. Management of conduction disturbances associated with transcatheter aortic valve replacement: JACC Scientific Expert Panel. J Am Coll Cardiol. 2019;74:1086–106.

136. January CT, Wann LS, Alpert JS, et al., American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2014;64:e1–76.

137. Testa L, Latib A, De Marco F, et al. Clinical impact of persistent left bundle-branch block after transcatheter aortic valve implantation with CoreValve Revalving System. Circulation. 2013;127:1300–7.

138. Surawicz B, Childers R, Deal BJ, et alAmerican Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology, American College of Cardiology Foundation, Heart Rhythm Society. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009;53:976–81.

139. Walther T, Manoharan G, Linke A, et al. Incidence of new-onset left bundle branch block and predictors of new permanent pacemaker following transcatheter aortic valve replacement with the Portico™ valve. Eur J Cardiothorac Surg. 2018;54:467–74.

140. Tracy CM, Epstein AE, Darbar D, et al. ACCF/AHA/HRS focused update incorporated into the ACCF/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2013;61:e6–75.

141. January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol. 2019;74:104–32.

142. Chamandi C, Regueiro A, Auffret V, et al. Reported versus "real" incidence of new pacemaker implantation post-transcatheter aortic valve replacement. J Am Coll Cardiol. 2016;68:2387–9.

143. Bagur R, Webb JG, Nietlispach F, et al. Acute kidney injury following transcatheter aortic valve implantation: predictive factors, prognostic value, and comparison with surgical aortic valve replacement. Eur Heart J. 2010;31:865–74.

144. Genereux P, Kodali SK, Green P, et al. Incidence and effect of acute kidney injury after transcatheter aortic valve replacement using the new Valve Academic Research Consortium criteria. Am J Cardiol. 2013;111:100–5.

145. Gargiulo G, Sannino A, Capodanno D, et al. Impact of postoperative acute kidney injury on clinical outcomes after transcatheter aortic valve implantation: a meta-analysis of 5,971 patients. Catheter Cardiovasc Interv. 2015;86:518–27.

146. Thongprayoon C, Cheungpasitporn W, Srivali N, et al. AKI after transcatheter or surgical aortic valve replacement. J Am Soc Nephrol. 2016;27:1854–60.

147. Ferro CJ, Law JP, Doshi SN, et al. Dialysis following transcatheter aortic valve replacement: risk factors and outcomes: an analysis from the UK TAVI (Transcatheter Aortic Valve Implantation) registry. J Am Coll Cardiol Intv. 2017;10:2040–7.

148. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGo clinical practice guideline for acute kidney injury. Kidney Int Suppl. 2012;2:1–138.

149. Shacham Y, Rofe M, Leshem-Rubinow E, et al. Usefulness of urine output criteria for early detection of acute kidney injury after transcatheter aortic valve implantation. Cardiorenal Med. 2014;4:155–60.

150. Koifman E, Segev A, Fefer P, et al. Comparison of acute kidney injury classifications in patients undergoing transcatheter aortic valve implantation:

predictors and long-term outcomes. Catheter Cardiovasc Interv. 2016;87:523–31.

151. Arbel Y, Ben-Assa E, Halkin A, et al. Forced diuresis with matched hydration in reducing acute kidney injury during transcatheter aortic valve implantation (Reduce-AKI): study protocol for a randomized sham-controlled trial. Trials. 2014;15:262.

152. Rodes-Cabau J, Gutierrez M, Bagur R, et al. Incidence, predictive factors, and prognostic value of myocardial injury following uncomplicated transcatheter aortic valve implantation. J Am Coll Cardiol. 2011;57:1988–99.

153. Paradis JM, Maniar HS, Lasala JM, et al. Clinical and functional outcomes associated with myocardial injury after transfemoral and transapical transcatheter aortic valve replacement: a subanalysis from the PARTNER Trial (Placement of Aortic Transcatheter Valves). J Am Coll Cardiol Intv. 2015;8:1468–79.

154. Ribeiro HB, Dahou A, Urena M, et al. Myocardial injury after transaortic versus transapical transcatheter aortic valve replacement. Ann Thorac Surg. 2015;99:2001–9.

155. Ribeiro HB, Larose É, de la Paz Ricapito M, et al. Myocardial injury following transcatheter aortic valve implantation: insights from delayed-enhancement cardiovascular magnetic resonance. EuroIntervention. 2015;11:205–13.

156. Ribeiro HB, Nombela-Franco L, Muñoz-García AJ, et al. Predictors and impact of myocardial injury after transcatheter aortic valve replacement: a multicenter registry. J Am Coll Cardiol. 2015;66:2075–88.

157. Koskinas KC, Stortecky S, Franzone A, et al. Postprocedural troponin elevation and clinical outcomes following transcatheter aortic valve implantation. J Am Heart Assoc. 2016;5:e002430.

158. Kim W-K, Rolf A, Liebetrau C, et al. Detection of myocardial injury by CMR after transcatheter aortic valve replacement. J Am Coll Cardiol. 2014;64:349–57.

159. Paradis JM, Fried J, Nazif T, et al. Aortic stenosis and coronary artery disease: what do we know? What don't we know? A comprehensive review of the literature with proposed treatment algorithms. Eur Heart J. 2014;35:2069–82.

160. Sankaramangalam K, Banerjee K, Kandregula K, et al. Impact of coronary artery disease on 30-day and 1-year mortality in patients undergoing transcatheter aortic valve replacement: a meta-analysis. J Am Heart Assoc. 2017;6:e006092.

161. Faroux L, Guimaraes L, Wintzer-Wehekind J, et al. Coronary artery disease and transcatheter aortic valve replacement: JACC state-of-the-art review. J Am Coll Cardiol. 2019;74:362–72.

162. Paradis JM, White JM, Genereux P, et al. Impact of coronary artery disease severity assessed with the syntax score on outcomes following transcatheter aortic valve replacement. J Am Heart Assoc. 2017;6:e005070.

163. Ramee S, Anwaruddin S, Kumar G, et al. The rationale for performance of coronary angiography and stenting before transcatheter aortic valve replacement: from the interventional section leadership council of the American College of Cardiology. J Am Coll Cardiol Intv. 2016;9:2371–5.

164. Kotronias RA, Kwok CS, George S, et al. Transcatheter aortic valve implantation with or without percutaneous coronary artery revascularization strategy: a systematic review and meta-analysis. J Am Heart Assoc. 2017;6:e005960.

165. Vilalta V, Asmarats L, Ferreira-Neto AN, et al. Incidence, clinical characteristics, and impact of acute coronary syndrome following transcatheter aortic valve replacement. J Am Coll Cardiol Intv. 2018;11:2523–33.

166. Thygesen K, Alpert JS, Jaffe AS, et al. ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019;40:237–69.

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

168. Garcia-Garcia HM, McFadden EP, Farb A, et al., Academic Research Consortium. Standardized end point definitions for coronary intervention trials: the Academic Research Consortium-2 consensus document. Eur Heart J. 2018;39:2192–207.

169. Thygesen K, Alpert JS, Jaffe AS, et al. Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the University Definition of Myocardial Infarction. Fourth Universal Definition of Myocardial Infarction (2018). J Am Coll Cardiol. 2018;72:2231–64.

170. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Rev Esp Cardiol (Engl Ed). 2018;71:1–62.

171. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;70:252–89.

172. Hammermeister K, Sethi GK, Henderson WG, et al. Outcomes 15 years after valve replacement with a mechanical versus a bioprosthetic valve: final report of the Veterans Affairs randomized trial. J Am Coll Cardiol. 2000;36:1152–8.

173. Oxenham H, Bloomfield P, Wheatley DJ, et al. Twenty year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses. Heart. 2003;89:715–21.

174. Head SJ, Celik M, Kappetein AP. Mechanical versus bioprosthetic aortic valve replacement. Eur Heart J. 2017;38:2183–91.

175. Puskas J, Gerdisch M, Nichols D, et al. Reduced anticoagulation after mechanical aortic valve replacement: interim results from the prospective randomized on-X valve anticoagulation clinical trial randomized Food and Drug Administration investigational device exemption trial. J Thorac Cardiovasc Surg. 2014;147:1202–10; discussion 1210–1.

176. Puskas JD, Gerdisch M, Nichols D, et al. Anticoagulation and antiplatelet strategies after on-X mechanical aortic valve replacement. J Am Coll Cardiol. 2018;71:2717–26.

177. Rotman OM, Kovarovic B, Chiu WC, et al. Novel polymeric valve for transcatheter aortic valve replacement applications: in vitro hemodynamic study. Ann Biomed Eng. 2019;47:113–25.

178. El-Hamamsy I, Eryigit Z, Stevens LM, et al. Long-term outcomes after autograft versus homograft aortic root replacement in adults with aortic valve disease: a randomised controlled trial. Lancet. 2010;376:524–31.

179. Mazine A, Rocha RV, El-Hamamsy I, et al. Ross procedure vs mechanical aortic valve replacement in adults: a systematic review and meta-analysis. JAMA Cardiol. 2018;3:978–87.

180. Capodanno D, Petronio AS, Prendergast B, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2017;38:3382–90.

181. Mylotte D, Andalib A, Theriault-Lauzier P, et al. Transcatheter heart valve failure: a systematic review. Eur Heart J. 2015;36:1306–27.

182. Del Trigo M, Muñoz-Garcia AJ, Wijeysundera HC, et al. Incidence, timing, and predictors of valve hemodynamic deterioration after transcatheter aortic valve replacement: multicenter registry. J Am Coll Cardiol. 2016;67:644–55.

183. Ruel M, Kulik A, Rubens FD, et al. Late incidence and determinants of reoperation in patients with prosthetic heart valves. Eur J Cardiothorac Surg. 2004;25:364–70.

184. Lancellotti P, Pibarot P, Chambers J, et al. Recommendations for the imaging assessment of prosthetic heart valves: a report from the European Association of Cardiovascular Imaging endorsed by the Chinese Society of Echocardiography, the Inter-American Society of Echocardiography, and the Brazilian Department of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2016;17:589–90.

185. Dvir D, Bourguignon T, Otto CM, et al., VIVID (Valve in Valve International Data) Investigators. Standardized definition of structural valve degeneration for surgical and transcatheter bioprosthetic aortic valves. Circulation. 2018;137:388–99.

186. Pepe MS, Mori M. Kaplan-Meier, marginal or conditional probability curves in summarizing competing risks failure time data? Stat Med. 1993;12:737–51.

187. Rajeswaran J, Blackstone EH. Competing risks: competing questions. J Thorac Cardiovasc Surg. 2017;153:1432–3.

188. He X, Chen X, Lei L, et al. A Simple method for estimating confidence intervals for exposure adjusted incidence rate and its applications to clinical trials. J Biom Biostat. 2015;6:238.

189. Chakravarty T, Søndergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet. 2017;389:2383–92.

190. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med. 2015;373:2015–24.

191. Blanke P, Leipsic JA, Popma JJ, et al. Leaflet thickening or immobility following aortic valve replacement: results from the evolut low risk substudy. J Am Coll Cardiol. 2020;75:2430–42.

192. De Backer O, Dangas GD, Jilaihawi H, et al. Reduced leaflet motion after transcatheter aortic-valve replacement. N Engl J Med. 2020;382:130–9.

193. Blanke P, Weir-McCall JR, Achenbach S, et al. Computed tomography imaging in the context of transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR): an expert consensus document of the Society of Cardiovascular Computed Tomography. J Am Coll Cardiol Img. 2019;12:1–24.

194. Hansson NC, Grove EL, Andersen HR, et al. Transcatheter aortic valve thrombosis: incidence, predisposing factors, and clinical implications. J Am Coll Cardiol. 2016;68:2059–69.

195. Pache G, Schoechlin S, Blanke P, et al. Early hypoattenuated leaflet thickening in balloon-expandable transcatheter aortic heart valves. Eur Heart J. 2016;37:2263–71.

196. Yanagisawa R, Hayashida K, Yamada Y, et al. Incidence, predictors, and mid-term outcomes of possible leaflet thrombosis after TAVR. J Am Coll Cardiol Img. 2016;10:1–11.

197. Sondergaard L, De Backer O, Kofoed KF, et al. Natural history of subclinical leaflet thrombosis affecting motion in bioprosthetic aortic valves. Eur Heart J. 2017;38:2201–7.

198. Makkar R. PARTNER 3 low-risk computed tomography substudy: subclinical leaflet thrombosis in transcatheter and surgical bioprosthetic valves, TCT. San Francisco, CA; 2019.

199. Dangas GD, Tijssen JGP, Wohrle J, et al. A controlled trial of rivaroxaban after transcatheter aortic-valve replacement. N Engl J Med. 2020;382:120–9.

200. Latib A, Naganuma T, Abdel-Wahab M, et al. Treatment and clinical outcomes of transcatheter heart valve thrombosis. Circ Cardiovasc Interv. 2015;8:e001779.

201. Mangieri A, Montalto C, Poletti E, et al. Thrombotic versus bleeding risk after transcatheter aortic valve replacement: JACC review topic of the week. J Am Coll Cardiol. 2019;74:2088–101.

202. De Marchena E, Mesa J, Pomenti S, et al. Thrombus formation following transcatheter aortic valve replacement. J Am Coll Cardiol Intv. 2015;8:728–39.

203. Abdel-Wahab M, Simonato M, Latib A, et al. Clinical valve thrombosis after transcatheter aortic valve-in-valve implantation. Circ Cardiovasc Interv. 2018;11:e006730.

204. Zoghbi WA, Chambers JB, Dumesnil JG, et al. Recommendations for evaluation of prosthetic valves with echocardiography and doppler ultrasound: a report From the American Society of Echocardiography's Guidelines and Standards Committee and the Task Force on Prosthetic Valves, developed in conjunction with the American College of Cardiology Cardiovascular Imaging Committee, Cardiac Imaging Committee of the American Heart Association, the European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography and the Canadian Society of Echocardiography, endorsed by the American College of Cardiology Foundation, American Heart Association, European Association of Echocardiography, a registered branch of the European Society of Cardiology, the Japanese Society of Echocardiography, and Canadian Society of Echocardiography. J Am Soc Echocardiogr. 2009;22:975–1014. quiz 1082–4.

205. Baumgartner H, Hung J, Bermejo J, et al. Echocardiographic assessment of valve stenosis: EAE/ASE recommendations for clinical practice. J Am Soc Echocardiogr. 2009;22:1–23. quiz 101–2.

206. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63:2438–88.

207. Hahn RT, Leipsic J, Douglas PS, et al. Comprehensive echocardiographic assessment of normal transcatheter valve function. J Am Coll Cardiol Img. 2019;12:25–34.

208. Bonow RO, Carabello BA, Chatterjee K, et al. 2006 Writing Committee Members; American College of Cardiology/American Heart Association Task Force. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease): endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Am Coll Cardiol. 2008;52:e1–142.

209. Vahanian A, Alfieri O, Andreotti F, et al., Authors/Task Force Members. Guidelines on the management of valvular heart disease (version 2012). The joint task force on the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur J Cardiothorac Surg. 2012;42:S1–44.

210. Zoghbi WA, Asch FM, Bruce C, et al. Guidelines for the evaluation of valvular regurgitation after percutaneous valve repair or replacement: a report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Angiography and Interventions, Japanese Society of Echocardiography, and Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr. 2019;32:431–75.

211. Pibarot P, Hahn RT, Weissman NJ, Monaghan MJ. Assessment of paravalvular regurgitation following TAVR: a proposal of unifying grading scheme. J Am Coll Cardiol Img. 2015;8:340–60.

212. Pibarot P, Dumesnil JG. Prosthetic heart valves: selection of the optimal prosthesis and long-term management. Circulation. 2009;119:1034–48.

213. Michel PL, Vahanian A, Besnainou F, Acar J. Value of qualitative angiographic grading in aortic regurgitation. Eur Heart J. 1987;8:11–4.

214. Schultz CJ, Slots TL, Yong G, et al. An objective and reproducible method for quantification of aortic regurgitation after TAVI. EuroIntervention. 2014;10:355–63.

215. Wood DA, Tops LF, Mayo JR, et al. Role of multislice computed tomography in transcatheter aortic valve replacement. Am J Cardiol. 2009;103:1295–301.

216. Leipsic J, Gurvitch R, LaBounty TM, et al. Multidetector computed tomography in transcatheter aortic valve implantation. J Am Coll Cardiol Img. 2011;4:416–29.

217. Sellers RD, Levy MJ, Amplatz K, Lillehei CW. Left retrograde cardioangiography in acquired cardiac disease: technic, indications and interpretations in 700 cases. Am J Cardiol. 1964;14:437–47.

218. Croft CH, Lipscomb K, Mathis K, et al. Limitations of qualitative angiographic grading in aortic or mitral regurgitation. Am J Cardiol. 1984;53:1593–8.

219. Ribeiro HB, Orwat S, Hayek SS, et al. Cardiovascular magnetic resonance to evaluate aortic regurgitation after transcatheter aortic valve replacement. J Am Coll Cardiol. 2016;68:577–85.

220. Ferreira-Neto AN, Merten C, Beurich H-W, et al. Effect of aortic regurgitation by cardiovascular magnetic resonance after transcatheter aortic valve implantation. Am J Cardiol. 2019;124:78–84.

221. Mihara H, Shibayama K, Jilaihawi H, et al. Assessment of post-procedural aortic regurgitation after TAVR: an intraprocedural TEE study. J Am Coll Cardiol Img. 2015;8:993–1003.

222. Ruiz CE, Hahn RT, Berrebi A, et al. Clinical trial principles and endpoint definitions for paravalvular leaks in surgical prosthesis: an expert statement. J Am Coll Cardiol. 2017;69:2067–87.

223. Athappan G, Patvardhan E, Tuzcu EM, et al. Incidence, predictors, and outcomes of aortic regurgitation after transcatheter aortic valve replacement: meta-analysis and systematic review of literature. J Am Coll Cardiol. 2013;61:1585–95.

224. Pibarot P, Hahn RT, Weissman NJ, et al. Association of paravalvular regurgitation with 1-year outcomes after transcatheter aortic valve replacement with the SAPIEN 3 valve. JAMA Cardiol. 2017;2:1208–16.

225. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Roelandt JRTC, on behalf of the European Association of Echocardiography. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease). Eur J Echocardiogr. 2010;11:223–44.

226. Hahn RT, Pibarot P, Weissman NJ, et al. Assessment of paravalvular aortic regurgitation after transcatheter aortic valve replacement: intra-core laboratory variability. J Am Soc Echocardiogr. 2015;28:415–22.

227. Arnold SV, Spertus JA, Lei Y, et al. Use of the Kansas City Cardiomyopathy Questionnaire for monitoring health status in patients with aortic stenosis. Circ Heart Fail. 2013;6:61–7.

228. Supino PG, Borer JS, Franciosa JA, et al. Acceptability and psychometric properties of the Minnesota Living With Heart Failure Questionnaire among patients undergoing heart valve surgery: validation and comparison with SF-36. J Card Fail. 2009;15:267–77.

229. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. Am Heart J. 1992;124:1017–25.

230. Green CP, Porter CB, Bresnahan DR, Spertus JA. Development and evaluation of the Kansas City

Cardiomyopathy Questionnaire: a new health status measure for heart failure. J Am Coll Cardiol Intv. 2000; 35:1245–55.

231. Arnold SV, Reynolds MR, Wang K, et al. Health status after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis at increased surgical risk: results from the CoreValve US Pivotal Trial. J Am Coll Cardiol Intv. 2015;8:1207–17.

232. Baron SJ, Arnold SV, Reynolds MR, et al. Durability of quality of life benefits of transcatheter aortic valve replacement: long-term results from the CoreValve US extreme risk trial. Am Heart J. 2017;194:39–48.

233. Baron SJ, Arnold SV, Wang K, et al., for the PARTNER 2 Investigators. Health status benefits of transcatheter vs surgical aortic valve replacement in patients with severe aortic stenosis at intermediate surgical risk: results from the PARTNER 2 randomized clinical trial. JAMA Cardiol. 2017;2:837–45.

234. Reynolds MR, Magnuson EA, Wang K, et al. Cost-effectiveness of transcatheter aortic valve replacement compared with standard care among inoperable patients with severe aortic stenosis: results from the placement of aortic transcatheter valves (PARTNER) trial (Cohort B). Circulation. 2012; 125:1102–9.

235. Reynolds MR, Magnuson EA, Wang K, et al. Health-related quality of life after transcatheter or surgical aortic valve replacement in high-risk patients with severe aortic stenosis: results from the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A). J Am Coll Cardiol. 2012;60:548–58.

236. Arnold SV, Spertus JA, Vemulapalli S, et al. Quality-of-life outcomes after transcatheter aortic valve replacement in an unselected population: a report from the STS/ACC transcatheter valve therapy registry. JAMA Cardiol. 2017;2:409–16.

237. Ware JE Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care. 1992;30:473–83.

238. Ware J Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. 1996;34:220–33.

239. Shaw JW, Johnson JA, Coons SJ. US valuation of the EQ-5D health states: development and testing of the D1 valuation model. Med Care. 2005;43:203–20.

240. Spertus J, Peterson E, Conard MW, et al., Cardiovascular Outcomes Research Consortium. Monitoring clinical changes in patients with heart failure: a comparison of methods. Am Heart J. 2005;150: 707–15.

241. Wyrwich KW, Spertus JA, Kroenke K, et al. Heart Disease Expert Panel. Clinically important differences in health status for patients with heart disease: an expert consensus panel report. Am Heart J. 2004;147: 615–22.

242. Ware JE, Kosinski M, Bjorner JB, et al. UserishManual for the SF-36v2 Health Survey. 2nd ed. Lincoln, RI: QualityMetric Incorporated, 2007.

243. Baron SJ, Magnuson EA, Lu M, et al. Health status after transcatheter vs. surgical aortic valve replacement in low-risk patients with aortic stenosis. J Am Coll Cardiol. 2019;74:2833–42.

244. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation. 2016;133:601–9.

245. Wolbers M, Koller MT, Stel VS, et al. Competing risks analyses: objectives and approaches. Eur Heart J. 2014;35:2936–41.

246. Dizon JM, Nazif TM, Hess PL, et al. Chronic pacing and adverse outcomes after transcatheter aortic valve implantation. Heart. 2015;101:1665–71.

247. Nazif TM, Dizon JM, Hahn RT, et al. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (Placement of AoRtic TraNscathetER Valves) trial and registry. J Am Coll Cardiol Intv. 2015;8 Pt A: 60–9.

248. Nazif TM, Chen S, George I, et al. New-onset left bundle branch block after transcatheter aortic valve replacement is associated with adverse long-term clinical outcomes in intermediate-risk patients: an analysis from the PARTNER II trial. Eur Heart J. 2019; 40:2218–27.

249. Chamandi C, Barbanti M, Munoz-Garcia A, et al. Long-term outcomes in patients with new-onset persistent left bundle branch block following TAVR. J Am Coll Cardiol Intv. 2019;12: 1175–84.

250. Silaschi M, Conradi L, Wendler O, et al. The JUPITER registry: one-year outcomes of transapical aortic valve implantation using a second generation transcatheter heart valve for aortic regurgitation. Catheter Cardiovasc Interv. 2018;91: 1345–51.

251. Zhu D, Hu J, Meng W, Guo Y. Successful transcatheter aortic valve implantation for pure aortic regurgitation using a new second generation self-expanding J-Valve(TM) system—the first in-man implantation. Heart Lung Circ. 2015;24:411–4.

252. Schafer U, Schirmer J, Niklas S, et al. First-in-human implantation of a novel transfemoral selfexpanding transcatheter heart valve to treat pure aortic regurgitation. EuroIntervention. 2017;13: 1296–9.

253. Seiffert M, Bader R, Kappert U, et al. Initial German experience with transapical implantation of a second-generation transcatheter heart valve for the treatment of aortic regurgitation. J Am Coll Cardiol Intv. 2014;7:1168–74.

KEY WORDS definitions, endpoints, surgical aortic valve replacement, transcatheter aortic valve implantation, transcatheter aortic valve replacement, Valve Academic Research Consortium

APPENDIX For supplemental material, please see the online version of this paper.