Joint Surgical Associations (EACTS, LACES, ASCVTS, AATS and STS) position statement regarding the VARC-3 definitions for aortic valve clinical research

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Classifications: cardiac; clinical trials; aortic valve, replacement; aortic valve, repair
Word count: 2038

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Conducting optimal clinical research is complex, resource-intensive and time-consuming. A critical part of improving the evidence to guide our cardiovascular clinical practice is clinical trials' methodological design and choices of outcomes and endpoints. The Academic Research Consortia were created to define the most critical and standardized definitions of outcome measures. The Valve Academic Research Consortium (VARC) has substantially improved the quality of trials on aortic valve interventions through its multiple iterations. The latest VARC-3 definitions[1] aim to add more granularity and a patient focus to a rapidly evolving field and are particularly useful in providing a standard definition of bioprosthetic valve failure. This position statement considers the strengths and limitations of the VARC-3 document, identifies areas of concern and proposes a way forward to further improve these definitions.

Re-Hospitalization

Re-hospitalization, defined as any admission after the index hospitalization or study enrollment, was added to the VARC-3 recommended endpoints. Given the range of challenges, we do not endorse the blanket inclusion of re-hospitalization as a component of the primary composite outcome in comparative effectiveness trials of SAVR versus TAVI. The primary outcome of a trial should be the variable capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the experimental study (randomized clinical trial).[5] It is unclear whether hospital re-admission rates correlate with major morbidity and mortality outcomes. Additionally, re-hospitalizations outnumber mortality events, especially in short follow-up trials that include patients with low periprocedural risks, and quickly become the primary driver of the composite endpoint.

Time to event analyses are powered by the event count, and the rationale for including re-hospitalization in the primary composite outcome for low-risk trials is to address the challenge created by the sparse number of conventional events. However, re-hospitalization was not included in the primary composite endpoint of the Medtronic Evolut LR trial.[4] The 1-year results of PARTNER-3 showed the superiority of transcatheter aortic valve implantation (TAVI) using this primary composite outcome driven by substantially more re-hospitalizations in the surgical aortic valve replacement (SAVR) arm.[2] At 2-years follow-up, however, this superiority was waning. The difference in hard clinical outcomes (the composite of all-cause death, or stroke) reduced from a hazard ratio (HR) of 0.34 (95% confidence intervals (CI): 0.12 to 0.97, p = 0.04) at 1-year to non-significant (HR 0.77, 95% CI: 0.39 to 1.55, p = 0.47) at 2-years.

Even the VARC-3 attempt to divide re-hospitalization into categories, depending on whether they were linked to the index procedure, is flawed. Re-hospitalization for acute myocardial infarction (MI) after TAVI would not be considered procedure-related, even though patients in the TAVI arm of PARTNER-2,[3] -3[2] and Evolut Low Risk (LR)[4] trials underwent considerably fewer coronary interventions at the time of TAVI procedure, compared to the SAVR arm. In a necessarily unblinded trial, the decision to admit a patient is appropriately undertaken with the knowledge of the prior treatment, which can systematically affect the judgement of the admitting doctor. Those with experience in the adjudication process are well aware of the challenges of blinding adjudication materials, obtaining adequate evidence and avoiding ascertainment bias.

An alternative, which could be explored further, would be to introduce a 30-day blanking period for re-hospitalization, especially for those undergoing invasive procedures such as surgery. Additionally, limiting hospitalizations to those which are unplanned can substantially improve the reliability and validity of this measure.

Thrombus

Prosthetic valve thrombosis is defined in VARC-3 as a clinically significant thrombus. It is laudable to use patient-centered and clinically relevant criteria as endpoints. However, valve thrombus is thought to contribute to early structural valve deterioration (SVD), and this issue should not be minimized, although it remains hypothetical. In the PARTNER-3 results at 2-years, a significantly larger number of VARC-2 defined thromboses occurred after TAVI (2.6%) than after SAVR (0.7%, p = 0.02) and elicited concern for later follow-up. With the VARC 3 proposed updated definition, the incidence of valve thrombosis for the TAVI arm would be arbitrarily decreased. While recognizing that the long-term durability data for SAVR in prior studies are less than ideal given a lack of protocolized follow-up, the major TAVI trials have the potential to provide the first core-lab adjudicated, per-protocol follow-up of surgical bioprostheses. Patients with clinically insignificant valve thrombosis should be monitored as an important outcome for long-term valve durability and SVD. Finally, based on the current definition in the VARC-3 document, the diagnosis of hypoattenuating leaflet thickening (HALT) may be difficult to confirm in some health economies because of limitations in access to 4D-CT and advanced imaging.

Bleeding

VARC-3 defines bleeding into 4 categories, with the same thresholds for TAVI and SAVR. The second level (type 2) of bleeding is defined by, among other criteria, a drop of hemoglobin of >3 g/dL. Cardiopulmonary bypass required for SAVR is associated with acute hemodilution, extending to a hemoglobin drop to >3 g/dL without bleeding. It can also reduce the hemoglobin level to a point where any bleeding during or after the procedure, as routinely present after surgery, can make the hemoglobin drop below this threshold. To mitigate this risk, VARC-3 recommends that different thresholds be used when bleeding is integrated into a composite outcome (≥2 for TAVI, ≥3 for SAVR). This important point should be described clearly in Table 5 in addition to the text on composite outcomes.

Myocardial Infarction

The proposed definition of MI without clinical confirmation is suboptimal in surgical interventions. SAVR requires a period of ischemia during aortic cross-clamping and is inherently associated with a release of cardiac enzymes that do not represent a MI. There are two inconsistent definitions for MI in the cardiovascular research literature. The modified Society for Cardiovascular Angiography and Intervention (SCAI) definitions for type 5 (periprocedural) MI rely solely on biomarkers ≥10x UNL without clinical correlation to diagnose a type 5 MI. In contrast, the regularly updated Universal Definitions of Myocardial Infarction (UDMI), which was developed by the leading societies in the field, including the European Society of Cardiology, American College of Cardiology, American Heart Association, and World Heart Federation, recognizes the pitfalls of isolated elevated biomarkers and requires clinical confirmation. Available data suggest that periprocedural MIs were more prognostically significant when diagnosed with UDMI than the modified SCAI definitions for surgical patients.[6-8] While for valve thrombosis and bleeding, a clinical confirmation has appropriately been advocated by the VARC-3 authors, we propose that a clinical validation

for perioperative MI should also be advocated. Further clarity and consistency in the VARC-3 document should be provided and we would endorse requiring clinical confirmation.

New Left Bundle Branch Block

The need for a new permanent pacemaker has been added to the early composite safety and the VARC-3 authors should be congratulated. Although clinical evidence has been growing regarding the negative impact of new left bundle branch block (LBBB),[9] the authors state that "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". We believe this a missed opportunity and suggest considering new LBBB as an endpoint in the VARC-3 document.

Preservation of the Heart Team and Multidisciplinary Collaboration

The previous iterations of VARC were also simultaneously published in the surgical journals (European Journal of Cardiothoracic Surgery, Journal of Thoracic and Cardiovascular Surgery, and The Annals of Thoracic Surgery), indicating their importance of the concept of the entire Heart Team. However, the VARC-3 definitions manuscript was simultaneously published in the European Heart Journal and the Journal of the American College of Cardiology, two of the most prominent cardiology journals. Morevoer, the writing committee was composed of only 2 practicing cardiac surgeons among 23 authors. Contrary to VARC and VARC-2, regulators were not among the authorship group of this iteration.

The authors of VARC-3 are renowned experts in the field of valvular heart disease. Content expertise for such definitions is desirable. A more diverse writing group, with full representation of stakeholders, would be desirable and may help mitigate issues related to the duality of interests. It would be valuable that the VARC-3 authors continue this collaboration by publishing simultaneously in surgical journals to promote the critical culture of the multidisciplinary heart team decision making. We further recommend a review and endorsement process including societies and individuals with minimal relationships with industry and no direct involvement in the relevant trials' leadership related to the definitions.

The path forward

This position statement recognizes the contribution and positive progress as well as substantive concerns regarding the recent VARC-3 document on aortic valve replacement (surgical and transcatheter) proposed definitions and endpoints. In trials comparing SAVR to TAVI, we would favor focusing on death and stroke as the primary endpoint and reserving other endpoints as secondary. As patient advocates, the heart team approach with thoughtful surveillance with regards to long-term clinical outcomes and prosthetic performance should be enthusiastically embraced.

Trials on human subjects should keep as a central tenet; the altruism and generosity of our patients who participate in research to advance our field by applying sound, unbiased and reasonable methodologies. We applaud the VARC work through the years, in improving the definitions of outcome measures and study endpoints, which has helped to improve the conduct and reporting of clinical trials. While there are many important contributions from the VARC-3 project, some important areas of concern require clarity and improvement. We recommend the development of a new set of definitions, with fully disclosed relationships with industry and including stakeholders from non-invasive cardiology, surgery, regulators and patient representatives, and with a more diverse, worldwide involvement. The definitions

in VARC-3 should be a living document and we would encourage adoption of the constructive suggestions highlighted in this position statement as we look to future clinical research.

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