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Clinical endpoints in transcatheter aortic valve implantation: a call to ARC for standardised definitions

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Several investigators have reported favourable clinical outcomes after transcatheter aortic valve implantation (TAVI)[1-7]. These studies, however, are characterised by a great deal of heterogeneity involving the definition of clinical endpoints. Several organisations with an interest in TAVI have alluded to the need for standardising reporting practices[8-11]. The purpose of this editorial is to create awareness of the challenges associated with clinically assessing TAVI and, more importantly, to call for consistency among endpoint definitions used for reporting the results of transcatheter valvular interventions.

One complicating factor when trying to evaluate available data stems from the fact that the components of safety and efficacy have differed across TAVI studies. Some investigators include both device and procedural success, whereas others report only procedural success. Discrepancies also exist in how different research teams define these particular endpoints (see Table). From this table we can also appreciate the variations that exist for reporting major adverse cardiovascular and cerebrovascular events (MACCE).

How are we to proceed? To make the best use of empirical knowledge, we can learn from the Academic Research Consortium (ARC) that developed a set of consensus definitions for coronary stent trials[12]. This informal collaboration between organisations in the United States and Europe acknowledged the mixed perspectives of physicians, regulatory bodies, and manufacturers. Therefore, the consortium enlisted academics, clinical trialists, device manufacturers, and representatives of the US Food and Drug Administration (FDA). Two aspects of the group's effort are of note: first, it was suggested that endpoint definitions should relate to overall device safety and effectiveness. Specifically, safety endpoints were meant to include any adverse event, whether device-related or not, and effectiveness was related to the effects of early and late relief of coronary obstruction (pathophysiological mechanism of action). Second, patient-oriented composite endpoints (e.g., all-cause mortality, any myocardial infarction [MI], and need for repeat revascularisation) were contrasted with device-oriented endpoints (cardiac death, MI, or repeat procedure) to highlight the patients' perspective and capture the complex interplay between patient baseline characteristics, procedural factors, device performance, and possibly unrecognised factors affecting outcomes.

We may face as great or even greater challenges developing standardised reporting for TAVI. Some common ground for clinical endpoint reporting would be required to allow valid treatment comparisons between TAVI and surgical aortic valve replacement (SAVR). The vast body of knowledge and experience of the cardiac surgeon in the field of valvular heart disease cannot be overstated. Recently, Akins et al published updated guidelines on the reporting of mortality and morbidity after cardiac valve interventions[10]. The authors of the guidelines included key experts in the field of cardiac surgery. Their updated document was intended to facilitate the analysis, reporting, and comparison of clinical studies of various therapeutic approaches to valvar heart disease, including TAVI. A closer examination of the guidelines would suggest that well-accepted definitions, such as structural and non-structural valve dysfunction and reintervention, would need reconsideration in order to make them more applicable to TAVI[11]. A heart team (specifically an interventional cardiologist and cardiac surgeon) would be best suited to address these issues[13].

The benefits of standardised clinical endpoints are many, but primarily they allow for effective communication among all interested parties, including patients. To this end, they would serve

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Table 1. Heterogeneity in endpoint analysis among various transcatheter aortic valve implantation outcome reports.

Endpoint	Device or technical success	Procedural success	MACCE
1. Cribier et al JACC 2006; 47; 1214-23	Not reported	Accurate placement of the PHV in the subcoronary position with associated improvement of haemodynamic parameters (≥30% reduction in mean transvalvular aortic gradient) and absence of severe aortic regurgitation (grade 4)	Death, MI, emergent cardiac surgery, and cerebrovascular accident
2. Webb et al Circulation 2007; 116:755-763	Not reported	Implantation of a functioning PHV within the aortic annulus and without in-laboratory mortality	Not reported
3. Grube et al Circulation 2006; 144:1616-1624 4. Grube et al JACC 2007; 50:69-76	Stable device placement and function as assessed by angiography and echocardiography	Device success with no periprocedural MACCE in the 48 hours after device implantation	Death from any cause, major arrhythmia, MI with CK MB > 2x ULN, cardiac tamponade, stroke, urgent or emergent conversion to surgery or balloon valvuloplasty, emergent PCI, cardiogenic shock, endocarditis, or aortic dissection
5. Schofer et al Circu Cardiovasc Interv 2008;1;126-133	Not reported	Correct placement of the prosthesis in the subcoronary position with an associated absolute reduction in the mean transvalvular pressure to less than 25 mmHg, in absence of severe aortic regurgitation	Death, MI, emergent cardiac surgery, CVA) or other valve-related adverse events
6. Piazza et al Eurointervention 2008; 4:438-442	Not reported	"Adequate technical placement of the device within the aortic root, adequate functionality of the device immediately after implantation, and the event where the patient leaves the catheterisation laboratory alive. "Adequate technical placement of the device within the aortic root" evaluated the system's ability to (1) load the valve into the delivery catheter; (2) access the vasculature; (3) cross the arch of the aorta (4) access the aortic valve with the delivery catheter; (5) deploy the valve accurately across the aortic native valve annulus and; (6) remove the intact delivery catheter system. "Functionality of the device" was defined by a reduction in the mean transaortic valve gradient to less than 20 mmHg and aortic regurgitation grade ≤ 2 as assessed by invasive haemodynamic methods implementing fluid-filled catheters and contrast aortography or echocardiography"	Procedural-related death, stroke, and MI
7. Grube et al Circ Cardiovasc Interv 2009; 1:167-175	Stable device placement and adequate function in the first attempt as assessed by angiography and echocardiography	Device success with absence of periprocedural major adverse cardiovascular and cerebral events including cardiac tamponade in the first 24 hours after device implantation	Death from any cause, myocardial infarction (creatine kinase-myocardial band > 2 times the upper limit of normal), and stroke (as assessed by routine neurological assessment before and after procedure and before hospital discharge)

both regulatory and clinical purposes. Moreover, comparisons and subsequent generalisations of studies would become more credible. Standardised definitions, however, would need to find sensible balance between being too liberal or too strict. Furthermore, they should be flexible enough to accommodate the rapidly changing technology and practice paradigms.

One question remains: Have we achieved a sufficient level of understanding of the benefits and risks associated with TAVI to begin discussions on the standardisation of clinical-endpoints? It is our opinion that it is time for a collaborative effort among interventional cardiologists, cardiac surgeons, regulatory bodies, and device manufacturers and that just such a consortium would provide the initial momentum to guide us in the right direction. The need for randomised controlled trials to adequately assess the outcomes of TAVI demands standardised definitions and the involvement of central core laboratories will be essential in their implementation.

Let us not make the same mistake as in stent trials - This editorial is a call for a Valvular Academic Research Consortium (VARC).

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