Editorial

Early cerebrovascular events after transcatheter aortic valve replacement: patient- and procedure-specific predictors

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Aortic stenosis is the most common valvular heart disease in the elderly; and, when severe and symptomatic, it significantly effects survival. Surgical aortic valve replacement (SAVR) via a median sternotomy is currently the default treatment strategy for those who are low to intermediate surgical-risk candidates. However, a significant proportion of elderly and high-risk patients do not undergo surgery for a variety of reasons, which include increased operative risk, advanced age, comorbidity, and patient choice. Transcatheter aortic valve replacement (TAVR) is a less-invasive alternative for patients who are at high risk of complications or death with open-heart surgery, and those who are deemed inoperable. It has evolved rapidly over the past 10 years, with international trials demonstrating superiority over medical therapy in inoperable patients, and non-inferiority over SAVR both in high and, more recently, intermediate-risk patients (1-4).

The landmark PARTNER trials (1,2) randomised patients to undergo TAVR utilising the Edwards SAPIEN balloon-expandable heart-valve system (Edwards Life sciences) versus either SAVR or medical therapy, for high-risk and inoperable patients, respectively. Whilst proof-of-concept and overall benefit was demonstrated resoundingly in these studies, cerebrovascular events (CVEs) emerged as a worrisome complication. In PARTNER cohort B, stroke or TIA occurred in 6.7% of the patients within the first 30 days, versus just 1.7% of those treated with standard (medical) therapy (P=0.03). In PARTNER cohort A, over the first 30 days stroke or TIA occurred in 5.5% undergoing TAVR versus 2.4% randomised to SAVR (P=0.04). Since these early trial results were published, there has been widespread concern that CVEs might occur at a significantly-higher rate than previously experienced in intervention or cardiac surgery (5), and this issue has remained an area of intense scrutiny.

Why CVEs occur during and soon after TAVR is not entirely clear (6). Clinical syndromes vary widely, from transient neurological deficits which completely resolve (TIA); to subtle, clinically-apparent stroke which may lie undetected; to minor or major stroke, or even death. Additionally, clinically-silent events have been detected at an alarming rate by magnetic resonance imaging (MRI) (7), with an incidence of 60% even among intermediate-risk patients (8). However, the impact of subclinical or silent CVEs over both the short- and long-term remains controversial (9).

The aetiology of CVEs is multi-factorial, but can be broadly divided into two categories: acute and sub-acute. Acute CVEs occur during the index procedure and are related to the embolisation of atheroma, debris or thrombus from the diseased native aortic valve or aortic arch. The manipulation of stiff wires and large-bore catheters within the aorta, and the positioning of the transcatheter valve within the diseased and calcified native aortic valve leads to the embolisation of fibrin, calcium and connective tissue, as

previously demonstrated by the histopathological analysis of debris captured using a filter-based embolic protection device (10). Of equal importance are thrombotic emboli that form acutely secondary to the pro-thrombotic nature of the procedure (endothelial damage, non-endothelialized surfaces, etc.); and sub-acutely secondary to both the transcatheter valve-native valve complex causing altered rheology and a nidus for thrombus formation, and to atrial fibrillation (AF). For patients with previously-identified AF, interrupting anticoagulation for the procedure may permit thrombus formation; for those without, the peri-operative phase is a high-risk period for developing new-onset AF, particularly in the trans-apical cohort (11). Furthermore, elderly patients with aortic stenosis often have widespread atherosclerotic disease and are at risk of CVEs, unrelated to the risk of the procedure. Finally, haemorrhagic stroke is a rare, but potentially-fatal form of CVE, often related to the haemorrhagic transformation of an ischemic infarct or secondary to anticoagulation (6).

One of the first and most auspicious steps for preventing CVEs in patients undergoing TAVR is to identify event predictors and risk factors. In volume 68, issue No. 7, 2016 of the *Journal of the American College of Cardiology*, Auffret *et al.* (12) describe their systematic review of studies that reported on the incidence of CVEs over the first 30 days post TAVR. Based upon recent studies and reviews, the authors selected 16 patients or procedure-related variables to investigate. Using comprehensive, advanced search functions, they then identified 64 relevant original studies published between 2003 and 2015. In total, 72,318 patients were analysed, including 2,385 patients (3.3%) with a CVE within the first 30 days; the median CVE risk was 4% across the included studies.

New-onset atrial fibrillation (NOAF) was identified as the strongest predictor of early CVEs after TAVR, with a relative risk (RR) of 1.85 (95% CI 1.20–2.85, P=0.005). The importance of this finding cannot be understated: NOAF occurs in up to one-third of patients who are continuously monitored post TAVR (13). Even short episodes of AF increase the risk of CVE (13), and between one and 30 days (sub-acute TIA/stroke) is the highest-risk period (14). This suggests that AF-related thromboembolism is the predominant pathophysiological mechanism within this time interval. Identifying NOAF as a major predictor of CVEs prompts further study into whether the increased detection and treatment of AF (largely with anticoagulation) will lead to fewer CVEs post TAVR. Conversely, previously-diagnosed AF was not found to be a predictor of CVEs on meta-analysis (RR 1.10; 95% CI, 0.78–1.57), potentially due to more aggressive peri-operative antithrombotic regimes.

Female gender was identified as a potential predictor of CVEs, though statistical significance was lost when the analysis was restricted to studies involving larger (≥200) cohorts. A smaller aortic annulus and smaller aortic valve area were shown to predict stroke in the PARTNER trials (15); the authors hypothesised that these might increase mechanical interaction within the aortic root, thereby elevating CVE rates in women. A sensitivity analysis performed as part of Auffret *et al.*'s meta-analysis detected no significant increase in RR among women when studies under 200 patients were excluded, casting some doubt on the conclusions drawn.

Chronic kidney disease (CKD) has been consistently identified as a strong risk factor for CVEs (16), and the current meta-analysis yielded a significantly-elevated RR of 1.29 (95% CI, 1.03–1.63; P=0.03) among those with versus without CKD. Multiple disease processes overlap in this patient group, including advanced atherosclerotic disease, altered calcium/phosphate metabolism, and high rates of AF. Compounding these risk factors, anticoagulation has been implicated in increased rates of bleeding in CKD patients and could be underutilised peri-procedurally (17).

Balloon post-dilation (BPD) of transcatheter heart valves has been used to reduce paravalvular aortic regurgitation, which is a predictor of late mortality (18). This increases procedural time and complexity, and there is ongoing debate as to whether this practice is associated with increased CVE rates. The current meta-analysis fails to demonstrate any increase in the rate of CVEs in patients with BPD (RR 1.43, 95% CI, 0.97–2.10; P=0.07), though including outcomes out to 30 days post procedure could dilute the effect size, and a previous analysis of the PARTNER I trial identified an increased risk of stroke at seven days when BPD was performed (19). In fact, the only procedure-related factor identified by Auffret *et al.* occurred among those patients undergoing the procedure within the first versus second half of a centre's experience (RR 1.55; 95% CI, 1.16–2.08; P=0.003). Interestingly, in a recent analysis of PARTNER 1 trial data, this finding was discovered to be secondary to more careful patient selection and device evolution, rather than to improved operator performance (20).

The theoretical propensity for various procedural techniques to generate emboli has logically led to assumptions regarding the risks versus benefits of different valve types and access approaches. As Auffret *et al.* highlight, reduced manipulation of the ascending aorta and arch with

an anterograde (transapical) versus retrograde approach (transfemoral and transaortic) has been suggested to reduce the risk of CVEs, though this has not been documented consistently. Conversely, the trans-apical approach has previously been implicated as a strong predictor of NOAF. In this analysis involving a large number of patients (n=17,031), Auffret *et al.* failed to detect any association between non-transfemoral (versus transfemoral) access and NOAF (RR 1.03; 0.83–1.27). However, it must be noted that merging transapical, transaortic and non-femoral arterial access could mask individual differences between these approaches. Similarly, previous suggestions that the Medtronic CoreValve may be associated with increased emboli during the implantation phase, due to the slower, grating nature of deployment, does not appear to increase the risk of CVEs versus the Edwards SAPIEN valve (RR 1.16; 0.89–1.52) in Auffret *et al.*'s analysis. It will be interesting to observe how the increasing trend towards using repositionable valves affects this risk.

The literature pertaining to peri-operative neurologic injury is fraught with heterogeneity, compromising the capacity to conduct effective meta-analyses. Reporting of and applied definitions for CVE endpoints vary between the studies, and a hierarchical order was used to include the best-available CVE endpoints. In the majority of studies, clinically-apparent CVEs documented by the study investigators were reported, with independent routine neurologist reviews or neuroimaging performed in only a small proportion of patients. While the authors uncovered no difference between those studies that specifically adjudicated neurological events and those that did not, significant differences in stroke rates between neurologist- versus treating-clinician assessments have already been reported (21). However, it is likely that such a difference is significant only for the detection of subtle stroke symptoms. It must also be noted that the vast majority of included studies were observational in nature, and thereby plagued by inherent methodological drawbacks.

Within the constraints of the methodological issues that plague this field of research, Auffret *et al.* provide valuable insights into the predictors of CVEs based upon available evidence. Such an understanding aids in the identification of patients at high risk for early CVEs, and in tailoring management to be more patient-specific. Moreover, by highlighting these CVE predictors, this study paves the way to proceed beyond the characterization of injury towards the investigation and active implementation of risk-minimization strategies.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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