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EDITORIAL COMMENT

The Paradoxes of Transcatheter Aortic Valve Replacement Cardioembolic Protection Devices*

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Transcatheter aortic valve replacement (TAVR) has become the treatment of choice for symptomatic aortic valve stenosis in elderly patients or patients at increased surgical risk (1). Neurological complications are among the most feared TAVR-related complications (2). In randomized trials, 30-day stroke rates ranged from 1.4% in the NOTION trial (Nordic Aortic Valve Intervention Trial) (3) to 6.7% in the PARTNER I (Placement of AoRTic TraNscathetER Valve Trial) (cohort A) (4), depending on various factors including baseline hazard, access route, device type, and others. Over the past years, TAVR technologies substantially improved, which may be best seen when complication rates are directly compared with the benchmark of surgical valve replacement. Although in the PARTNER I trial (cohort B), 30-day rates of stroke or transitory ischemic attack were more than twice as high with TAVR compared with surgical valve replacement (5.5% vs. 2.4%) (5), this relation is now balanced or even reversed in the recent PARTNER II (Placement of AoRTic TraNscathetER Valves) trial (6.4% vs. 6.5%) (6) or SURTAVI trial (Safety and Efficacy Study of the Medtronic CoreValve® System in the Treatment of Severe, Symptomatic Aortic Stenosis in Intermediate Risk Subjects Who Need Aortic Valve Replacement) (4.5% vs. 6.5%) (7). However, crude stroke rates may only draw an incomplete picture of the cerebral embolic damage that can be caused by TAVR. Serial MRI studies revealed that new ischemic lesions, as assessed by diffusion-weighted imaging, are detectable in up to 84% of patients post TAVR (8). Considering this huge number, it appears paradox that no study so far established a clear link between new diffusion-weighted imaging lesion number or volume and cognitive decline after TAVR (8,9).

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An in-depth-analysis of the SENTINEL (Cerebral Protection in Transcatheter Aortic Valve Replacement) trial published by Lazar et al. (10) in this issue of *JACC: Cardiovascular Interventions* provides some answers to that question, but also raises new issues. The SENTINEL trial, published in 2016, tested the safety and efficacy of a transcatheter embolic protection device for patients undergoing TAVR (11). The device consists of 2 filters that are delivered via a transradial or transbrachial access and positioned in the brachiocephalic and the left common carotid arteries. In the trial, 363 patients were randomized 1:1:1 to safety (n = 123), device imaging (n = 121), and control imaging (n = 119). Mechanically, the device worked exceptionally well, because debris in the filters, consisting of thrombus, calcification, valve tissue, artery wall, and foreign material, was found in 99% of the patients. However, protecting the brain against this obvious embolic burden did not translate into significantly better clinical outcomes. Neurocognitive function during follow-up was similar in protected and unprotected patients. Also, new lesion volume in protected cerebral areas, the primary efficacy endpoint, was not statistically different, although numerically lower (102.8 mm^3 in the device arm vs. 178.0 mm^3 in the control arm; p = 0.33). The huge standard deviations of new

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lesion volume suggested a substantial interindividual variability of the treatment effect. Post hoc, the SENTINTEL investigators identified 2 important factors that significantly influenced the treatment effect and that were not as apparent when the trial was planned. The first was valve type, the second was pre-existing white matter disease as assessed by baseline T2-weighted fluid-attenuated inversion recovery volume. After adjustment for these factors, the reduction in new lesion volume by the protection device became significant. In other words, patients who already had lesions on their baseline MRI were significantly more likely to develop new lesions during TAVR (11).

When there is pre-existing neurocognitive dysfunction, the investigators now call another factor into play (10), adding yet another level of complexity. First of all, assessing neurocognitive dysfunction in octo- and nonagenarians is a tremendous task, and the investigators need to be commended on accomplishing this in their study. In fact, the 1-h tests that covered 5 different domains from attention to visual memory were so comprehensive that some researchers even considered fatigue as a confounding factor resulting in inaccurate results (12). Corrected for normative means, the distributions of the *z*-scores showed a markedly skewed distribution for all domains, indicating pre-existing cognitive impairment in a significant proportion of patients. Importantly, those changes could not be detected by neurological screening tests, such as the Mini-Mental State Examination, which have often been used in previous TAVR studies. Hence, the SENTINEL trial sets a new standard for preprocedural neurological assessment. Because there was a significant inverse relation of neurocognitive function with baseline lesion volume, the study supports longstanding cerebrovascular disease as the most likely cause of neurocognitive dysfunction.

These interesting findings bring us back to the question, why it is so difficult to measure a clinical effect of a protection device that appears to work well from a technical perspective. The authors speculate that pre-existing neurocognitive impairment might cause a "floor effect," with new procedure-related lesions having little to no additional impact on an already damaged brain. Although this explanation appears plausible, the positive relationship between pre-existing white matter disease and new lesion volume is somewhat contradictory. In theory, one would expect a protection device to prove more efficient in patients with a higher embolic burden. Thus, we might face another paradox: The clinical efficacy of a cardioembolic protection device might be best detectable in patients who are least prone to cardioembolic cerebral damage.

In any case, the SENTINEL trial and its thorough analyses have clear implications for future trials investigating the neurological impact of any cardiovascular procedure, which from now on should include a careful stratification according to baseline neurocognitive function and MRI lesion burden as a conditio sine qua non.

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