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The challenging realm of neurocognitive evaluation following transcatheter aortic valve implantation.

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Following the first transcatheter aortic valve implantation (TAVI) performed by Cribier and colleagues in 2002 [1], this procedure has evolved considerably to the point where it is now on the verge of posing a viable treatment option amongst intermediate surgical-risk patients with symptomatic severe aortic stenosis [2]. In the early days of TAVIs' evolution, cerebrovascular events were considered as the iceberg standing in the way of the "TAVI Titanic" [3]. Recent randomized trials reflecting improved patients' selection, increased operators' experience, and iterated devices have somewhat dissipated those fears, with a similar incidence of cerebrovascular events already demonstrated between TAVI and surgical aortic valve replacement [2, 4]. However, these clinically overt events seem to be the tip of the iceberg, with silent cerebral micro-embolization and its potential cognitive consequences, lurking beneath the surface [5]. The emergence of embolic protection devices (EPDs), along with the trend towards treating lower surgical-risk patients, shed further light on these specific issues, which are increasingly recognized as a surrogate burden of the ischemic cerebral insult imparted during TAVI [6, 7].

In the setting of surgical aortic valve replacement, a recent review reported rates of 50 to 70% of cognitive decline (CD) within a week of cardiac surgery whereas 10 to 20% of patients exhibited persistent CD at 1 year [8]. A few seminal studies attempted to navigate the deep and dark waters of cognitive evaluation early post-TAVI, mainly demonstrating preserved, and even improved, cognition [5]. However, most of these studies focused on global cognition or memory during a short-term follow-up period without serial evaluations. Moreover, changes in cognitive function were assessed by performing formal statistical tests on the mean or median cognitive scores in the setting of small sample-size, therefore implying the risk of type II error. By contrast, recent studies evaluating the use of EPD suggested that rates of early CD, on the basis of the Montréal Cognitive Assessment (MoCA) measurement, may be as high as 50 to 72% at day 2 post-TAVI and 37 to 55% at discharge [6, 7]. Interestingly, the use of EPDs seemed to mitigate this deleterious effect on cognition. Nonetheless, these studies defined CD as a drop of at least 1 point in the MoCA score, thus failing to properly take into account the variability of changes across tests, which depends on the stability and reliability of the assessment tool [9, 10]. In other words, in the worst case scenario, these findings only reflect random variability.

To avoid this pitfall of cognitive evaluation, some studies used specific methods to account for this inherent variability [5, 11, 12]. In the first of its type, Ghanem et al. [11] evaluated the cognitive trajectory of 111 TAVI recipients, 32 of whom were followed for up to 2 years, using the repeatable battery for the assessment of neuropsychological status (RBANS) with alternate forms to counterbalance practice effects. Post-TAVI CD was defined as a drop of > 1 standard deviation compared with a subject's score pre-TAVI, which occurred in 9% of patients overall. Early CD (within 3 days of TAVI) was apparent in 5.4% of patients, persisting in 50% of them, whereas 3.6% of TAVI recipients suffered from late CD (≥ 3 months post-TAVI). Only age associated with the occurrence of CD. Among 229 patients ≥ 70 years old undergoing TAVI, Schoenenberger et al. [12], using the Mini-Mental State Examination (MMSE) and also defining CD with the use of the baseline standard deviation, reached roughly similar conclusions. In their cohort, 29 patients (12.7%) demonstrated CD (≥ 3 points decrease in MMSE) at 6 months post-TAVI including 8 patients exhibiting a major decrease (≥ 5 points) for whom review of their records identified an obvious medical cause. Of note, the authors failed to isolate multivariable predictors of CD. These 2 studies used tests allowing an integrative measure of global cognition through measurements of several cognitive domains. However, the standard deviation method used in these studies may be prone to overclassifying CD compared with more stringent methods such as practice-corrected reliable change index (RCI) or regression based methods [10]. Besides, both the MMSE and RBANS lack sensitivity in the detection of mild cognitive impairment. By contrast, the MoCA, albeit less commonly performed than the MMSE, demonstrated a greater sensitivity in the detection of subtle cognitive changes, due to the inclusion of a more comprehensive evaluation of executive functions which are predominantly impaired in vascular cognitive impairment [13].

Recently, we reported the cognitive trajectory of 51 TAVR recipients during a 1 year follow-up period, using the MoCA and practice-corrected RCI to define cognitive changes [5]. On the basis of the RCI of MoCA score, 4 patients (7.8%) presented with 30-day CD, which persisted at 1 year in 1 patient (2.0%). Overall, 11.8% of patients exhibited CD at 1 year post-TAVI. Using 5 specific tests for some complex executive functions, we demonstrated that a quarter of TAVI recipients experienced a deterioration in at least one of these tests at 1 month post-TAVI, which was transient in 60% of these

patients and sustained in 40 % of them (10% of the global cohort). Interestingly, we failed to demonstrate a meaningful association between cognitive changes and subsequent quality-of-life or functional status. Overall, the available evidences suggest that mid-term CD affects \approx 10 to 15% of TAVI recipients. Early CD (i.e. the most likely to result from the procedure itself) occurs in 2 to 10% of patients when considering global cognition, may affect 25% of them when specific cognitive domains are evaluated, and seems to persist in 25 to 50% of these patients.

On the contrary, an early and sustained cognitive improvement post-TAVI has also been demonstrated in a sizeable proportion of TAVI recipients [5, 6, 12], ranging from 8 to 38% depending on the assessment tool, timing of the evaluation and methods used to define cognitive changes. This improvement seems more likely amongst patients cognitively-impaired at baseline [5, 12]. Importantly, Schoenenberger et al. [12] demonstrated a lower pre-TAVI aortic valve area amongst patients with post-procedure cognitive improvement; supporting the hypothesis that improvements in cardiac output and, consequently, in cerebral blood flow post-TAVR may reverse some of the baseline alterations.

Admittedly, the current literature leaves us with as many questions as answers, highlighting the tremendous complexity of cognitive evaluation using heterogeneous methods and definitions. That being said, what should we expect from our scientific journey on the still largely unexplored and winding path of post-TAVI cognition? First and foremost, we urgently need to validate and harmonize a suitable battery of neurocognitive tests for TAVI candidates, particularly within the setting of treating lower surgical-risk patients, especially given the growing interest surrounding neuroprotective strategies such as EPDs. In keeping with the prior point, stringent methods that take into account cognitive tests' variability should be mandatory to define significant cognitive changes post-TAVI in future studies. To fairly evaluate TAVI's role in cognitive evolution, we also need to unravel the specific cognitive trajectory of the elderly population with medically-managed severe aortic stenosis, as this has not been specifically assessed so far. Future research should aim at precisely elucidating the underlying mechanisms of post-TAVI CD. Indeed, most studies so far have focused on the cerebral embolic insult as the leading cause of CD. Although silent cerebral infarcts could conceivably be a major cause of early CD, they may be transient and thus their implication in sustained CD remains

questionable. Moreover, only one study demonstrated a relationship between cerebral embolism and the occurrence of CD following surgical aortic valve replacement [14]; a finding that has been recently reproduced in only one small study in the setting of TAVI, demonstrating a moderate but significant correlation between CD and the number and volume of new cerebral lesions on diffusion-weighted magnetic resonance imaging [15]. Identifying predictors of cognitive changes and evaluating neuroprotective strategies in high-risk subgroups are other areas of major interest. Finally, of particular importance is the impact of cognitive changes on TAVI recipients' quality-of-life and functional status; largely unknown to date. There is much still to be discovered in the fascinating land of post-TAVI cognition, and it is safe to say that this incredible journey is thus far from drawing to an end...

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