Neurological Injury After Transcatheter Aortic Valve Implantation
Are the Trees Falling Silently or Is Our Hearing Impaired?

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Subcortical ischemic damage occurs in 62% to 82% of patients who undergo transcatheter aortic valve implantation (TAVI), leaving clinicians and researchers with the difficult task of understanding the functional consequences of these often silent strokes.1 Furthermore, the patients for whom TAVI is the best option typically have additional age-associated systemic health complications, making it more difficult to determine the impact of such an injury on short- and long-term recovery. Repeat neurological examination, diffusion-weighted magnetic resonance imaging (DW-MRI), and neuropsychological assessment, as performed by Ghanem et al.,2 in this issue of Circulation: Cardiovascular Interventions are certainly helpful. In 111 patients with TAVI, they report cerebral embolization in 64% of the imaged subjects but early cognitive decline was diagnosed in only 5.4%, and late cognitive decline occurred at an even lower rate. However, in considering these silent infarcts, we start by asking whether it is appropriate to prioritize overall cognition (the forest) over individual cognitive domains (the trees) when assessing the effects of DW-MRI–detected embolization, a phenomenon that is usually random throughout the subcortex, neurologically subclinical, and often complicated by many perisurgical and postsurgical factors.

In most studies on the perioperative neurological impact of TAVI, the strokes are small, randomly scattered, and generally supratentorial, lesion characteristics that are less likely to produce observable change on standard neurological examination.1 Neuropsychological assessment improves detection of subtle postoperative cognitive decline (POCD) but is constrained by the relative sensitivity of available behavioral and self-report measures to capture clinically meaningful postinterventional differences associated with TAVI embolization. Nevertheless, this intersection between measurement selection and sensitivity and the relatively random neuroanatomical pattern of TAVI embolization may help to clarify whether we should target the forest or the trees of post-TAVI cognitive and functional outcomes.

Ghanem et al2 treated cognition as a unitary construct and indeed used this approach to define their primary cognitive outcome. This provides a single value in clinical trial investigations but is similar to viewing POCD as part of the overall cognitive health of the system. In this gestalt view of POCD, any functional consequences of silent embolization become detectable only if there is a significant impact to the forest, that is, if the functional impact of TAVI embolization approximates a globally progressive neurological condition, such as Alzheimer’s disease.

Consistent with this gestalt view of defining meaningful cognitive change post-TAVI, it is notable that Ghanem et al2 chose to measure cognitive outcomes in their study using the well-developed Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), a cognitive screening battery that was originally developed to detect cognitive changes associated with Alzheimer’s and Huntington’s diseases.3 The authors also used cutoff scores for their measurement of pre/post-TAVI cognitive change, which were based on what was necessary to maximize sensitivity, specificity, and odds ratios of RBANS scores between normal controls and patients with Alzheimer disease.4 This is a high bar that many of the often subtle cognitive changes associated with silent infarcts may not exceed, but is consistent with the more conservative notion that the consequences of TAVI embolization should be expressed through global cognitive decline. To the authors’ credit, in addition to the primary global cognition outcome variable, they examined 5 cognitive subdomains tapped by the RBANS, many of which showed little change over time. However, this relative lack of change within subdomains may again be a byproduct of the high bar for impairment established by cutoff scores derived from individuals with Alzheimer’s dementia.

The observed nature of TAVI-associated embolization is most similar to the random, but largely supratentorial, white matter damage seen in individuals with mild-to-moderate ischemic cerebrovascular disease. Cognitive deficit in these individuals is generally not produced on a global scale. Therefore, it is more important to look at the trees to consider the significance of relative behavioral change within cognitive domains that are more likely to be sensitive to the seemingly random nature of TAVI embolic damage.

Deficits in cognitive tasks that are heavily dependent on cortical/subcortical function or coordinated integration of multiple cortical regions are more prevalent when random disruption of white matter fiber tracts is the primary neurological insult.5
Notably, the single RBANS cognitive subdomain that shows a consistent downward trend in the Ghanem et al. TAVI sample (ie, visuospatial/constructional skills) is dependent on greater distributed processing demands across the cortex, and also involves posterior cerebral watershed regions. Another investigation of cognitive outcomes and DW-MRI–detected emboli postcoronary artery bypass graft and valve replacement supports the notion that sensitivity to detect the functional effect of silent lesions is improved by looking not only at global cognition, but also at impairment across multiple cognitive domains, of which psychomotor speed, mental flexibility, and memory are most affected at 6 weeks postintervention.6

Ghanem et al.2 and Gaita et al.,7 who attempted to detect cognitive deficits associated with atrial fibrillation and silent cerebral ischemia, should be commended for having the foresight to choose a neuropsychological screening battery with alternate forms that allows for reasonable capture of both the cognitive forest (global) and trees (multiple cognitive subdomains). Repeatable cognitive assessment measures with alternate forms help to reduce test-retest practice effects but in no way completely control for them. In addition to practice effects, each of the tasks that make up the RBANS screening battery has variable test-retest reliability that should also be accounted for in clinical trials. Both of these repeated measures factors can be controlled by using reliable change indices or standardized regression–based methods,4 but this requires a well-matched control sample for deriving the normative test-retest and practice effect estimates used to quantitatively define meaningful cognitive change. The developers of the RBANS have tried to address the test-retest issue by constructing RCIs based on the age-corrected normative sample; however, this correction only holds for 2 time-point administration and would be of questionable help in determining whether significant change occurred during the 5 time points in the current study.

In the absence of a study control group, Ghanem et al.2 have chosen to convert the RBANS scores to standard scores based on RBANS performances of a normative comparison sample. Normative comparisons of neuropsychological test data can be extremely valuable in characterizing a study sample, assuming that matching characteristics between the study sample and the normative comparison sample are appropriate. The problem presented by normative comparison of cognitive data in older cardiac surgical samples is that cardiac and cerebrovascular risk factors are likely to be exclusionary criteria for determining the normative group; thus, although generally matched on major demographic factors, such as age or education level, the groups may actually be significantly different on the primary variable of interest. Nonetheless, normative score conversion can provide a rough estimate of the general cognitive performance levels of the study population, which, in turn, provides valuable information for determining study generalizability.

In the current TAVI study group, which included a cognitively impaired subgroup, comparison of the RBANS standard scores (which, based on their references, seem to be derived from the age-corrected performance data for native English-speaking rather than German-speaking individuals) reveals that the study sample is significantly skewed toward cognitive impairment at baseline. The mean baseline global cognition score in the TAVI group was 12th percentile relative to the RBANS age-corrected normative sample, and ranged from 2nd to 45th percentile, whereas the mean global cognition score in the subgroup identified as having mild cognitive impairment (MCI) was 1st percentile ranging from <1st to 4th percentile. This suggests that a proportion of the subjects in the TAVI group manifested cognitive problems at baseline that were indicative of MCI, whereas the latter, smaller group, defined by the authors as having MCI, had global cognition difficulties on average in the moderate-to-severe impairment range, far lower cognitive performance than is typically associated with MCI.

Furthermore, by setting the cut score at 1 SD for determining meaningful decline in a group that is already performing in the below average to significantly impaired range, the likelihood of running afoul of test floor effects increases. Floor effects occur when performance on a particular neuropsychological test measure is already low at baseline with little remaining performance variance to measure change at subsequent testing time points. Floor effects, as well as ceiling effects, can result in measurement error that gives the illusory impression of no appreciable cognitive decline/improvement (floor effects) or cognitive improvement (ceiling effects). Reliable change or standardized regression–based conversion methods can be used to minimize these effects because decline or improvement over time can still be determined if the expected change score value (based on control sample characteristics) differs significantly from the study participant’s actual change.

We applaud the efforts of Ghanem and colleagues to evaluate cognitive trajectory systematically after TAVI using neurocognitive assessment, brain imaging, and longer term follow-up in a large sample of patients. Unfortunately, the study likely underestimates the true incidence of cognitive decline because of (1) reliance on a global cognitive score as the primary variable after an injury that likely results in patchy neurocognitive deficits in varying performance domains; (2) measurement error related to the floor effect in a sample with a sizable proportion of individuals already within impairment range at baseline; (3) cut scores that are based on single-assessment diagnostic discrimination between normal elderly and patients with Alzheimer disease, and that do not take repeated (>2) measures effects into account; and (4) availability of only 50% of the DW-MRI data at follow-up.

Future studies in this population should (1) use a comprehensive neurocognitive testing battery that can adequately assess cortical/subcortical function or coordinated integration of multiple cortical regions; (2) avoid legacy cut scores based on previous published research but in which the patient samples between studies are not similar; (3) account for the floor effect in a cohort that is likely to be cognitively impaired at baseline; (4) carefully select normative test data that are well matched with the patient group of interest across important demographic and health factors, including regional/language-specific normative data, for better generalizability of study results; (5) include study-specific well-matched controls to account for serial assessment characteristics, such as test-retest reliability and practice effects; and (6) consider more
sophisticated DW-MRI neuroimaging techniques that may be more sensitive to the cerebral disruption caused by generally random patterns of cerebral embolism, for example, diffusion-tensor imaging tractography. These efforts will enhance our ability to define the functional significance of silence.

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References

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