# Does Transcatheter Aortic Valve Implantation for Aortic Stenosis Impact on Cognitive Function?

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**Abstract:** Aortic stenosis (AS) is the most common valvular heart disease among elderly patients in developed countries. Surgical valve replacement is indicated for severe AS to relieve the obstructed outflow tract. Transcatheter aortic valve implantation (TAVI) has emerged as an alternative for patients with severe AS, particularly in those with high surgical risk. TAVI is a less invasive approach with favorable survival outcomes in high-risk patients compared with open surgery. Despite the remarkable success of TAVI, there is a growing concern on the incidence of postprocedural cognitive impairment. This review aims to evaluate the incidence of cognitive impairment following TAVI and to identify the potential contributing factors.

**Key Words:** aortic stenosis, transcatheter aortic valve implantation, cognitive impairment, cognitive function, cognitive status, cerebral embolism

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Aortic stenosis (AS) is the most common valvular heart disease among older patients in developed countries.[1] The prevalence of AS increases with age: 20% in patients 65–75 years of age, 35% in those 75–85 years of age, and 48% in patients older than 85 years.[2] Symptoms of AS include angina, syncope, fatigue, and breathlessness. Surgical aortic valve replacement (SAVR) is indicated for severe AS to relieve the obstructed outflow tract and transcatheter aortic valve implantation (TAVI), a less invasive approach, has emerged as an alternative, particularly in those with high surgical risk.[1] Despite the remarkable success of TAVI, there is a growing concern for the incidence of postprocedural cognitive impairment. This review aims to evaluate the incidence of cognitive impairment following TAVI and to identify the potential contributing factors.

## METHOD

A literature search was carried out on Medline and Embase from 2010 to 2018 with the following keywords: cognitive impairment, cognitive function, cognitive status, transcatheter aortic valve implantation, aortic stenosis, and cerebral embolism.

## AORTIC STENOSIS

AS is the most common acquired valvular heart disease among older patients in developed countries.[1] AS occurs when there is obstruction of flow at the level of the aortic valve and does not include the subvalvular and supravalvular forms of the disease. Aortic valve stenosis is usually defined as restricted systolic opening of the valve leaflets, with a mean transvalvular pressure gradient of at least 10 mm Hg. The progressive valve narrowing and the pathophysiological adaptive mechanisms cause symptoms such as shortness of breath, chest pain, fatigue, and syncope. Severe AS, which is accompanied by these symptoms, is considered to be a fatal disease if left untreated. The annual mortality in such individuals is estimated to be 25%, and the average survival is only 2–3 years.[1]

The most common causes of AS are degenerative calcific AS and congenital bicuspid AS. These 2 can be distinguished clinically by age at onset and by their characteristic echocardiographic findings. Calcific AS affects trileaflet aortic valves and often presents in patients between 70 and 90 years. Congenital bicuspid aortic valve patients are predominantly men who are often known to have a heart murmur for many years but usually start experiencing symptoms between the ages of 40 and 60 years.[1]

In patients with symptomatic severe native aortic valve stenosis, treatment strategies include SAVR, TAVI, or no intervention based upon estimated surgical risk and other factors. Conventionally, SAVR was the mainstay of treatment of severe AS. However, TAVI has become an alternative to SAVR for high-risk surgical patients.[1] TAVI has been shown to improve survival, with a lower postoperative mortality at one year than SAVR,[3] and is associated with better long-term outcomes including improved functional capacity and quality of life.[4]

## TRANSCATHETER AORTIC VALVE IMPLANTATION

TAVI is a relatively recent intervention which was initially offered to individuals with severe symptomatic AS at prohibitive surgical risk. This minimally invasive intervention was initially introduced experimentally, and was first performed in humans in 2002 by Cribier et al.[5] It uses a percutaneously implanted heart valve composed of 3 bovine pericardial leaflets mounted within a balloon-expandable stent. Several large multicenter registries, as well as prospective randomized trials, have confirmed with definitive clinical data that this therapeutic modality is a feasible and effective alternative to traditional SAVR in high-risk and nonoperable patients.

### Cognitive Trajectory Following Transcatheter Aortic Valve Implantation

Cognitive function is assessed by various different methods as displayed in Table 1.[6–13] Recent data from randomized controlled trials suggest a higher risk of neurological events for up to 1 year after TAVI in comparison to SAVR, despite the reduced rates of death from all-causes after the same period.[3,4] It appears that these neurological events as well as the cognitive decline (CD) seen in some patients after TAVI procedures are associated with the silent microemboli seen on diffuse weighted magnetic resonance imaging (DW-MRI) of the brain after the procedure.[14] Kahlert et al[15] isolated two major sources of microemboli during the TAVI procedure: balloon

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**TABLE 1.** Summary of Different Cognitive Assessment Toools

| Types of Cognitive Functional Assessments | Parameters Evaluated |
|---|---|
| Montreal Cognitive Assessment scores[6] | 30-Point test<br>Available in 55 languages<br>Basic form available for patients with lower education<br>Domains assessed<br>Short-term memory recall<br>Visuospatial abilities<br>Executive functions<br>Attention, concentration, and working memory<br>Language<br>Orientation to time and place |
| Clinical Dementia Rating Sum of Box scores[7] | Used to stage dementia severity<br>Evaluates<br>Memory<br>Orientation<br>Judgement and problem solving<br>Community affairs<br>Home and hobbies<br>Person care |
| Trail-Making Test Part A[8] | Neuropsychological test of visual attention and task switching<br>Join a set of 25 dots as quickly whilst maintaining accuracy (1,2,3,4…)<br>Provides information on visual search speed, scanning, speed of processing, and mental flexibility |
| Trail-Making Test Part B[9] | Connecting a sequence of consecutive numbers and letters (eg, 1, A, 2, B, 3…) |
| Rey Auditory Verbal Learning Test[10] | Evaluates: short-term auditory and verbal memory; rate of learning; learning strategies; presence of confabulation or confusion in memory |
| Logical Memory I and II from Wechsler Memory Scale[11] | Logical memory I: testing short-term memory<br>Logical memory II: testing log-term memory (eg, a story is told to the participant)<br>Task 1: retell the story<br>Task 2: answer questions based upon the story |
| Digit span[10] | Participants see or hear a sequence of numerical digits and recall the sequence correctly<br>Measures working memory |
| Boston Naming Test[12] | Neuropsychological assessment tool to measure confrontational word retrieval in individuals with aphasia or language disturbance<br>Naming of common and intellectual objects |
| Stroop Color and Word test[13] | Used in psychophysiological studies<br>Problem-solving task to elicit mental stress<br>Tasks evoke beta-adrenergically driven responses<br>Participants required to identify name of color printed in a conflicting color<br>Test reveals activation in the frontal lobe |

valvuloplasty and positioning of the prosthetic valve itself. This was the basis for the 2 recent neuroprotective procedural strategies; namely, the direct TAVI approach without valvuloplasty and the use of cerebral embolic protection devices (EPDs).[14]

A systematic review of 6 studies that assessed the overall cognitive function before and after TAVI (on average 5 days post-TAVI) using the mini-mental status examination (MMSE) demonstrated cognitive improvement or preservation of cognitive function following TAVI,[3] possibly due to improvements in hemodynamic status.[3,4] Three out of the 6 studies followed TAVI patients over a period of 3 months and 2 of them demonstrated a significant improvement in MMSE scores.[3]

Ghanem et al[14] conducted a study to monitor the cognitive trajectory after TAVI. One hundred eleven patients undergoing TAVI were followed up for 2 years using the repeatable battery for the assessment of neuropsychological status (RBANS) to assess the cognitive function before (E1), 3 days (E2), 3 months (E3), 1 year (E4), and 2 years (E5) after TAVI. A DW-MRI was conducted at E1 and E2 only. Before TAVI, the cognitive performance of patients was low on average (mean RBANS total score at E1, 82.9 ± 14.6). Thirty patients (27%) were considered as a subgroup with mild cognitive impairment (MCI; RBANS total score at E1 = 65.5 ± 8.0); >1.5 standard deviation (SD) below the adjusted population norms. Early post-procedural testing (E2) demonstrated incident CD in only 6 patients (5.4%; RBANS total score of 60.0 ± 11.3), while late onset of CD (at E3, E4, or E5) was seen in 4 patients (3.6%). Fifty-six patients (50.4%) completed the imaging protocol (DW-MRI), and cerebral embolization was seen in 36 of them (64%). There was no significant difference in cognitive function between those patients with cerebral emboli and the rest of the population. It was concluded that CD in the first 2 years after TAVI could be ruled out in the majority of patients (91%), and only patient age was independently associated with CD, linking higher age to cognitive impairment along the first 2 years after TAVI.[14]

Abdul-Jawad Altisent et al[4] conducted a study to compare the extent of neurological injury in intermediate surgical risk patients with severe AS undergoing either TAVI or SAVR, as assessed with both DW-MRI and a validated cognitive examination. They compared 46 patients undergoing TAVI with 37 patients undergoing SAVR. Baseline cognitive performance of patients was lower compared with an age-, sex-, and education-matched population across both groups, although there were no significant differences among the two groups themselves. Sixty-seven (80.7%) patients underwent a postprocedural DW-MRI; 40 (87%) in the TAVI group and 27 (73%) in the SAVR group. Focal DW-MRI abnormalities consistent with acute ischemic lesions were documented in 18 patients (45%) in the TAVI group versus 11 patients (40.7%) in the SAVR group. In general, postprocedural cognitive assessment showed no significant changes in global cognitive scores, neither in the TAVI group nor in the SAVR group. However, the reliable change index showed mild cognitive changes. While 15 patients (27.8%) demonstrated global CD [9 (26.5%) in the TAVI and 6 (30.0%) in the SAVR], 11 (20.3 %) demonstrated global cognitive improvement [7 (20.6%) in the TAVI group and 4 (20.0%) in SAVR group]. In the 42 patients with both postprocedural DW-MRI and complete cognitive assessment, no significant association was found between the occurrence of acute postprocedural lesions on DW-MRI and CD. Similarly, no relation was apparent between the total lesion volume or number of lesions and cognitive impairment in terms of reliable change index. An older age was a predictor of the occurrence of acute lesions, and the use of vitamin-K antagonist therapy had a protective effect regardless of the type of intervention.[4]

In a study by Schoenenberger et al,[16] the cognitive function of 229 patients (age > 70 years) was measured at baseline and 6 months after TAVI using MMSE. Cognitive function improved in 37.5% of patients with impaired baseline cognition (18 out of 48 patients). In those patients, the baseline aortic valve area was significantly lower as compared with the baseline aortic valve area of patients in whom cognitive function did not improve at 6-month follow-up, suggesting that patients with the most severe AS benefit more cognitively following TAVI. However, 29 out of the 229 patients (12.7%) in the study population had deterioration in the MMSE score (3 or more points decrease).

A recent study was conducted to assess the impact of acute (procedural) and postacute cerebrovascular embolic events (CVEs) on cognitive performance using different types of MRI protocols before (baseline), early (FU1) and at least 30 months after TAVI (FU2) to quantify embolic burden and MMSE.[17] Twenty-eight patients were followed up for a mean period of 34 months. At baseline, no patient had CVEs in DW-MRI and 10 patients (35.7%) had 14 subclinical brain infarctions (SBIs) (range 1 ± 3/patient). During the follow-up period, no clinically apparent cerebrovascular accident was observed. At FU1, 17 out of the 28 patients (60.7%) demonstrated 61 acute postprocedural CVEs in DW-MRI (range 1 ± 14/patient). At FU2, all patients were negative for DW-CVEs. Notably, 17 of 28 patients demonstrated 32 SBIs (60.7%, range 1 ± 5/patient), 12 of these patients had 18 new SBIs at FU2. The mean MMSE scores of the entire cohort at baseline and FU2 demonstrated no significant difference and were 26.6 ± 2.9 and 26.7 ± 3.7, respectively ($P = 0.88$). In contrast, the presence of new SBIs at FU2 negatively impacted MMSE-trajectories during follow-up (new SBI: MMSE −1.4/no new SBI: MMSE +1.5, $P = 0.067$), indicating a negative functional effect of new SBIs, but not DW-CVE on cognitive function.[17]

### Incidence of Global Cognitive Impairment After Transcatheter Aortic Valve Implantation

Data evaluating post-TAVI cognitive function over the long term are scarce, with only a few studies reviewing patients for at least 6 months. Ghanem et al[14] reported that 91% of the patients undergoing TAVI did not experience CD at any time within 2 years post-TAVI.[15] Of the 9% of patients with CD, 5.4% had early onset (within 3 days), while 3.6% had late onset (3 months to 2 years). Similarly, Schoenenberger et al[16] found 12.7% of patients developed CD at 6-month review. Auffret et al[18] discovered that cognitive function remained stable in 80% of patients, whereas 11.8 and 7.8% of patients presented with CD and improvement, respectively, at 1-year review.

Studies assessing-specific domains involved in CD following TAVI are particularly interested in establishing the correlation between TAVI and subcortical vascular insult. The key features of subcortical ischemic vascular injury include loss of control of executive cognitive functioning, forgetfulness, changes in speech and emotion, all as a result of interruption of the responsible prefrontal-subcortical circuits by ischemic lesions.[19] Knipp et al[20] explored changes in delayed recall, working memory, verbal learning, and fluency in patients undergoing TAVI. No significant changes were found in any of these domains immediately and 3 months after TAVI. On the other hand, visual attention and delayed recall have been shown to improve shortly after TAVI in the study by Lansky et al.[21]

In contrast, Auffret et al[17] demonstrated that about 25% of patients had an early decline in at least one of the tests specifically assessing executive function, processing speed and abstract reasoning, which persisted in 40% at 1-year follow-up. In addition, Ghanem et al[14] found that CD was predominantly characterized by delayed memory and visual constructional reasoning. While these domains are specifically associated with vascular dementia, CD may be a result of subcortical vascular insult following TAVI.

## CHARACTERISTICS ASSOCIATED WITH DECLINE OR IMPROVEMENT IN COGNITIVE FUNCTION

### Preexisting Cognitive Impairment

A number of studies have evaluated the potential impact of TAVI on preexisting cognitive impairment (Table 2).[15–17,22] Ghanem et al[14] reported that patients with or without MCI prior to TAVI achieved similar cognitive performance 2 years after TAVI. Interestingly, patients with MCI improved significantly ($P < 0.05$) within the first 12 months, possibly due to improved hemodynamics after TAVI. This particular finding was further investigated by Schoenenberger et al[16] in a larger study population of 229 patients. It was demonstrated that TAVI improved cognitive performance in 37.5% of patients who previously had lower cognitive function at a 6-month review and proposed a similar hypothesis. Similarly, Auffret et al[18] demonstrated that 35% of patients who were cognitively impaired prior to TAVI improved remarkably at 30-day review and remained stable over the 1-year study period. More recently, Abawi et al[22] provided further evidence to show that patients suffering from cognitive impairment may significantly improve at 4-month follow-up.

**TABLE 2.** List of studies evaluating the effect on TAVI on preexisting cognitive impairment

| Publication | Year | Mean Age of Patients (yr) | Sample Size | Length of follow-Up After TAVI |
|---|---|---|---|---|
| Ghanem et al[14] | 2013 | 80 | 111 | 2 yr |
| Auffret et al[18] | 2016 | 80 | 51 | 1 year |
| Schoenenberger et al[16] | 2016 | 83.4 | 229 | 6 months |
| Abawi et al[22] | 2018 | 81 | 30 | 4 months |

TAVI, transcatheter aortic valve implantation.

### Age of Patients

Most patients undergoing TAVI have higher surgical risk with advanced age and multiple comorbidities. Cognitive impairment after TAVI is particularly important in older patients as it may further increase their morbidity and lower their quality of life after the procedure. Notably, a study by Ghanem et al[14] demonstrated increasing patient age as the only independent risk factor ($P = 0.012$) for CD after TAVI, but not cognitive status, prior cerebrovascular events, direct TAVI, use of EPDs, or silent cerebral embolism.

### Procedural Characteristics

A prospective study done by Schoenenberger et al[16] revealed that patients with lower aortic valve area (median 0.60 $cm^2$) are specifically prone to cognitive improvement after TAVI, which again strengthens the hemodynamic hypothesis. TAVI is known for its strong association with silent cerebral embolism which may subsequently lead to cognitive impairment. Studies by Ghanem et al[14] and Kahlert et al[15] reported that new-onset silent cerebral embolism was detected on DW-MRI in 72.7% and 84% of patients after TAVI, respectively. Moreover, it has been suggested that a high incidence of cerebral embolism is likely due to procedural factors.[15,23]

### Procedural Route

Transfemoral (TF) TAVI is a more commonly used approach compared with transapical (TA) TAVI. TF-TAVI involves inserting a catheter through the aortic arch and retrograde crossing the native valve, while TA-TAVI involves direct puncturing of the ventricular apex through a small left lateral thoracotomy. TF-TAVI may potentially increase the risk of arch atheroma plaque dislodgement leading to a higher rate of cerebral embolism. However, while having a relatively small sample size, Rodés-Cabau et al[23] reported that there is no significant difference beteween patients undergoing TF-TAVI and TA-TAVI with respect to cerebral embolism detected on DW-MRI. The results showed that there was no significant difference regarding percentage of patients with new ischemic lesions (TF-TAVI 66%, TA-TAVI 71%; $P = 0.78$), the median number of lesions per patient (TF-TAVI 3, TA-TAVI 4; $P = 0.38$), or in lesion size (TF-TAVI 92% < 1 cm, TA-TAVI 91%; $P = 1.00$). On the other hand, Tse et al[24] revealed that TA-TAVI had a significant increased risk of postprocedural delirium; 53% and 12% in patients undergoing TA-TAVI and TF-TAVI, respectively. This finding is particularly important as postprocedural delirium was reported to be associated with long-term cognitive impairment despite its acute presentation.[25]

## BALLOON AORTIC VALVE PREDILATATION

Balloon aortic valve predilatation was considered a fundamental measure to prepare the calcified aortic valve for positioning and deployment of the transcatheter valve during the early days of TAVI. In line with the trend toward simplification of TAVI procedures, direct TAVI may have an advantage of less interruption of the native valve and could therefore reduce procedural complications such as silent or clinically apparent cerebral embolism.[26] However, the direct approach appeared to have no significant effect on patients' cognitive function after TAVI in the study by Ghanem et al[14] with RBANS total score at 3 days, 3 months, and 3 years: +1.7, +2.4, and +2.3 (direct) versus +3.3, +0.4, and +0.1 (conventional); $P = 0.88$, $P = 0.6$, and $P = 0.71$, respectively.

## EMBOLIC PROTECTION DEVICE

Embolic protection during TAVI has been previously evaluated.[27,28] A recent study by Bagur et al[29] suggested that the use of EPD during TAVI may be associated with a smaller volume of silent ischemic lesions; however, it may not lead to reduction in total number of lesions. This evidence is supported by a few studies showing no statistical significance in long-term cognitive function in patients with or without EPD. Lansky et al[21] showed that while, at baseline, the use of an EPD improved cognitive function versus control in visual attention and vigilance ($P = 0.06$) and in episodic memory ($P = 0.022$), these differences were not apparent at 30 days. Further to this Rodés-Cabau et al[30] reported no differences in neurological evaluations with the National Institute of Health Stroke Scale, the modified Ranking scale, and the Barthel Index when comparing EPD with control ($P < 0.15$). It is not clear why patients with diffuse weight imaging lesions following TAVI do not go on to develop CD.

## DISCUSSION

Studies assessing cognitive performance in patients undergoing TAVI have generally found cognitive preservation, with only a small proportion of patients experiencing either cognitive improvement or deterioration. Cognitive improvement was found to be more pronounced in patients who were cognitively impaired before the intervention. An increase in cardiac output following TAVI and subsequent improvement in cerebral blood flow could explain the correlation between hemodynamic improvement and cognitive function. Moreover, it has been shown that impaired cerebral blood flow may be reversible and its restoration can lead to improved cognitive performance.[31,32] Hence, TAVI should not be withheld in patients with preprocedural cognitive impairment.

Studies have suggested that domains involved in CD following TAVI were predominantly features of subcortical vascular insult, such as impaired executive function and delayed recall. This is in line with the study indicating frontal lobe as the region with the most significant number of microemboli detected on DW-MRI after TAVI.[20]

Most patients undergoing TAVI are of advanced age with a high morbidity burden. In addition, both advanced age and preexisting cardiovascular disease are known risk factors for subcortical ischemic vascular dementia,[19] which exposes patients to a higher risk of cognitive impairment despite the intervention, and therefore a potential overestimation of the incidence of TAVI-induced CD. However, it has been proven that increasing age is an independent risk factor for CD after TAVI.[14]

Studies have shown a high incidence of new-onset silent cerebral embolism on DW-MRI after TAVI (72.7–84%) and suggest that it is likely due to procedural factors.[14,15] In terms of procedural route, TF-TAVI and TA-TAVI were found to have a similar incidence of cerebral embolism detected by DW-MRI.[23] Notably, TA-TAVI was reported to have a fourfold increased risk of post-TAVI delirium, while delirium was reported to be associated with long-term cognitive impairment in previous studies.[24,25] On the other hand, both direct TAVI without balloon predilatation and the use of EPDs have shown no significant effect on cognitive function in patients undergoing TAVI.[21,30] Despite the high incidence of new-onset silent cerebral embolism following TAVI, a correlation between silent cerebral embolism and cognitive function was not found.[14,20]

## LIMITATIONS

Most of the studies are of small sample size and therefore have inadequate statistical power. Only a few studies to date have reviewed patients' cognitive function long term, that is, for at least 6 months. The definition of CD has varied from study to study, often defined simply by a decrease in mean scores in neurocognitive tests. Furthermore, different neurocognitive tests performed in the studies made it hard to compare data due to arguable sensitivity and accuracy. The educational level and functional status of patients should also be taken into consideration when performing baseline cognitive testing.

Future research is required to review patients more frequently in order to identify the pattern of CD; for example, a progressive stepwise decline in vascular dementia. The definition of cognitive impairment should be standardized to avoid overestimation of the incidence of CD after TAVI. Larger study populations and longer study periods should be considered in future studies in order to investigate the cause of cognitive impairment after TAVI.

## CONCLUSIONS

The majority of patients undergoing TAVI have not experienced cognitive impairment at any time within 2 years. Cognitive improvement was more pronounced among patients with impaired baseline cognition, possibly due to improved cerebral blood flow following TAVI. A small proportion of patients experienced CD after TAVI and predominantly presented with impaired executive function and delayed recall, which is suggestive of subcortical vascular insult. Despite a high incidence of new-onset silent cerebral embolism detected by DW-MRI following TAVI, a correlation between silent cerebral embolism and cognitive function was not found. The increasing age of patients was proved to be an independent risk factor of post-TAVI cognitive impairment.

## REFERENCES

1. Carabello BA, Paulus WJ. Aortic stenosis. *Lancet.* 2009;373:956–966.
2. Supino PG, Borer JS, Preibisz J, et al. The epidemiology of valvular heart disease: a growing public health problem. *Heart Fail Clin.* 2006;2:379–393.
3. Lai KSP, Herrmann N, Saleem M, et al. Cognitive outcomes following transcatheter aortic valve implantation: a systematic Review. *Cardiovasc Psych Neurol J.* 2015;3:198–204.
4. Abdul-Jawad Altisent O, Ferreira-Gonzalez I, Marsal JR, et al. Neurological damage after transcatheter aortic valve implantation compared with surgical aortic valve replacement in intermediate risk patients. *Clin Res Cardiol.* 2016;105:508–517.
5. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. *Circulation*. 2002;106:3006–08.
6. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53:695–699.

7. O'Bryant SE, Waring SC, Cullum CM, et al; Texas Alzheimer's Research Consortium. Staging dementia using Clinical Dementia Rating Scale Sum of Boxes scores: a Texas Alzheimer's research consortium study. *Arch Neurol.* 2008;65:1091–1095.
8. Tombaugh TN. Trail making test A and B: normative data stratified by age and education. *Arch Clin Neuropsychol.* 2004;19:203–214.
9. Arbuthnott K, Frank J. Trail making test, part B as a measure of executive control: validation using a set-switching paradigm. *J Clin Exp Neuropsychol.* 2000;22:518–528.
10. Khosravi FE, Keelor JL, Akbarzadeh BAR, et al. Comparison of Rey auditory verbal learning test (RAVLT) and digit test among typically achieving and gifted students. *Iran J Child Neurol.* 2016;10:26–37.
11. Brooks DN. Wechsler Memory Scale performance and its relationship to brain damage after severe closed head injury. *J Neurol Neurosurg Psychiatry.* 1976;39:593–601.
12. Mack WJ, Freed DM, Williams BW, et al. Boston naming test: shortened versions for use in Alzheimer's disease. *J Gerontol.* 1992;47:P154–P158.
13. Van der Elst W, Van Boxtel MPJ, Van Breukelen GJP, et al. The stroop color-word test. 2006;13:62–79.
14. Ghanem A, Kocurek J, Sinning JM, et al. Cognitive trajectory after transcatheter aortic valve implantation. *Circ Cardiovasc Interv.* 2013;6:615–624.
15. Kahlert P, Knipp SC, Schlamann M, et al. Silent and apparent cerebral ischemia after percutaneous transfemoral aortic valve implantation: a diffusion-weighted magnetic resonance imaging study. *Circulation.* 2010;121:870–878.
16. Schoenenberger AW, Zuber C, Moser A, et al. Evolution of cognitive function after transcatheter aortic valve implantation. *Circ Cardiovasc Interv*. 2016;9:e003590.
17. Ghanem A, Dörner J, Schulze-Hagen L, et al. Subacute subclinical brain infarctions after transcatheter aortic valve implantation negatively impact cognitive function in long-term follow-up. *PLoS One.* 2017;12:e0168852.
18. Auffret V, Campelo-Parada F, Regueiro A, et al. Serial changes in cognitive function following transcatheter aortic valve replacement. *J Am Coll Cardiol.* 2016;68:2129–2141.
19. Román GC, Erkinjuntti T, Wallin A, et al. Subcortical ischaemic vascular dementia. *Lancet Neurol.* 2002;1:426–436.
20. Knipp SC, Kahlert P, Jokisch D, et al. Cognitive function after transapical aortic valve implantation: a single-centre study with 3-month follow-up. *Interact Cardiovasc Thorac Surg.* 2013;16:116–122.
21. Lansky AJ, Schofer J, Tchetche D, et al. A prospective randomized evaluation of the TriGuard™ HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial. *Eur Heart J.* 2015;36:2070–2078.
22. Abawi M, de Vries R, Stella PR, et al. Evaluation of cognitive function following transcatheter aortic valve replacement. *Heart Lung Circ.* 2018;27:1454–1461.
23. Rodés-Cabau J, Dumont E, Boone RH, et al. Cerebral embolism following transcatheter aortic valve implantation: comparison of transfemoral and transapical approaches. *J Am Coll Cardiol.* 2011;57:18–28.
24. Tse L, Bowering JB, Schwarz SK, et al. Postoperative delirium following transcatheter aortic valve implantation: a historical cohort study. *Can J Anaesth.* 2015;62:22–30.
25. MacLullich AM, Beaglehole A, Hall RJ, et al. Delirium and long-term cognitive impairment. *Int Rev Psychiatry.* 2009;21:30–42.
26. Bernardi FLM, Ribeiro HB, Carvalho LA, et al. Direct transcatheter heart valve implantation versus implantation with balloon predilatation. Insights from the Brazilian transcatheter aortic valve replacement registry. *Circ Cardiovasc Interv*. 2016;9:e003605.
27. Seeger J, Kapadia SR, Kodali S, et al. Rate of peri-procedural stroke observed with cerebral embolic protection during transcatheter aortic valve replacement: a patient-level propensity-matched analysis. *Eur Heart J.* 2019;40:1334–1340.
28. Teitelbaum M, Kotronias RA, Sposato LA, et al. Cerebral embolic protection in TAVI: friend or foe. *Interv Cardiol.* 2019;14:22–25.
29. Bagur R, Solo K, Alghofaili S, et al. Cerebral embolic protection devices during transcatheter aortic valve implantation: systematic review and meta-analysis. *Stroke.* 2017;48:1306–1315.
30. Rodés-Cabau J, Kahlert P, Neumann FJ, et al. Feasibility and exploratory efficacy evaluation of the Embrella Embolic Deflector system for the prevention of cerebral emboli in patients undergoing transcatheter aortic valve replacement: the PROTAVI-C pilot study. *JACC Cardiovasc Interv.* 2014;7:1146–1155.
31. Gruhn N, Larsen FS, Boesgaard S, et al. Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. *Stroke.* 2001;32:2530–2533.
32. Huang CC, Chen YH, Lin MS, et al. Association of the recovery of objective abnormal cerebral perfusion with neurocognitive improvement after carotid revascularization. *J Am Coll Cardiol.* 2013;61:2503–2509.


 