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THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Imaging and Functional Testing to Assess Clinical and Subclinical Neurological Events After Transcatheter or Surgical Aortic Valve Replacement

A Comprehensive Review

Marco Spaziano, MD,* Dominic P. Francese, MPH,† Martin B. Leon, MD,†‡ Philippe Généreux, MD*†‡

ABSTRACT

Neurological events after transcatheter (TAVR) or surgical aortic valve replacement (SAVR) are potentially devastating and associated with a poor prognosis. With technological improvements and increased operator experience, their incidence is markedly declining, justifying the need for surrogate endpoints to be used in future comparative trials. Moreover, imaging studies after TAVR and SAVR suggest that neurological events are mainly embolic in nature; however, there is significant discrepancy between imaging findings and clinically overt symptoms, raising the possibility of more subtle subclinical cognitive decline. Different modalities have been used to assess both overt and subclinical neurological events after SAVR and TAVR. The purpose of this report is to systematically review and describe currently used imaging, functional, and neurocognitive testing modalities and to better understand how they could be integrated in future prospective studies. (J Am Coll Cardiol 2014;64:1950–63) © 2014 by the American College of Cardiology Foundation.

Transcatheter aortic valve replacement (TAVR) has emerged as a full-fledged therapeutic alternative for patients with severe aortic stenosis. After the publication of the PARTNER (Placement of Aortic Transcatheter Valves) trial, the main concern was the occurrence of post-procedural stroke or transient ischemic attack (TIA), with reported incidences ranging from 5.5% in high-risk patients (Cohort A) to 6.7% in inoperable patients (Cohort B) at 30 days (1,2). By comparison, the 30-day rate of stroke or TIA after surgical aortic valve replacement (SAVR) was reported at 2.4% in PARTNER Cohort A and 1.7% in the medical treatment group of PARTNER Cohort B. As expected in this very fragile population, the prognosis after major stroke is dismal (3–5).

However, recent reports have shown that stroke rates are decreasing, with in-hospital reported incidences now as low as 2% in certain registries (6). Additionally, the recently published CoreValve High-Risk cohort trial, which compared the CoreValve transcatheter heart valve (Medtronic, Minneapolis, Minnesota) to SAVR in a high-risk but operable population, demonstrated a lower rate of major stroke with TAVR (5.8%) compared with SAVR (7.0%) at 1 year (7). Reasons for this progressive drop in neurological events (NE) in the TAVR population can be attributed to multiple factors such as technological

From the *Hôpital du Sacré-Coeur de Montréal, Montréal, Québec, Canada; †Cardiovascular Research Foundation, New York, New York; and the ‡Columbia University Medical Center/New York-Presbyterian Hospital, New York, New York. Dr. Leon has received travel reimbursements from Edwards Lifesciences related to his activities as an unpaid member of the PARTNER Executive Committee. Dr. Généreux has received speaker's fees from Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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advances, increased operator experience, and better patient selection. Although more definitive large-scale prospective studies are needed, continued decreases in NE rates might also be expected with the use of neurological embolic protection devices (8). By contrast, using detailed and systematic post-operative neurological evaluation, a recently published registry of nearly 200 patients undergoing SAVR demonstrated a rate of 17% for clinically significant stroke, higher than previously reported (9). Together, these findings underline the importance of standardized post-procedural neurological evaluation and appropriate imaging testing if fair and meaningful comparisons between interventions are to be performed.

CLINICAL AND SUBCLINICAL NE. Several mechanisms for the occurrence of post-procedural NE have been suggested. Initial diffusion-weighted magnetic resonance imaging (DW-MRI) reports showed multiple and diffuse lesions appearing after TAVR, leading to the currently accepted hypothesis of embolization as the probable etiology (10,11). Among others, Van Mieghem et al. (12) confirmed the solid nature of embolic debris captured during TAVR procedures using a cerebral protection device.

Importantly, there is manifest discordance between the incidence of cerebral emboli and that of clinically significant events. Indeed, the majority of patients display new, apparently asymptomatic, cerebral lesions after TAVR. However, whether these cerebral microinfarcts cause long-term cognitive and behavioral changes is largely unknown. Whether these changes can be predicted by periprocedural imaging modalities, such as DW-MRI and transcranial Doppler (TCD), is also unknown. Various neurocognitive tests have also been utilized to describe medium-term and long-term outcomes.

The purpose of this review is to explore how TCD, DW-MRI, and neurocognitive tests have been used to assess stroke and neurocognitive changes in both TAVR and SAVR, and how they should be integrated as surrogate endpoints of NE in future research.

TRANSCRANIAL DOPPLER

DESCRIPTION. This test looks for high-intensity "chirps" in the Doppler signal of an intracranial artery (usually the middle cerebral artery). Examples are displayed in **Figure 1**. The tracings are obtained with ultrasound transducers attached to a patient's head bitemporally over the preauricular transcranial "window."

SURGICAL AORTIC VALVE REPLACEMENT. A total of 22 reports investigating TCD in SAVR were published between 1994 and 2012 (**Table 1**) (13–34). Although 1,732 patients were studied, only 165 underwent biological SAVR. Studies report either the incidence or absolute count of high-intensity transient signals (HITS) per patient.

Hypotheses concerning the nature of HITS detected by TCD include: 1) solid microemboli of thrombotic origin; 2) cavitation or gaseous bubbles; and 3) artifacts. Various algorithms have been implemented in Doppler equipment in order to help discriminate the nature of the signals and to eliminate artifacts, but their validity has never been confirmed, either histologically or pathologically (33).

One of the main limitations of studies involving TCD is heterogeneity in the timing of recording. In all but 3 studies where TCD was done during surgery (16,28,32), the reported time of recording ranged from 4 h to 12 years after SAVR, reflecting more acute, subacute, and long-term prosthesis embolic potential, rather than procedural risk.

In one of the studies using TCD during surgery, the use of an intra-aortic filter device to reduce NE was compared with placebo in 24 patients (28). Investigators found more HITS in patients who received the filter (385.5 HITS) compared with those who did not (99 HITS). There were no clinical strokes or TIAs, and both DW-MRI and neuropsychological studies were similar before and after surgery in both groups. Electron microscopy of the retrieved material from the filter showed that all but 1 particle were <1 mm, and 75% contained atheromatous material, 25% contained platelet-fibrin, and 25% contained thrombus.

Most importantly, NE were rare in these studies, and there was no relationship between HITS and occurrence of stroke or TIA (21,26,27,31). Keeping in mind the small sample sizes, these studies may suggest that, despite a significant number of HITS, patients may experience no significant clinical events and display normal DW-MRI and neuropsychological studies.

TRANSCATHETER AORTIC VALVE REPLACEMENT. A total of 6 reports (5 peer-reviewed articles and 1 abstract) were published between 2011 and 2012 where TCD was used to evaluate NE after TAVR (**Table 1**) (35–40). Studies were small, enrolling between 21 and 83 patients.

Contrary to most SAVR studies, in all of these reports, TCD was done during the procedure, allowing analysis of HITS during different phases of aortic valve manipulation. All patients presented HITS during TAVR. Interestingly, there seems to be

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

DW-MRI = diffusion-weighted magnetic resonance imaging

HITS = high-intensity transient signals

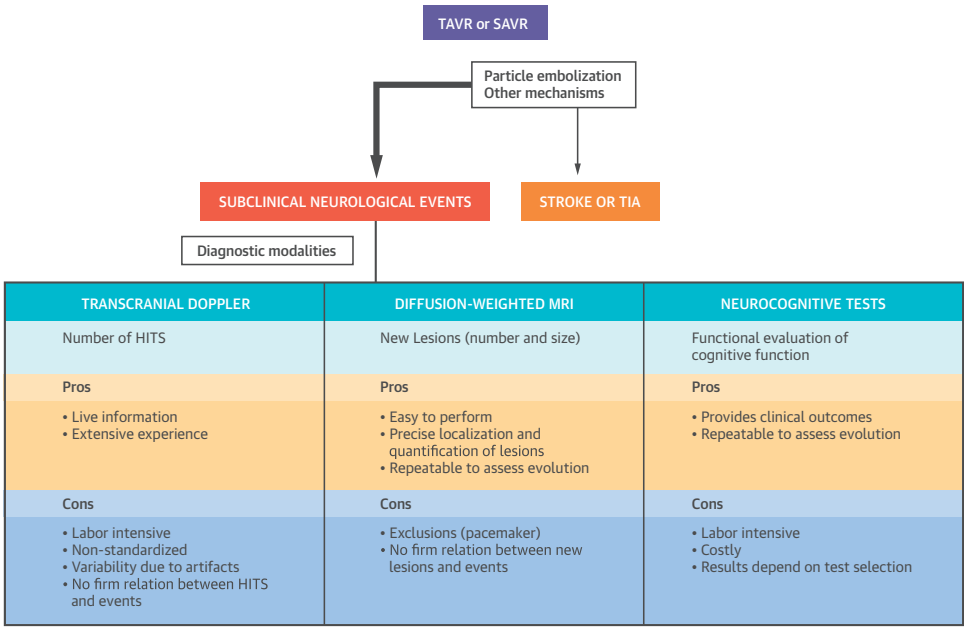
NE = neurological events

SAVR = surgical aortic valve replacement

TAVR = transcatheter aortic valve replacement

TCD = transcranial Doppler

TIA = transient ischemic attack



Spaziano, M., et al., J Am Coll Cardiol. 2014; 64(18):1950–63.

CENTRAL ILLUSTRATION Imaging and Functional Assessment of NE After TAVR or SAVR

Neurological events (NE) after transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR) are mainly due to particle embolization during or soon after the procedure. Subclinical neurological events, in contrast to stroke or TIA, are frequent during TAVR or SAVR procedures. Current modalities to detect and assess subclinical neurological events include transcranial Doppler, diffusion-weighted MRI, and neurocognitive testing. HITS = high-intensity transient signals; MRI = magnetic resonance imaging; TIA = transient ischemic attack.

significant variability in the number of recorded HITS between studies, even when stratifying results by prosthesis type and access site. For example, transfemoral TAVR using the SAPIEN valve (Edwards Lifesciences, Irvine, California) generated an average of 674 HITS in one study, but only 375 in another (35,37). This discrepancy may relate to procedural characteristics, duration of TCD

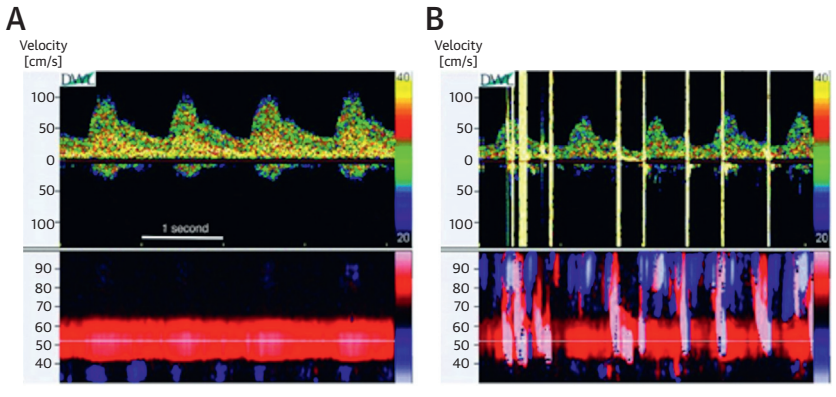


FIGURE 1 TCD Reading During TAVR

No high-intensity transient signals were observed at rest **(A)**, whereas several signals were monitored during valve deployment **(B)**. Reproduced with permission from Kahlert et al. (52). TAVR = transcatheter aortic valve replacement; TCD = transcranial Doppler.

recordings, or artifact-elimination algorithms. The procedure segments that yielded the most HITS were valve positioning and deployment.

Clinical events were rare in all these studies, with stroke incidence ranging from 0% to 4.5%, similar to SAVR studies involving TCD assessment. Most importantly, no relationship between HITS and NE was established.

COMPARATIVE STUDIES: TAVR VERSUS SAVR. Two abstracts compared TAVR and SAVR in terms of HITS (**Table 1**) (41,42). In a nonrandomized study, Alassar et al. (41) showed significantly fewer HITS during TAVR than SAVR (most HITS occurred coming off cardiopulmonary bypass) in a total of 60 patients ($p = 0.04$). There was 1 clinical stroke in each group.

Similarly, Kempfert et al. (42) reported significantly fewer HITS in the transapical TAVR group compared with the transfemoral TAVR and the SAVR groups. Interestingly, this study compared TCD with DW-MRI findings. Although transapical TAVR patients presented the fewest HITS, one-half presented new DW-MRI lesions; this was true for only 29% of SAVR patients. Despite the high rate of DW-MRI findings, no significant differences in neurocognitive outcomes were found between groups using the Trail Making, Pegboard, and verbal learning tests.

Table 2 summarizes the advantages and limitations of TCD for assessment of neurological outcomes after TAVR and SAVR.

DIFFUSION-WEIGHTED MAGNETIC RESONANCE IMAGING

DESCRIPTION. DW-MRI allows diffusion of molecules (mainly water) to be mapped in biological tissues. When applied to the brain, locations of acute ischemia, where the water diffusion rate is low, appear brighter than surrounding tissues.

SURGICAL AORTIC VALVE REPLACEMENT. Three reports were published between 2004 and 2006 using DW-MRI as the main endpoint (**Table 3**) (43–45). Although new DW-MRI lesions were found in 38% to 47% of patients undergoing SAVR, the stroke rate was between 0% and 9%. Knipp et al. (44) reported and compared DW-MRI findings with 11 neuropsychological tests in 30 patients undergoing SAVR. Although there were no clinical strokes, there was significant decline in 5 of 13 neurocognitive tests at 5 days, with a return to baseline at 4 months. Interestingly, no correlation was found between new lesions and impaired neurocognitive function at 5 days. Finally, Floyd et al. (45) reported no definitive correlation between lesion size or number and stroke. None of the studies explored whether new DW-MRI lesions persist over time.

TRANSCATHETER AORTIC VALVE REPLACEMENT. A total of 7 reports (5 peer-reviewed articles, 2 abstracts) using DW-MRI as an endpoint have been published (**Table 3**) (10,46–51). Studies were relatively small, enrolling between 12 and 61 TAVR patients. Of note, the main issue with DW-MRI after TAVR is the exclusion of at least one-third of patients in all studies because of either post-procedural instability or the need for a permanent pacemaker.

Observational studies showed that more than two-thirds of patients undergoing TAVR present with new DW-MRI lesions, mostly multiple and dispersed, suggesting an embolic pattern (10,47,48,50–56). In only 2 abstracts was the proportion of patients with new lesions less elevated (46,49). **Figure 2** displays typical DW-MRI findings after TAVR.

Although most patients displayed new ischemic lesions, clinical strokes were rare in these observational studies, with rates ranging from 0% to 6.5%. Only 1 study established a relationship between MRI lesions and NE: Fairbairn et al. (50) suggested that stroke might be associated with a greater number and volume of lesions. However, given that it is on the basis of only 2 clinical events, this conclusion should be treated with circumspection.

COMPARATIVE STUDIES: TAVR VERSUS SAVR. Five studies compared TAVR patients with SAVR controls, either concomitant or historical (**Table 3**) (52–56). Because these were nonrandomized studies, there were marked differences in patient age and baseline characteristics (EuroSCORE), with SAVR patients being at significantly lower risk. In all studies, more TAVR patients showed new DW-MRI lesions than SAVR patients. Lesions in TAVR patients were more often larger in volume than in SAVR patients; however, clinical strokes were rare, ranging from 0% to 4.4% in TAVR patients and between 0% and 4.8% in SAVR groups. No relationship between number or size of MRI lesions and clinical events was made in any of these comparative reports. In 2 studies where DW-MRI was done again at 3 or 6 months, 80% of lesions showed no residual signal change in one (52) and completely resolved in the other (56), with either procedure.

In brief, after SAVR or TAVR, a significant proportion of patients develop presumably embolic cerebral lesions, which may regress with time. No significant relationship has been established between these findings and clinical events. The pros and cons of DW-MRI use in this setting are described in **Table 2**.

TABLE 1 Selected Publications Reporting the Use of TCD in SAVR and TAVR

First Author (Ref. #)	Year	n	Procedure	Age (yrs)	Outcomes	Timing	Duration of TCD Reading (Min)	Main Findings
SAVR studies								
Grosset et al. (13)	1994	64	a) mAVR: 50 b) bAVR: 14	a) 62 b) 63	HITS incidence	1 week–12 yrs	2 min per site (carotid, vertebral)	a) 88% had HITS b) 14% ($p < 0.01$) More HITS in carotid artery vs. vertebral More HITS in patients with 2 vs. 1 prostheses
Müller et al. (14)	1994	100	mAVR, mMVR, mMVR+AVR	NA	HITS incidence	<3 weeks (n = 50), >3 months (n = 50)	10	66% had HITS at <3 weeks, 42% at >3 months
Brækken et al. (15)	1995	92	mAVR	64	HITS incidence	2–4 d (n = 36), 1 yr (n = 34), 5 yrs (n = 22)	30	77.8% had HITS 2–4 d, 91.2% at 1 yr, 95.5% at 5 yrs
Georgiadis et al. (16)	1996	19	mAVR (n = 2), healthy volunteers (n = 5), patients with potential embolic sources (n = 12)	NA	Total HITS count	During AVR	30	862 HITS (2 patients undergoing mAVR)
Nötzold et al. (17)	1997	29	a) Ross procedure: 8 b) mAVR: 9 c) control: 12	a) 51 b) 67 c) 22	HITS incidence	a) 18.8 weeks b) 152.8 weeks	60	a) 2 of 8 had HITS b) 9 of 9 c) 0 of 12
Georgiadis et al. (18)	1997	123	mAVR, mMVR, mMVR+AVR	63	HITS incidence	17 months	45	>48% had HITS
Kaps et al. (19)	1997	5	mAVR	58–75	Median HITS count	8 months–5 yrs	30	Median HITS count: 9 per 30 min
Lievense et al. (20)	1998	60	a) mAVR: 20 b) Homograft AVR: 20 c) Control: 20	a) 59 b) 48 c) 40	HITS incidence, total HITS count	a) 4.3 yrs b) 8.1 yrs	30	a) 16 of 20 had HITS b) 8 of 20 c) 1 More HITS in mAVR (n = 13) vs. homograft (n = 3)
Sliwka et al. (21)	1998	580	a) mAVR: 515 b) bAVR: 65	62	Median HITS count, HITS incidence	15 ± 1 month	30	a) 70.3% had HITS b) 26.2% Higher HITS count in mAVR (6 vs. 0) Higher HITS count in patients with 2 prostheses vs. 1 11.4% had neurological event at a median of 37 ± 5 months No difference in HITS counts or incidence between those with and those without neurological events
Georgiadis et al. (22)	1998	10	mAVR, mMVR, mMVR+SAVR	38	Median HITS count at CCA vs. MCA/ACA	18 ± 2 months	30	112 HITS at CCA; 30 HITS at MCA/ACA
Geiser et al. (23)	1998	52	a) mAVR, mMVR, mMVR+SAVR: 26 b) Control: 26	a) 62 b) NA	Median HITS count, HITS incidence	5.2 ± 4.6 yrs	30	a) 81% had HITS b) 0% Median HITS count: 24 Significantly more HITS in patients with previous neurological events than those without
Milano et al. (24)	1999	83	mAVR, mMVR, mMVR+SAVR, bAVR, homograft, mitral valve repair	NA	HITS incidence, HITS incidence rate	Discharge, 3 months, 1 yr	30	85% mechanical prosthesis had HITS; 10% biological prosthesis; 0% homograft/mitral repair 55 ± 79 HITS/h
Baumgartner et al. (25)	2001	15	mAVR, mMVR, mMVR+SAVR	52	Median HITS count	Post-op	30	Median: 20 HITS
Stefani et al. (26)	2002	47	mAVR, mMVR	NA	HITS incidence, total HITS count	≥6 months	45	38.3% had HITS Those with lower INR had more HITS ($p < 0.01$) No difference in HITS between AVR and MVR 5 focal neurological deficits >6 months in mAVR; no association with HITS
Kofidis et al. (27)	2002	52	a) Sorin mAVR: 22 b) Tekna mAVR: 20 c) Control: 10	a) 58 b) 54 c) 52	HITS incidence rate, HITS incidence	Post-op	NA	a) 14 of 22 had HITS; 16.4 ± 19 HITS/h; 5 TIA/PRIND b) 15 of 20 had HITS; 14.4 ± 24 HITS/h; 7 TIA/PRIND + 1 stroke c) 0 of 10 had HITS; 0; 0 events No correlation between HITS and clinical events

Continued on the next page

TABLE 1 Continued

First Author (Ref. #)	Year	n	Procedure	Age (yrs)	Outcomes	Timing	Duration of TCD Reading (Min)	Main Findings
Eifert et al. (28)	2003	24	CABG (n = 17); SAVR (n = 4); CABG+SAVR (n = 3) Aortic filter in 12 of 24	Filter: 64 No filter: 61	Total HITS count, DW-MRI, neuropsy, electron microscopy	TCD: during AVR, others: pre-op, 5-7 d	NA	More HITS with filter (385.5) than without (99) (p = NS) All particles retrieved from filter smaller than 1 mm, but 1 of 4.5 mm; 75% atheromatous material, 25% platelet-fibrin, 25% thrombus DW-MRI: no new lesions post-op No clinical strokes, no change in cognitive performance
Laas et al. (29)	2003	30	mAVR: a) Bileaflet: 20 b) Tilting disc: 10	58–78	HITS incidence rate	≥9 months	30	a) 32–108 HITS/h b) 0.2 HITS/h
Uekermann et al. (30)	2005	40	mAVR	62	Median HITS count, neuropsy	5.3 yrs	30	Patients divided into HITS-high and HITS-low groups according to median HITS-high scored lower on verbal memory and showed executive deficits Patients showed verbal and visual memory deficits compared with controls
Warnecke et al. (31)	2006	150	mAVR	62	Total HITS count	3–36 months	NA	Linear association between valve size and HITS count No strokes, 8 TIAs with no correlation with HITS or valve size
Schönburg et al. (32)	2006	41	SAVR DBT in 22 of 41	DBT: 59 No DBT: 58	Total HITS count	during AVR	66	DBT significantly reduced absolute number of HITS during CPB + crossclamp, but not after aorta is unclamped No strokes
Guerrieri Wolf et al. (33)	2008	60	a) mAVR: 30 b) bAVR: 30	a) 55 b) 71	HITS incidence, discriminated (solid vs. gaseous)	Pre-op, 5 d, 3 months	30	Pre-op: a) 6 of 30 had gaseous HITS; b) 6 of 30 5 d: a) 29 of 30 had HITS, 24 of 29 solid; b) 21 of 30, 12 of 21 solid 3 months: a) 29 of 30 had HITS, 28 of 29 solid; b) 18 of 30 HITS, 4 of 18 solid
Al-Atassi et al. (34)	2012	56	bAVR	72	HITS incidence, biomarkers (PFA, P-selectin)	4 h, 1 month	30	At 4 h: a) 68% had HITS b) 82% 1 month: a) 46% had HITS; b) 43% All p values >0.05 No strokes; no difference in biomarkers between groups

Continued on the next page

NEUROCOGNITIVE TESTING

DESCRIPTION. Neurocognitive tests are heterogeneous and meant to evaluate higher-order cerebral functions such as memory, learning, attention, and language skills. Some tests are specific to 1 function, whereas others are integrative. Simple tests may be performed at the bedside by the clinician, but more complex tests may require a neuropsychologist's expertise. A brief profile of each neurocognitive test described in this review is displayed in **Table 4**.

SURGICAL AORTIC VALVE REPLACEMENT. A total of 6 studies report neurocognitive outcomes after SAVR as their primary endpoint (**Table 5**) (57–62).

An Austrian group published a series of 4 papers between 2002 and 2012 using auditory evoked potentials as the main neurocognitive outcome (58–61). This highly reproducible test consists of objective measurements related to information processing, allowing quantification of cognitive brain dysfunction. Their first study showed impaired cognition at 7 days compared with baseline in 2 groups of 30 patients undergoing either biological SAVR or coronary artery bypass grafting (CABG) (58). Interestingly, the CABG group returned to baseline at 4 months, but the SAVR group showed progressive cognitive decline. The Mini-Mental State Examination and the Trail Making Test showed no difference between groups, indicating lower discrimination.

TABLE 1 Continued

First Author (Ref. #)	Year	n	Procedure	Age (yrs)	Outcomes	Timing	Duration of TCD Reading (Min)	Main Findings
TAVR studies								
Brinkman et al. (35)	2011	42	a) TF-TAVR: 21 b) TA-TAVR: 21	NA	Total HITS count	During TAVR	NA	Total HITS count : a) 674; b) 542 ($p = 0.1$) Valve-related manipulations generated more HITS than BAV-related manipulations
Drews et al. (36)	2011	50	TA-TAVR (ES)	80	Total HITS count, divided in HITS and MES	During TAVR	122 min	Total HITS count: 730 ± 1,717, detected in all patients Total MES: 140 ± 327, detected in all patients; most of the MES were recorded during valvuloplasty and positioning of the prosthetic valve in the aortic position No clinical strokes
Szeto et al. (37)	2011	28	a) TF-TAVR: 18 (ES) b) TA-TAVR: 10 (ES)	a) 85 b) 81	Total HITS count	During TAVR	NA	Total HITS count: a) 375; b) 440 ($p = 0.58$) Most HITS during wire manipulation in the aortic arch and during valve insertion
Erdoes et al. (38)	2012	44	a) TF-TAVR: 32 (ES/CV) b) TA-TAVR: 12 (ES)	a) 79 b) 74	Median HITS count, neuropsy	During TAVR, neuropsy: 1 dat, 4-6 days	75 ± 18 a) 67 b) 83	Median HITS: 548 Most HITS during valve deployment, regardless of access site or valve type More HITS with CV than ES ($p = 0.024$) 2 clinical strokes within 2 weeks, no change on neuropsy score
Kahlert et al. (39)	2012	83	a) TF-TAVR: 32 (CV) b) TF-TAVR: 26 (ES) c) TA-TAVR: 25 (ES)	a) 80 b) 83 c) 80	Total HITS count, neuropsy	Pre-procedure, during TAVR, 3 months	30 min (pre-op, 3 months)	Total HITS count: 528.7 Most HITS during valve positioning (ES > CV) and implantation (CV > ES) No difference in total HITS between ES and CV, or between TF and TA No HITS at baseline or at 3 months Mean transaortic gradient is a predictor of more HITS 2 clinical strokes total
Reinsfelt et al. (40)	2012	21	TF-TAVR (CV)	81	Total HITS count, biomarker (S100β)	During TAVR	NA	Total HITS count: 282 (mean) Timing of HITS: 37% during manipulation of the aortic arch/root/valve by guidewires and catheters, 22% after balloon dilatation of the native valve, 41% during frame expansion of the valve prosthesis Positive correlation ($r = 0.68$) between HITS count and AUC of biomarker No clinical strokes
Comparative studies								
Kempfert et al. (42)	2010	121	a) TF-TAVR: 44 (CV) b) TA-TAVR: 50 (ES) c) SAVR: 27	a) 80 b) 82 c) 82	DW-MRI, total HITS count, neuropsy	NA	NA	Least HITS in TA group, TF and SAVR had similar HITS New MRI lesions: a) 59%; b) 50%; c) 29% No difference in neurocognitive outcomes between groups Strokes: a) 1 of 44; b) 0 of 50; c) 1 of 27
Alassar et al. (41)	2013	60	a) TAVR: 46 b) SAVR: 14	NA	Median HITS count	a) During TAVR b) During SAVR	NA	Median HITS: a) 168; b) 244 ($p = 0.04$) During TAVR, most HITS during valve implantation During SAVR, most HITS during coming off CPB Strokes: a) 1 of 46; b) 1 of 14

Values are mean unless otherwise indicated.

ACA = anterior cerebral artery; AUC = area under the curve; BAV = balloon aortic valvuloplasty; bAVR = surgical aortic valve replacement with bioprosthesis; CABG = coronary artery bypass graft; CCA = common carotid artery; CPB = cardiopulmonary bypass; CV = Medtronic CoreValve; DBT = dynamic bubble trap; DW-MRI = diffusion-weighted magnetic resonance imaging; ES = Edwards SAPIEN; HITS = high-intensity transient signals; INR = international normalized ratio; mAVR = surgical aortic valve replacement with mechanical prosthesis; MCA = middle cerebral artery; MES = microembolic signals; mMVR = surgical mitral valve replacement using mechanical prosthesis; NA = not available; neuropsy = neuropsychological testing; PFA = platelet function analysis; PRIND = prolonged reversible ischemic neurological deficit; SAVR = surgical aortic valve replacement; TA = transapical; TAVR = transcatheter aortic valve replacement; TCD = transcranial Doppler; TF = transfemoral; TIA = transient ischemic attack.

Their next study compared mechanical versus biological SAVR in 82 patients (59). Cognitive dysfunction was found at 7 days in both groups, but the mechanical SAVR group returned to normal at 4 months, whereas the biological SAVR group showed progressive decline. Return to baseline values in mechanical SAVR patients at 3 years was confirmed in another of their studies (60).

In brief, these findings suggest that auditory evoked potential testing may be a more refined tool to detect subtle cognitive decline after SAVR. Reasons for the decline in patients undergoing biological SAVR compared to mechanical SAVR remain to be explored, but may relate to the age of patients or to the presence of vascular disease and other comorbidities.

TRANSCATHETER AORTIC VALVE REPLACEMENT. Only 1 study and 1 abstract using neurocognitive tests as their primary endpoint in TAVR patients were published (**Table 5**) (63,64). These studies are larger, more recent, and have longer clinical follow-ups than previously mentioned studies using imaging modalities.

Ghanem et al. (63) followed 111 patients for at least 1 year after TAVR. Patients underwent the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at 3 days, 4 months, 1 year, and 2 years after the procedure. DW-MRI was also done at 3 days. Again, although nearly two-thirds of patients showed new cerebral lesions on DW-MRI, there were no early clinical strokes. The Repeatable Battery for the Assessment of Neuropsychological Status showed new-onset cognitive dysfunction at 3 days in 6 patients, which persisted at 3 months or more in 3 patients. Most importantly, cerebral embolism detected by DW-MRI was not a predictor of cognitive dysfunction in this study.

The relatively low incidence of cognitive decline in this study has been criticized (65). Deterioration of cognition may be underestimated because of reliance on a global score after an injury that likely results in patchy deficits, and because of a floor effect (i.e., little room for deterioration as patients are already within impairment range at baseline), among others. These deficits may be palliated by tests assessing coordinated integration of multiple cortical regions.

COMPARATIVE STUDIES: TAVR VERSUS SAVR. Two studies compared SAVR with TAVR in terms of neurocognitive function (**Table 5**) (66,67). The first used the Syndrom Kurz Test and the Alzheimer's Disease Assessment Scale at 3 days after the index procedure (66). Because this study was nonrandomized, patients undergoing TAVR were significantly older and had a significantly higher EuroSCORE than those undergoing SAVR. Results showed significant cognitive decline in both groups at 3 days, with no difference between groups, but a trend in favor of TAVR ($p = 0.1$).

Knipp et al. (67) reported a high incidence of cognitive decline in their TAVR group, using integrative tests. At discharge (mean 10.7 days), 4 of 22 patients (18%) presented cognitive dysfunction, and 2 still had cognitive decline at 3 months. More than half of patients had new DW-MRI lesions, but there was no relationship between MRI findings and cognitive dysfunction. A nonrandomized control group of SAVR patients showed that close to one-half exhibited cognitive dysfunction at discharge that completely resolved by 3 months.

In summary, cognitive decline seems to occur after TAVR, but its incidence varies according to the clinical tool used to assess its presence. Although integrative tests may represent the best way to assess cognitive decline in this population, auditory evoked potentials, which made their mark in SAVR, were not used in any of the TAVR studies and may be an interesting avenue of future research. The strengths and weaknesses of neurocognitive testing in TAVR and SAVR are presented in **Table 2**.

TABLE 2 Advantages and Disadvantages of Neurological Testing Modalities Used to Assess Neurological Outcomes After SAVR and TAVR

Modality	Advantages	Disadvantages
Transcranial Doppler	Provides live information allowing the identification of potentially problematic segments of the procedure Has been used extensively in the surgical literature	Labor intensive Data analysis method has not been standardized Artifacts may increase variability between patients No consistent relationship has been shown between high-intensity transient signals and overt or subclinical events
Diffusion-weighted magnetic resonance imaging	Easy and relatively inexpensive Provides precise anatomical localization of neurological lesions Can be repeated in time to evaluate lesion evolution	Many patients excluded because of instability or pacemaker No consistent relationship has been shown between diffusion-weighted magnetic resonance imaging lesions and overt or subclinical events
Neurocognitive tests	Results represent the true clinical outcome of interest Can be repeated in time to evaluate deficit evolution	Results are highly dependent on test selection Labor intensive Costly if tests are performed by trained professionals

Abbreviations as in Table 1.

LIMITATIONS OF THE CURRENT LITERATURE, AND FUTURE PERSPECTIVES

Although robust definitions were proposed for clinically significant NE (68), proper diagnosis requires

TABLE 3 Selected Publications Reporting the Use of DW-MRI in SAVR and TAVR

First Author (Ref. #)	Year	n	Procedure	Age (yrs)	Outcomes	Timing	Main Findings
SAVR studies							
Stolz et al. (43)	2004	37	a) mAVR: 24 b) bAVR: 12	66	New DW-MRI lesion incidence, biomarkers (S100β, NSE)	Pre-op, 1-6 days	New MRI lesions in 14 of 37; 11 of 14 with >1 lesion 3 strokes, all in patients with lesions No association between biomarkers and DW-MRI lesions
Knipp et al. (44)	2005	30	SAVR (n = 24); MVR (n = 2); SAVR+MVR (n = 2); AVR+MV repair (n = 2)	65	New DW-MRI lesion incidence, neuropsy	Pre-op, 5 days, 4 months	New MRI lesions in 14 of 30, 10 of 14 with >1 lesions No clinical strokes, 1 clinically silent cerebellar infarct Decline in 5 of 13 neurocognitive tests at 5 days, return to baseline at 4 months No correlation between new lesions and impaired neurocognitive function at 5 days
Floyd et al. (45)	2006	34	a) SAVR: 6 b) SAVR + other: 9 c) MVR: 2 d) CABG: 13 e) MVR+CABG: 4	67	New DW-MRI lesion incidence	Pre-op, 6 ± 2 days	New MRI lesions: a) 2 of 6; b) 4 of 9; c) 0 of 2; d) 0 of 13; e) 0 of 4 3 clinical strokes: 2 in patients with lesions, 1 with no lesion No definitive correlation between lesion size/number and stroke Pre-op white matter lesion burden may predict new post-op lesion
TAVR studies							
Gasparetto et al. (46)	2010	29	TF-TAVR: 26 (CV); 3 (ES)	NA	New DW-MRI lesion incidence	Pre-TAVR, 3 days	20 of 29 had chronic asymptomatic lesions at baseline 17 of 29 underwent DW-MRI at 3 days 4 of 17 had new lesions, mostly multiple and dispersed No neurological impairment in 29 of 29
Ghanem et al. (10)	2010	30	TAVR: CV	79	New DW-MRI lesion incidence, biomarker (NSE)	Pre-TAVR, ≤3 days, 3 months	22 of 30 underwent DW-MRI 16 of 22 had new lesions, mostly multiple and dispersed 3 of 30 had a neurological event, 1 of which was permanent Biomarker did not correlate with new DW-MRI lesions
Maier et al. (47)	2010	46	TF-TAVR: CV	81	New DW-MRI lesion incidence	Pre-TAVR, ≤6 days	25 of 46 underwent DW-MRI 23 of 25 had new lesions, mostly multiple Strokes: 0 of 46
Rodés-Cabau et al. (48)	2011	60	a) TF-TAVR: 29 (ES) b) TA-TAVR: 31 (ES)	a) 84 b) 81	New DW-MRI lesion incidence	Pre-TAVR, ≤6 days	New MRI lesions: 41 of 60, lesions mostly multiple and dispersed No difference between TF and TA in lesion number and size Stroke at 24 h: a) 1 of 29; b) 1 of 31
Eder et al. (49)	2012	12	TAVR: CV	84	New DW-MRI lesion incidence, geriatric assessment	Pre-TAVR, ≤1yr	New lesions in 2of 12, clinically silent, not related to change in geriatric assessment 1 of 12 deteriorated, 1 of 12 improved on geriatric assessment at 1 yr
Fairbairn et al. (50)	2012	31	TAVR: CV	81	New DW-MRI lesion incidence, QoL scores	DW-MRI: pre-TAVR, 5 days QoL: pre-TAVR, 30 days	New MRI lesions: 24 of 31, lesions mostly multiple and dispersed Strokes: 2 of 31; stroke associated with greater number and volume of lesions Improvement in SF-12 physical; no change in SF-12 mental, EQ-5D, Visual Analog Scale
Ghanem et al. (51)	2013	61	TAVR: CV	80	New DW-MRI lesion incidence, biomarker (NSE), self-sufficiency, 1-yr survival	Pre-TAVR, 3 days	New MRI lesions: 28 of 39 Neurologic deficit: 4 of 61 Incidence of NSE increase: 29 of 59 Plasma levels of NSE and new MRI lesions not related to self-sufficiency or survival at 1 yr

Continued on the next page

systematic pre-procedural and post-procedural expert neurological assessment. This is often lacking in published studies and is impractical to implement prospectively in all clinical settings. More importantly, the declining rate of clinically detectable events makes any comparison, at least for future randomized trials (SAVR vs. TAVR, TAVR vs. TAVR), challenging.

Conversely, no real imaging and functional standardization of endpoints exists for the frequent, but most often subclinical, neurocognitive changes that may result from embolic events during SAVR or TAVR. It remains unclear whether TCD and DW-MRI are adequate surrogate endpoints for either overt or subclinical NE. Although TCD does seem to report cerebral embolic events and has the advantage of showing these "live" during the procedure, there is no firm relationship between HITS and clinical events. Another important issue for future comparative trials is that mechanical prostheses

TABLE 3 Continued

First Author (Ref. #)	Year	n	Procedure	Age (yrs)	Outcomes	Timing	Main Findings
Comparative studies							
Kahlert et al. (52)	2010	53	a) TAVR: 10 (CV); 22 (ES) b) Historical control: 21 (SAVR)	a) 80 b) 67	New DW-MRI lesion incidence, neuropsy (MMSE)	Pre-TAVR, 3.4 days, 3 months	New DW-MRI lesions: a) 27 of 32, lesions mostly multiple and dispersed; b) 10 of 21 ($p = 0.016$) Smaller volume of TAVR lesions than SAVR lesions ($p < 0.001$) No residual signal change at 3 months in 80% of lesions In-hospital stroke: a) 0 of 32; b) 1 of 21 MMSE unchanged at 3 months in TAVR group
Astarci et al. (53)	2011	48	a) TF-TAVR: 21 (ES) b) TA-TAVR: 14 (ES) c) SAVR: 13	a) 86 b) 83 c) 76	New DW-MRI lesion incidence	Pre-TAVR, 2 days	New MRI lesions: a) 19 of 21; b) 13 of 14; c) 1 of 13 In groups a) and b), lesions mostly multiple (mean number of lesions = 6), in group c) 1 new lesion ($p < 0.05$) Strokes: a) 0 of 21; b) 0 of 14; c) 0 of 13
Ensminger et al. (54)	2012	92	a) TAVR: 48 b) SAVR: 44	a) 81 b) 78	New DW-MRI lesion incidence, cerebral microbleeds	Pre-TAVR, <6 days	New MRI lesions: a) 30 of 48; b) 19 of 44 Strokes: a) 1 of 48; b) 0 of 44 Microbleeds: a) 6 of 48; b) 28 of 44
Uddin et al. (56)	2013	66	a) TAVR: 45 b) SAVR: 21	a) 80 b) 69	New DW-MRI lesion incidence	Pre-TAVR, <7 days, 6 months	New MRI lesions: a) 37 of 45; b) 10 of 21; higher lesion volume in a) than b) Strokes: a) 2 of 45; b) 0 of 21 At 6 months: New microinfarct: a) 1 of 17; b) 1 of 18, both subclinical; all previously detected lesions had completely resolved
Astarci et al. (55)	2013	77	a) TF-TAVR: 26 (ES) b) TA-TAVR: 18 (ES) c) BAV: 11 d) SAVR: 22	a) 86 b) 83 c) 83 d) 78	New DW-MRI lesion incidence	Pre-TAVR, ≤4 days	New MRI lesions: a) 24 of 26; b) 17 of 18; c) 3 of 11; d) 6 of 22; a) and b) vs. c) and d): $p < 0.0001$ More lesions and larger lesions in a) and b) vs. c) and d) ($p < 0.0001$) Strokes: a) 0 of 26; b) 1 of 18; c) 0 of 11; d) 0 of 22

Values are mean unless otherwise specified.

MMSE = Mini-Mental State Examination; NSE = neuron-specific enolase; QoL = quality of life; SF-12 = 12-item Short-Form Questionnaire; other abbreviations as in Table 1.

consistently generate more HITS than biological prostheses, potentially creating an uneven playing field for comparison between SAVR and TAVR in a low-risk population where mechanical prostheses are more likely to be chosen (Central Illustration).

By contrast, DW-MRI provides a more objective assessment of lesions after TAVR or SAVR. It is less labor-intensive and less costly than TCD or neurocognitive testing, and has the advantage of being repeatable to assess the evolution of lesions. However, although pathophysiologically plausible, it is unclear whether DW-MRI lesions translate into overt NE or cognitive dysfunction (Central Illustration).

Neurocognitive tests have the advantage of representing true clinical neurological decline; however, the incidence varies widely according to the type of test. Auditory evoked potential testing represents an interesting integrative test that remains objective, but has not yet been used in TAVR patients. Psychometric tests seem less useful to detect subtle cognitive decline and may be biased by long performance times, visual requirements (especially in elderly populations), and patient education levels. Finally, these tests can be fairly costly and time-consuming when executed by dedicated professionals (Central Illustration).

The lack of research comparing same-risk populations, especially lower-risk ones, is another

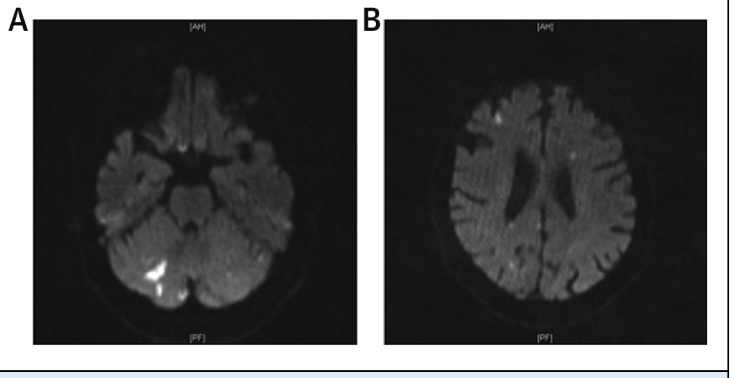


FIGURE 2 DW-MRI Findings After TAVR

Post-interventional diffusion-weighted magnetic resonance imaging (DW-MRI) of an 82-year-old female patient after successful transcatheter aortic valve replacement displaying 1 large (650 mm^3) and 2 smaller foci of restricted diffusion in the right lower cerebellar hemisphere **(A)** and multiple small foci dispersed in different territories **(A and B)**. Reproduced with permission from Kahlert et al. (52).

TABLE 4 Neurocognitive Tests

Test (Ref. #)	Description	Cognitive Functions Tested	Advantages	Disadvantages
Test Battery for Attention Performance (TAP) (28,44)	Computer software	Attention	No training required	License purchase; limited assessment of cognitive function
Wechsler Adult Intelligence Scale (30)	IQ test (paper/software)	Intelligence	No training required	Tests intelligence; not cognitive deficits
Trail Making Test (30,42,44,57–59)	Patient must connect circles respecting a certain sequence	Visual attention; task switching; motor skills	No training required; inexpensive	Limited assessment of cognitive function
Purdue Pegboard Test (42)	Pin placement test	Manual dexterity	No training required; inexpensive	Limited assessment of cognitive function
Confusion Assessment Method (38)	Subjective assessment by health professional	Presence of delirium	No training required; inexpensive	Subjective; cognitive deficits not specifically tested
Mini-Mental State Examination (MMSE) (39,52,58,59,63,67)	Widely used test for cognitive impairment	Orientation; attention; memory; language; complex commands; visual construction; calculation	No training required; inexpensive; integrative test	Poor sensitivity
Montreal Cognitive Assessment (MoCA) (39,64)	Test for mild cognitive impairment	Visuospatial; executive functions; language; memory; attention; abstraction; orientation	No training required; inexpensive; integrative test	Poor sensitivity
Verbal Learning Test (wordlist test) (44,67)	Patient must memorize new words	Verbal memory	Inexpensive	Limited assessment of cognitive function
Digit span subtest of Wechsler Adult Intelligence Scale (44,67)	Patient must repeat series of numbers	Attention; short-term memory; working memory	No training required; inexpensive	Limited assessment of cognitive function; part of a test battery
Corsi block-tapping test (44)	Patient must repeat a sequence of tapping identical blocks	Short-term memory; working memory	Inexpensive	Administered by neuropsychologist; part of a test battery
P300 auditory evoked potential (58–61)	Assessment of brain responses as patient is instructed to count occurrences of a specific sound	Stimulus evaluation; decision making	Good sensitivity	Administered by a neurologist/ neuropsychologist; resource intensive
Cognitive Failures Questionnaire (62)	Patient must answer a 25-item questionnaire	Perception; memory; motor function	No training required; inexpensive	Subjective
Digit Cancellation Test (62)	Patient must cross out identical numbers	Attention	Inexpensive	Administered by neuropsychologist; poor discrimination; part of a test battery
Regensburg Word Fluency Test (verbal fluency test) (62,67)	Patient must generate words starting with given letter	Verbal fluency	Inexpensive	Administered by neuropsychologist; poor discrimination; part of a test battery
Non-verbal learning test (62)	Patient must recognize symbols	Visual memory	Inexpensive	Administered by neuropsychologist; part of a test battery
Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (63)	Battery containing 12 subtests	Language; attention; visual and constructional skills; immediate memory; delayed memory	Integrative test	Administered by neuropsychologist
Syndrom Kurz Test and Alzheimer's Disease Assessment Scale (subtests) (62,66)	Battery containing 6 subtests	Working memory (visual/verbal); language; attention; delayed memory	Integrative test	Administered by neuropsychologist
Lawton Instrumental Activities of Daily Living Scale (IADL) (63)	Questionnaire containing 8 subscales	Independent living skills	No training required; inexpensive	Cognitive deficits not specifically tested

significant gap in current publications. As these studies become more common, insight will be gained concerning the strengths and limitations of each neurological testing modality according to the studied population. That being said, assessment of neurological complications after carotid endarterectomy or stenting faced similar challenges and is still a matter of debate. Although microembolization and new lesions are frequently detected, clinically significant NE are rare. DW-MRI, with quantification of number and size of lesions, better correlated with clinical events than TCD. Neurocognitive testing was more specific, but requires considerable resources (69).

In conclusion, given their increased sensitivity and relative ease of administration, and to gain further insight into the occurrence of NE, we believe that both TCD and DW-MRI should be used as effective surrogate endpoints for NE. When possible, they

TABLE 5 Selected Publications Reporting Use of Neurocognitive Testing in SAVR and TAVR

First Author (Ref. #)	Year	n	Procedure	Age (yrs)	Outcome Measure	Outcome Measure Timing	Main Findings
SAVR studies							
Nussmeler et al. (57)	1986	182	Valve replacement or repair, aneurysm resection, VSD closure a) 89 received thiopental during CPB b) 93 received standard anesthesia	a) 57 b) 55	Neuropsychiatric abnormalities incidence (orientation, affect, ideation, memory (recent and remote), Trail Making Test, neurological exam)	24 h, 10 days	Neuropsychiatric abnormalities at 24 h: a) 5.6%; b) 8.6% Neuropsychiatric abnormalities at 10 d: a) 0%; b) 7.5% Predictors of events: AVR, valvular calcifications, longer CPB, age ≥60 yrs
Zimpfer et al. (58)	2002	60	a) bAVR: 30 b) CABG: 30	a) 70 b) 70	P300 auditory evoked potentials, MMSE, Trail Making Test A	Pre-op, 7 days, 4 months	Impaired P300 at 7 d compared with pre-op in both groups ($p < 0.05$, no difference between groups) Return to normal of P300 at 4 months in group b); decline in P300 at 4 months in group a) ($p < 0.05$ between groups) MMSE and trail test: no difference between groups Strokes: a) 0 of 30; b) 0 of 30
Zimpfer et al. (59)	2003	82	a) bAVR: 53 b) mAVR: 29	a) 73 b) 58	P300 auditory evoked potentials, MMSE, Trail Making Test A	Pre-op, 7 days, 4 months	Impaired P300 at 7 d compared with pre-op in both groups ($p < 0.05$, no difference between groups) Return to normal of P300 at 4 months in group b); decline in P300 at 4 months in group a) ($p < 0.05$ between groups) MMSE and Trail Making Test: no difference between groups Strokes: a) 1 of 30; b) 0 of 30
Zimpfer et al. (60)	2006	60	a) mAVR: 32 b) control: 28	a) 51 b) 51	P300 auditory evoked potentials	Pre-op, 7 days, 4 months, 3 yrs	Impaired P300 at 7 d compared to pre-op in group a); no difference at 7 d in control Return to pre-op values at 4 months and 3 yrs Strokes: a) 0 of 32; b) 0 of 28
Fakin et al. (61)	2012	60	bAVR: mild hypothermic CPB (n = 30); normothermic CPB (n = 30)	a) 68 b) 66	P300 auditory evoked potentials, MMSE, Trail Making Test A	Pre-op, 7 days, 4 months	Impaired P300 at 7 d and at 4 months in both groups MMSE and Trail Making Test: no difference between groups Strokes: 0 of 60
Schwarz et al. (62)	2013	82	bAVR (67); mAVR (15)	69	Cognitive Failure Questionnaire assessed by family members, neuropsy	Pre-op, 3 months	Decline in all declarative memory function tests (p values <0.001–0.033) No change in Cognitive Failure Questionnaire
TAVR studies							
Ghanem et al. (63)	2013	111	TAVR: 95 (CV); 16 (ES) Embolic protection device in 20	80	RBANS, MMSE, frailty, QoL, IADL, mood, new DW-MRI lesion incidence	Pre-TAVR, 3 days, 3 months, 1 yr, 2 yrs (MRI only pre-op and 3 days)	Cognitive dysfunction at 3 d in 6 of 111 patients, persisting in 3 of 6 at follow-up Late-onset cognitive dysfunction (3 months, 1 yr, 2 yrs) in 4 of 111 DW-MRI done in 56 of 111; new DW-MRI lesions: 36 of 56 Age-predicted cognitive decline; new MRI lesions and embolic protection devices unrelated to cognitive decline Strokes: 1 of 111 (at 8 months)
Pelletier et al. (64)	2013	47	TAVR (ES)	81	Montreal Cognitive Assessment (MoCA)	Pre-TAVR, 6 months	No change in MOCA score at 6 months
Comparative studies							
Holinski et al. (66)	2013	100	a) SAVR: bAVR (n = 46); mAVR (n = 4) b) TF-TAVR: 50	a) 69 b) 80	6 scales from Syndrom Kurz Test and Alzheimer's Disease Assessment Scale	Pre-TAVR, 3 days	Significant cognitive decline at 3 d in both groups (p = 0.1 between groups, trend in favor of TAVR)
Knipp et al. (67)	2013	64	a) TA-TAVR: 27 (ES) b) SAVR: 37	a) 82 b) 68	Digit span test, wordlist test, verbal fluency test, MMSE, new DW-MRI lesion incidence	Pre-TAVR, pre-discharge (10.7 days), 3 months	Cognitive decline at discharge: a) 4 of 22, persistent in 2 of 4 at 3 months; b) 17 of 37, persistent in 0 of 17 at 3 months New-onset cognitive decline at 3 months: a) 3 of 18; b) 2 of 34 New MRI lesions: a) 7 of 12, lesions mostly multiple and dispersed; b) 12 of 35, lesions mostly multiple and dispersed No relationship between presence of MRI lesions and cognitive dysfunction Strokes: a) 1 of 27 (fatal); b) 1 of 37 (minor)

Values are mean unless otherwise specified.

IADL = Instrumental Activities of Daily Living; VSD = ventricular septal defect; other abbreviations as in Tables 1 and 3.

should be paired with appropriate neurological testing to detect subtler (but very important) neurocognitive decline post-TAVR or post-SAVR. Future research should focus on integrating imaging and neurocognitive testing to better identify future preventive or therapeutic strategies.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Philippe Généreux, Hôpital du Sacré-Coeur de Montréal, Université de Montréal, 5400 Boulevard Gouin Ouest, Montréal, Québec H4J 1C5, Canada. E-mail: pgenereux@crf.org.

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