Chapter 11
Cognitive Outcomes in Patients Undergoing Coronary Interventions and Transcatheter Aortic Valve Replacement

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11.1 Introduction

Non-focal neurological deficits are very common following cardiovascular procedures and are dreaded as independent predictors of morbidity and mortality (Maniar et al., 2016). Despite this, postoperative cognitive decline (POCD) is not reported systematically as a safety endpoint in cardiovascular interventional trials (Kappetein et al., 2012). Objectification and quantification of POCD is complicated, since deficits predominantly impair distinct domains (e.g., attention, psychomotor speed, and memory). However, POCD is often defined as a decrease of global cognitive function (e.g., >1 SD decline from baseline) after a cardiovascular intervention (Ghanem et al., 2010). Based on observational trials, the most conceivable mechanisms of cerebral injury and POCD are hemodynamic causes: cerebral embolism and hypoperfusion (Edmonds, 2000; Newman, Wilkinson, & Royse, 2014). However, neither embolization nor hypoperfusion demonstrate distinct morphological defects or functional deficits; therefore, a monocausal hemodynamic model for a very specific cognitive deficit profile is unlikely. Besides hemodynamics, further independent risk factors for mental impairment can be individual risk factors for cognitive decline.

Previously, we discussed the increasing risk of cerebral injury based on risk assessment of kidney injury criteria: *R*isk, *I*njury, *F*ailure, *L*oss, and *E*nd-stage disease (RIFLE; Ghanem, Naderi, Frerker, Nickenig, & Kuck, 2016). Most contributors of cerebral injury are in the subclinical risk and injury stage and therefore below clinical threshold. To depict this, we propose an "iceberg model of risk" (see Fig. 11.1). However, each RIFLE-criterion is independently associated with adverse

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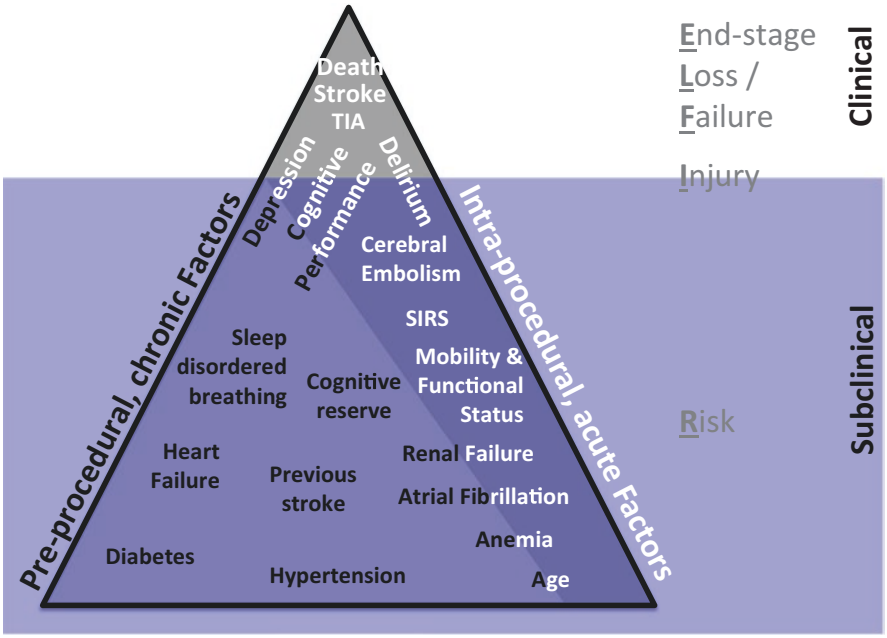

Fig. 11.1 Iceberg model of cognitive outcomes in the periprocedural context after TAVR. Cognitive outcomes are impacted by pre-, intra- and post-procedural factors in an interdependent and complex fashion. *TAVR* transcatheter aortic valve repair, *SIRS* systemic inflammatory response syndrome, *TIA* transitory ischemic attack

outcome and therefore of great clinical value, at least for renal injury. A different approach for the assessment of cognition is the time-dependent trajectory of performance with several variables (e.g., the procedure itself or consecutive hemodynamic alteration). This model is multifactorial and instructive, since an improvement of cognitive performance is also depicted, and quantified (Hogan, Shipolini, Brown, Hurley, & Cormack, 2013; Selnes et al., 2012). Both approaches integrate individual risk, pre-, intra- and post-procedural cerebral injury and their individual time courses, and are therefore valuable but abstract risk models. However, data on valid and independent risk factors of POCD after cardiovascular interventions are not available yet. Retrospectively, the available datasets from eligible studies did not address whether age, baseline cognitive function, prior stroke or transient ischemic attack (TIA), baseline cardiovascular disease severity, hypertension, diabetes, or depression modify the association between cardiovascular procedures and intermediate- or long-term cognitive outcomes in older adults. Furthermore, evidence exists linking chronic brain hypoperfusion induced by numerous cardiovascular disorders (e.g., atrial fibrillation, thrombotic events, hypertension, hypotension, heart failure, high serum markers of inflammation, coronary artery disease, low cardiac index, and valvular pathology) to the cognitive impairment preceding Alzheimer's disease (De La Torre, 2004). Hence, POCD holds a critical role and is an active target in

assessing postoperative recovery following cardiac interventions, as well as longer term outcomes and disease risks.

11.2 Coronary Interventions

Atherosclerosis is principally associated with an increased risk for silent stroke and cognitive impairment (Giele, Witkamp, Mali, & Van Der Graaf, 2004; Van Exel et al., 2002). As left heart catheterization and coronary angiography (CA) frequently lead to cerebral embolism, its impact on focal neurological deficits and cognitive performance are of utmost interest. Omran et al. (2003) found 22% of patients undergoing a retrograde catheterization of the aortic valve present with focal diffusion-weighted imaging (DWI) abnormalities in a pattern consistent with acute cerebral emboli. Three percent of these patients demonstrated focal neurological deficits. Patients without transvalvular passage were without evidence of cerebral embolisms (Omran et al., 2003). In contrast, in a later study of 46 patients with aortic valve stenosis undergoing CA including transvalvular passage, the incidence of new ischemic lesions was 2.2% and no patients presented with focal deficits (Hamon et al., 2006). Hamon et al. (2012) reported no significant impact of access route (femoral vs. radial) on the incidence of cerebral embolism. Putting this finding into perspective, Jurga et al. (2016) collected Montreal Cognitive Assessment (MoCA) test results and monitored intraoperative cerebral emboli by transcranial Doppler. The MoCA screening results were not significantly altered following the procedure, nor were there any significant correlations between MoCA change from pre- to postoperative recovery and the number of cerebral microemboli or any association with surgical access site. However, one-third of the patients presented with mild cognitive impairment with a baseline MoCA result <26 (Jurga et al., 2016).

With respect to focal neurological deficits related to percutaneous coronary intervention (PCI), Hoffmann, Altiok, Reith, and Brehmer (2014) elaborated on the neuroimaging patterns, ischemic mechanisms, and functional outcomes of ischemic strokes over a 16-year period. Infarctions were subclassified by radiological pattern and arterial territory as embolic, small subcortical, or hemodynamic. Modified Rankin Scale scores were used to assess functional outcome at 3 and 6 months and while PCI-stroke was radiologically confirmed in 35 patients, 91% of the strokes were of embolic pattern (9% subcortical). No watershed strokes were identified, although almost one-fifth of the patients experienced periprocedural hypotension. Functional outcomes among survivors of PCI-stroke were typically favorable in those who had single rather than multiple vascular territory involvement (Hoffmann et al., 2014). Concerning cognition, the Tilburg Health Outcome Registry of Emotional Stress after Coronary Intervention (THORESCI) study investigated 384 patients undergoing PCI and assessed impaired concentration and attention, mood and fatigue at baseline, 1-month and 12-month follow-up. In addition to poor perceived cognition outcomes, the authors found an association with poorer health-related quality of life (HRQL; Duijndam, Denollet, Nyklíček, & Kupper, 2017). In

regard to the long-term cognitive outcomes in patients undergoing PCI, Sauër et al. (2013) compared cognitive performance 7.5 years following off-pump coronary artery bypass surgery and PCI. Cognitive performance was assessed through a neuropsychological battery of nine tests that were summarized into a combined performance *Z*-score. After multivariable adjustment for potential confounders, no significant differences were observed (*Z*-score difference 0.14, 95% confidence interval −0.01 to 0.29, $p = 0.08$), though these seemingly negative results are difficult to interpret as a baseline measurement of cognitive function was lacking (Sauër et al., 2013).

11.3 Transcatheter Aortic Valve Replacement

Throughout the last decade, the numbers of structural heart interventions, such as transcatheter aortic valve replacement (TAVR) have increased (Eggebrecht & Mehta, 2016; Mylotte et al., 2013). The most recent clinical outcome data of TAVR are compelling, although some complications limit broad application (e.g., neurological complications; Leon et al., 2010; Smith, Leon, Mack, Miller, & Moses, 2011). The risk of procedural stroke in TAVR has decreased over time and has come to 1.5% in recent studies and this is notable since mortality after TAVR-related stroke is 50% (Mack et al., 2019; Popma et al., 2019; Stortecky, Wenaweser, & Windecker, 2012). To date, various studies have sought to clarify the interdependence of cardiovascular procedures, cerebral injury due to embolism and hypoperfusion, and cognitive performance, but root causes have not been consistent (Vermeer, Longstreth, & Koudstaal, 2007). In particular, the clinical impact of perioperative diffusion-weighted imaging (DWI) cerebrovascular embolism remains to be fully elucidated, whereas, the sequelae of clinically "silent" brain infarctions are well characterized (Vermeer et al., 2003). Observational studies reveal a strong relationship among these silent brain infarctions, cognitive decline and dementia in long-term and large-scale Rotterdam Scan Study participants (Vermeer et al., 2003). In contrast, DWI-detected emboli were neither related to loss of self-sufficiency or mortality (Ghanem, Muller, et al., 2013), nor to a decline in cognitive function testing for up to 2 years (Ghanem et al., 2010). Although POCD largely resolves within 1 year, its early occurrence appears to accelerate cognitive deterioration with an increased risk for future stroke (odds ratio: 2) and conversion to overt dementia (odds ratio: 3). Moreover, early cognitive dysfunction after cardiovascular interventions is independently related to a three-fold increase of mortality after 1 year (Maniar et al., 2016). Estimation of the overall risk for POCD and late cognitive outcomes is critical. But since these factors interact with each other in an unknown manner, and each has specific impact on distinct cognitive domains over time, the cumulative risk of POCD after TAVR remains elusive.

The incidence of POCD is reported with up to 50% within the first week after (surgical or transcatheter) aortic valve replacement, with gradual resolution between

3 months and 1 year (Ghanem, Kocurek, et al., 2013; Knipp et al., 2005). Cognitive deficits in short- and mid-term intervals were observed rarely after TAVR (<5%). Patients undergoing TAVR without extracorporal circulation and general anesthesia had an acceptable incidence of POCD, well below 10% throughout a 2-year follow-up (Ghanem, Kocurek, et al., 2013). Cognitive assessment of patients at baseline and 4 months post-TAVR using a cognitive battery that included tests of verbal-learning, delayed recall and recognition, an estimate of global cognition (i.e., Mini Mental State Examination, MMSE), and executive function (i.e., Trail Making Test, Clock-Drawing Test) revealed an improvement of immediate recall during follow up. Furthermore, among patients with lower presurgical cognitive abilities, MMSE and immediate memory recall were both significantly improved after TAVR. Though prevalent in the early phase (61%), procedural DWI lesions were observed only in a minority of patients at long-term follow-up (6.5%). The procedural DWI lesions did not impact the trajectory of white matter hyperintensities or cerebral atrophy. Functionally, these TAVR-associated perioperative DWI lesions did not significantly affect early postoperative cognitive function, but there was a trend toward cognitive deterioration at long-term follow-up. Interestingly, only a fraction of lingering white matter hyperintensities evolved from procedural DWI lesions (22.2%). The authors concluded that acquired white matter hyperintensities after TAVR, but not perioperative DWI lesions per se were associated with functional impairment after TAVR (Ghanem et al., 2017).

Numerous pre-procedural conditions are risk factors for POCD and accelerated cognitive decline. Cardiovascular risk factors, such as age, diabetes, smoking, and hypertension are known contributors to cognitive deterioration (De Galan et al., 2009; Knecht et al., 2008; Nash & Fillit, 2006; Plassman, Williams, Burke, Holsinger, & Benjamin, 2010; Roberts et al., 2008). Further, heart failure, sleep disordered breathing and depression are known risk factors for cognitive decline (Garcia et al., 2011; Gruhn et al., 2001; Zuccalà et al., 1997). A possible indicator of a valvular cause for decreased cerebral perfusion in aortic stenosis is resolution of central sleep apnea syndrome immediately after TAVR (Linhart et al., 2015).

From the mechanistical perspective, cerebral embolism may be the most accepted etiological cause of POCD following cardiac surgery. First, cerebrovascular etiologies have been posited as major contributors to clinical deterioration in neurodegenerative disease states (De La Torre, 2004; Van Oijen et al., 2007). Additionally, cognitive deterioration was shown to be based on cumulation of white matter hyperintensities over the period of 3–4 years (Vermeer et al., 2003). However, the application of this deductive approach on procedural lesions seen in DWI neuroimaging data remains controversial. In a comprehensive meta-analysis, perioperative DWI lesions were not associated with cognitive decline in six out of seven trials after open-heart surgery and TAVR (Kruis, Vlasveld, & Van Dijk, 2010). Notably, the trials investigated patients after cardiac surgery and not catheter-based procedures. Further, no systematic cognitive decline was seen after cardiovascular procedures in a recent review article by Fink et al. (2015) investigating 7802 patients with a maxi-

mum follow-up of 72 months. In particular, recent small-scale observational studies of TAVR demonstrate a low incidence of POCD (see Table 11.1). However, the relationship among individual risk, cerebral embolism and cognitive outcome following TAVR is not yet understood and is further complicated by the use of various neuroprotection devices meant to capture particulate matter during surgery.

Neuroimaging studies demonstrate a high embolic risk during the TAVR procedure (Astarci et al., 2011; Fairbairn et al., 2012; Ghanem et al., 2010; Kahlert et al., 2010, 2012; Rodés-Cabau et al., 2011). Almost every patient undergoing TAVR incur lesion events as detected by DWI. Functionally, though, only a small amount demonstrate focal neurological deficits following TAVR. Morphologically, only a small fraction of procedural lesions seen with DWI were visible as white matter hyperintensities on fluid-attenuated inversion recovery (FLAIR) MRI at mid-term follow-up (Ghanem et al., 2010), demonstrating a rather complex and yet not fully elucidated chronological relationship of cerebral morphology and function after TAVR. This discrepancy may additionally be explained by a paucity knowledge regarding the factors contributing to the longitudinal complexity of lesion and cognitive performance patterns, as depicted in Fig. 11.1. Besides thrombotic embolism, hypoperfusion is another conceivable mechanism of post-procedural onset or maintenance of POCD. More than mild aortic regurgitation leads to decay of diastolic perfusion pressure and impaired renal perfusion with excessive increase of renal artery resistance index (Sinning et al., 2014). This change in renal artery resistance index, in turn, could lead to cerebral hypoperfusion (Sinning, Scheer, et al., 2012). Additionally, systemic inflammatory response syndrome (SIRS) is a known hypoperfusion syndrome, often associated with patients with residual aortic regurgitation and is an independent predictor of adverse outcomes (Sinning, Hammerstingl, et al., 2012).

A prospective trial investigating cognitive function in a cohort of 229 patient years using the MMSE before and 6 months after TAVR found a cognitive deterioration in 12.7% overall, but no independent predictor thereof. However, patients with POCD revealed specific post-interventional traits, such as post-procedural stroke, progressive renal failure, progressive heart failure, or delirium as possible causes (Schoenenberger et al., 2016). Delirium is a known risk factor for POCD (Saczynski et al., 2012). It was found to be as frequent as 44% after TAVR (CARDELIR-Trial), but still significantly lower in comparison to surgical aortic valve replacement (e.g., 66%; Eide et al., 2015). This is of particular interest, since the onset of delirium is an independent predictor of mid-term cognitive deterioration (Saczynski et al., 2012). In a small-scale observational study ($n = 44$), no delirium cases were observed after TAVR (Erdoes et al., 2012). Wilbring and associates studied 508 patients in a case-control study and post-procedural delirium was present in 11.5% and 28.3% after TAVR and conventional surgical aortic valve replacement, respectively. These results suggest significantly less post-procedural delirium in TAVR relative to conventional surgical replacement (i.e., $p = 0.046$; Wilbring et al., 2013) and indicate possible neuroprotective superiority of TAVR. This hypothesis is further corroborated by a recent study of Maniar et al. (2016), who report on a decreased mortality in TAVR as compared to the surgical approach based on the association of delirium and mortality (Maniar et al., 2016).

Table 11.1 Observational data on cognitive performance after TAVR

Protocol			Cognitive domains									Outcome: Cognitive deficit								
Intervention/ Control	Tests	Included subjects (*n*)	MS	VMC	AT	SCW	SCL	VC	SASA	IP	AF	3 months-FU (*n*)	Loss-to-FU 3 months *n* (%)	Reasons *n* (%)	<7 days *n* (%)	≤3 months *n* (%)	>3 months *n* (%)	>12 months *n* (%)	Potential Min./ Max. PPCD incidence % (*n*)	Ref.
TAVR/SAVR	MMSE	51/NA	TAVR – SAVR +	TAVR + SAVR +	TAVR + SAVR +	TAVR + SAVR +	TAVR – SAVR +	TAVR – SAVR +	TAVR – SAVR +	TAVR – SAVR +	TAVR – SAVR +	32/21	19 (37%)	Death: 3 (6%), PPM: 5 (10%), Contraindication for MRI 9 (17%), refused: 2 (4%)	+ (0%)	+ (0%) (0/32)	–	–	Min 0% (0/50)/ Max 37% (19/50)	Kahlert et al. (2010)
TAVR/–	MMSE	81	–	+	+	+	–	–	–	–	–	60/–	21 (26%)	Death: 5 (6%), PPM: 6 (7%), refused: 6 (7%), hemodynamic or respiratory instability: 3 (4%), abortion of the procedure: 1 (1%)	+ (0%)	+ (0%) (0/60)	–	–	Min: 0% (0/81)/ Max: 26% (21/81)	Rodés-Cabau et al. (2011)
TAVR/–	MMSE, MoCA	204/–	+	+	+	+	+	+	+	+	–	73/–	131 (64%)	Death 10 (5%); unsuitable for transcranial Doppler : 107 (52%), refused: 14 (7%)	+ (0%)	+ (0%) (0/73)	–	–	Min 0% (0/204)/ Max 64% (131/204)	Kahlert et al. (2012)

(continued)

Table 11.1 (continued)

Protocol			Cognitive domains									Outcome: Cognitive deficit								
Intervention/ Control	Tests	Included subjects (*n*)	MS	VMC	AT	SCW	SCL	VC	SASA	IP	AF	3 months-FU (*n*)	Loss-to-FU 3 months *n* (%)	Reasons *n* (%)	<7 days *n* (%)	≤3 months *n* (%)	>3 months *n* (%)	>12 months *n* (%)	Potential Min./ Max. PPCD incidence % (*n*)	Ref.
TAVR/SAVR	MMSE+[a] (TAVR), STB (SAVR)	27/37	TAVR − SAVR +	TAVR + SAVR +	TAVR + SAVR +	TAVR − SAVR +	TAVR − SAVR +	TAVR − SAVR +	TAVR + SAVR +	TAVR − SAVR +	TAVR − SAVR +	18/34	TAVR: 9 (33%)/ SAVR: 3 (8%)	TAVR: Death: 7 (26%), refused 2 (7%)/SAVR: not reported: 3 (8%)	+ (TAVR: 18% (4/22) SAVR: 46% (17/37)	+ (TAVR: 28% (5/18) SAVR: 6% (2/34)	–	–	TAVR: Min 18% (5/27)/ Max 51% (14/27) SAVR: Min 5.4% (2/37)/ Max 13.5% (5/37)	Knipp et al. (2013)
TAVR/–	MMSE, RBANS	125/.	+	+	+	+	+	+	+	+	+	102	23 (18%)	Death: 10 (8%), post-procedural complications 13 (10%)	+ 6/111 (5%)	+ 7/102 (7%)	+ 7/86 (8%)	+ 4/32 (12%)	Min 4.8% (6/125)/ Max. 24% (30/125)	Ghanem, Kocurek, et al. (2013)

Abbreviation: *TAVI* transcatheter aortic valve implantation, *SAVR* surgical aortic valve replacement, *NA* not available, *n* number, *MS* motor skills, *VMC* verbal memory capacity, *AT* attention, *SCW* speed and capacity of working memory, *SCL* speed and capacity of long-term memory, *VC* visuospatial capacity, *SASA* selective and sustained attention, *IP* information processing, *AF* alternate forms of the tests, *MRI* magnetic resonance imaging, *PPM* permanent pacemaker, *MMSE* mini-mental state examination, *RBANS* repeatable battery for the assessment of neuropsychological status, *MoCA* Montreal Cognitive Assessment, *NIHSS* National Institutes of Health Stroke Scale, *STB* standardized testing battery consisting of 11 neuropsychological tests (digit span forward/backward, Corsi block tapping forward/backward, Horn test no. 3/9, Reitan Trail making A/B, Verbal Learning Test—immediate recall/ delayed recognition, Zimmermann divided attention test)

[a]Digit span subtest, wordlist test, Regensburg verbal fluency test

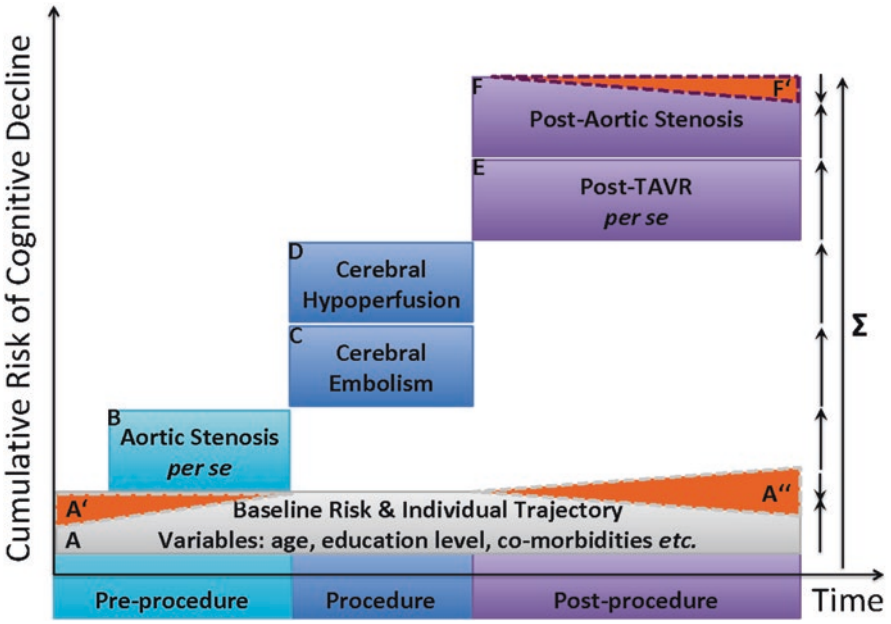

Fig. 11.2 Risk model of cumulative risk of cognitive decline in the periprocedural context. The cumulative risk of post-procedural cognitive decline over time is the integration of a complex interplay of six contributing factors with individual trajectories: baseline risk and individual trajectory (**A**) is attributed to the patient age and co-morbidities, pre- and postprocedural trajectories are individually variable and depicted as first and second derivative of (**A**), (**A′**), and (**A″**), respectively. With the onset of hemodynamic impairment based on the underlying disease of aortic stenosis until the time of treatment, the second component contributes to cognitive performance integrating the interplay with pharmacological hemodynamical effects, e.g., vasodilators commonly used in patients with hypertension and mild-to-moderate aortic stenosis (**B**). Periprocedural components of postoperative cognitive decline comprise cerebral embolism (**C**) and hypoperfusion (**D**), based on procedural dislodgement of valvular debris and rapid pacing runs, respectively. The postprocedural phase is characterized by a high-risk period of embolism, based on new-onset of atrial fibrillation and/or valvular thrombosis, each individually contributing to postprocedural cognitive decline. Ultimately, post-TAVR patients are also "post-stenosis" patients with improved cerebral hemodynamics (**F**). Despite age and comorbidities, cognitive trajectory might be beneficially affected (**F′**). Hence, cognitive performance after TAVR over time is the integrative sum (**Σ**) of these variables and/or derivatives

In patients undergoing TAVR, several factors contribute to the complexity of long-term longitudinal investigations of cognitive performance: (1) the individual, cerebral risk of the patient prior TAVR; (2) the chronic, hemodynamic contribution of the underlying disease aortic valve stenosis (e.g., low cardiac output and low cerebral perfusion); (3) acute, hypoperfusion during the TAVR procedure due to rapid pacing and/or anesthesia; (4) cerebral embolization during the procedure from valve positioning and deployment and/or post-dilatation, and (5) specific significant post-procedural risks (e.g., bleeding, SIRS, valve leaflet thrombosis, new-onset of atrial fibrillation; see Fig. 11.2). On the one hand, estimation of the overall risk for

POCD and late cognitive outcome is necessary. But, each of the factors above interact with the other in an unknown manner (additive? exponential?), and each has specific impact on distinct cognitive domains over time. As a result, the absolute risk and root etiologies of POCD after TAVR remain elusive. Complicating our ability to understand these risks and etiologies, no systematic cognitive declines were observed after cardiovascular procedures in a recent review article by Fink et al. (2015), who investigated 7802 patients with a maximum follow-up of 72 months. Additionally, after TAVR recent small-scaled observational studies demonstrate a low incidence of POCD (see Table 11.1). Ultimately, patients with and without DWI lesions demonstrate similar cognitive outcome for up to 2 years after TAVR (Ghanem, Kocurek, et al., 2013). Further, neuroimaging patterns differ in their impact on cognitive performance. While DWI lesions had no impact on survival, stroke rate and cognitive function in long-term observations, the incidence of FLAIR-positive lesions was associated with cognitive decline. Interestingly, FLAIR-positive white matter hyperintensities in long-term follow-up rarely result from procedural DWI lesion events. In all, the relationship of individual risk, timing of cerebral embolism and cognitive outcome is not fully elucidated in TAVR.

With respect to preventive measures, three trials (PRO-TAVI C, DEFLECT III, CLEAN-TAVI) investigated the impact of embolic protection devices (EPDs) on cerebral embolic burden during TAVR in a randomized, controlled clinical trials (Haussig et al., 2016; Lansky et al., 2015; Rodés-Cabau et al., 2014). In PRO-TAVI C, the Embrella™ deflection device failed to reduce the embolic burden during TAVR. In DEFLECT III trial, the investigators stated they found reduction of embolic burden and improvement of cognitive performance in patients undergoing TAVR protected by the Triguard™ device. However, besides other significant limitations, conclusions on the development of POCD were precluded in a study protocol with short-term follow-up. In CLEAN-TAVI trial, Haussig et al. (2016) observed a reduction in embolic burden with the Montage™ device, a dedicated distal embolic filter system. In a second trial, the use of cerebral embolic protection reduced the rate of disabling and nondisabling stroke significantly from 4.6% to 1.4% ($p = 0.03$). Furthermore, the rate of stroke-free survival compared with unprotected TAVR was significantly higher when the Montage™ System was utilized (Seeger, Gonska, Otto, Rottbauer, & Wöhrle, 2017). A prior meta-analysis of four randomized clinical trials ($n = 252$) showed that EPDs were associated with a lower total lesion volume ($p = 0.002$) on MRI, a smaller number of new ischemic lesions ($p = 0.03$), a trend toward lower risk for deterioration in National Institutes of Health Stroke Scale score at discharge ($p = 0.09$), as well as a higher post-procedural MoCA scores ($p = 0.03$). The risk for overt stroke and all-cause mortality, however, was nonsignificantly lower in the EPD group (Giustino, Sorrentino, Mehran, Faggioni, & Dangas, 2017). The assumption of EPD utility is further fueled by the findings of Pagnesi, who found EPDs to be associated with a significant reduction in total ($p = 0.02$) and single ($p = 0.0001$) lesion volume after TAVR. However, the number of new lesions per patient and the number of patients with new lesions were not significantly reduced (Pagnesi, 2016).

These EPD results seem encouraging, but have limitations. Firstly, imaging endpoints have been based on embolic burden with a skewed distribution pattern integrating micro- and macroembolic embolism. Inconsistently, the embolic burden has been lower in all vascular territories, a coincidental finding without causal context to the devices. Secondly, the devices themselves may be thrombogenic and positioning EPDs is capable of dislodging atherosclerotic debris leading to cerebral embolization. Imaging and clinical data on the safety and efficacy of EPDs lack controls undergoing sham procedure with a filter-free device. Thirdly, a significant number of patients with an overt stroke have not been subjected to post-procedural imaging protocols. Hence, the data on the reduction of embolic burden does not encompass the complete intention-to-treat cohort for which the studies were powered. But as TAVR shifts to younger and lower-risk patients, the prevention of procedure-related cerebral injury remains a significant but yet unmet clinical need (Latib & Pagnesi, 2017). It will be critical to further investigate the impact of these EPDs and post-procedural pharmacological management on neuroprotection in clinical trials with long-term follow-up.

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