Mechanisms And Prevention Of TAVI-Related Cerebrovascular Events

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INTRODUCTION
Aortic valve stenosis is the most common valve disease in the elderly with a prevalence of 3% among individuals ≥75 years of age and up to 10% in octogenarians [1-4]. Patients with symptomatic aortic stenosis have a poor prognosis with a rate of death estimated to be more than 50% at 2 years if untreated [5-7]. Over the last decade the introduction of transcatheter aortic valve implantation (TAVI) has resulted in a paradigm shift in the treatment of patients with severe aortic stenosis in patients with very high or prohibitive surgical risk [8, 9]. Despite the clear benefits of the TAVI procedure, patients are exposed to the risk of disabling stroke, complete heart block, paravalvular leakage, vascular complications, major bleeding, and valve migration [10]. Further, the occurrence of cerebrovascular events (CVEs) is one of the most worrisome complications in this frail and multimorbid patient population. More than 50% of CVEs occur during the acute phase after TAVI and therefore prediction as well as prevention of CVEs remains to be one of the major methodological challenges [11-13]. This article aims to comprehensively review the mechanisms of neurological injury per se, the read-outs of cerebrovascular events, and strategies currently used to predict and prevent stroke in transcatheter aortic valve implantation.

STROKE: DEFINITION, INCIDENCE AND PREVALENCE
Over the last 10 years multiple studies have reported upon the incidence of stroke after TAVI. Yet, in light of variable definitions of clinically apparent events and disregard of subclinical events the true incidence of CVEs after TAVI may not be reflected in some of these studies. In order to standardize clinical endpoints after TAVI, the Valve Academic Research Consortium (VARC) issued consistent definitions of CVEs, including the duration and neurological outcome of patients [14]. In order to enhance the accuracy in the description of a procedure-related stroke, VARC recommends using the terms “disabling” and “non-disabling” stroke in substitution for the old terms “major” and “minor” stroke.

The scientific evidence, which has established the foundation for the wide acceptance and use of TAVI is derived primarily from the pivotal cohorts A and B of the Placement of Aortic Transcathe-
MECHANISMS OF CVEs

As nearly half of the CVEs occur late, and therefore are not directly related to the procedure itself, different pathomechanisms of cerebral injury after TAVI were objectified [11, 17, 25]. Therefore, all neuroprotective approaches need to be tailored according to the underlying mechanism.

**MECHANISMS OF CVEs**

Currently, four different mechanisms of cerebral injury after TAVI are postulated, which could explain the temporal distribution of CVEs after TAVI.

CEREBRAL INJURY DUE TO DEBRIS EMBOLIZATION

Acute CVEs are almost exclusively ischemic in nature and are considered procedure related [11, 25]. A vast majority of patients undergoing TAVI have multiple cardiovascular risk factors including hypertension, hyperlipidemia, a history of smoking, and diabetes mellitus, which often lead to atherosclerotic disease in this aged patient population. Thus, it is conceivable that each and every manipulation during the TAVI procedure within the aortic arch and the stenosed, calcified aortic valve could potentially lead to embolic dislodgement of thrombotic, atheromatous or calcific debris [26]. Patients with severe aortic stenosis and with longer duration of catheterization are at increased risk of embolic ischemic stroke [27, 28]. Furthermore, repeated attempts to cross the often friable calcified valve as well as balloon post-dilation is associated with a higher rate of CVEs, with most strokes in patients who had balloon

Table 1. Definition, Classification, and Diagnostic criteria of Stroke and TIA [14]

**Diagnostic criteria**

Acute episode of a focal or global neurological deficit with at least 1 of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting 1 side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke.

**Stroke:** duration of a focal or global neurological deficit ≥24 hours; or <24 hours if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death.

**TIA:** duration of a focal or global neurological deficit <24 hours, any variable neuroimaging does not demonstrate a new hemorrhage or infarct.

No other readily identifiable nonstroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist*

Confirmation of the diagnosis by at least 1 of the following:

- Neurologist or neurosurgical specialist
- Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

**Stroke classification:**

- **Ischemic:** an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue.
- **Hemorrhagic:** an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic.

**Stroke definitions** **

- **Disabling stroke:** an mRS score of 2 or more at 90 days and an increase in at least 1 mRS category from an individual’s pre-stroke baseline.
- **Non-disabling stroke:** an mRS score of <2 at 90 days or one that does not result in an increase in at least 1 mRS category from an individual’s pre-stroke baseline.

mRS, Modified Rankin Scale. *Patients with nonfocal global encephalopathy will not be reported as a stroke without unequivocal evidence of cerebral infarction-based upon neuroimaging studies (CT scan or Brain MRI). **Modified Rankin Scale assessments should be made by qualified individuals according to a certification process [65-67].

In light of this, it is worthwhile looking at more recent studies which add to our knowledge about peri- and postinterventional stroke after TAVI, which include the French national transcatheter aortic-valve implantation registry [10], The Transcatheter Valve Treatment Sentinel Pilot Registry [20], the ADVANCE study [21], as well as the U.S. CoreValve Trial [22]. The results of these trials is very similar to previous studies, showing an incidence of stroke at 30 days of 3%, 4% in the FRANCE 2 study, 3.0% (1.2% major stroke, 1.8% minor stroke) in the ADVANCE study, 4.9% (3.9% major stroke, 1.0% minor stroke) in the U.S. CoreValve Trial, and 1.8% in the Transcatheter Valve Treatment Sentinel Pilot Registry (which did not report the 30 day incidence of stroke but the procedural/ in-hospital stroke rate). According to the recently presented data of the CoreValve US pivotal trial, patients had a all stroke risk of 10.9% and 16.6% two years after TAVI and SAVR with a strong trend towards better outcomes in patients undergoing TAVI (p=0.05). Besides, the superior survival seen at 1 year for TAVI over SAVR was maintained at 2 years. Thus, the CoreValve US Investigators conclude that TAVI should be considered the preferred treatment in patients with symptomatic severe AS at increased risk for surgery, and could be considered in patients at intermediate surgical risk [23]. Recent data of the NOTION-Trial demonstrate non-inferiority of TAVI as compared to surgical valve replacement even in patients at lower surgical risk [24].

Interestingly, CVEs demonstrate a time dependent distribution pattern after the procedure. Approximately 50% of CVEs occur within the first 24 hours after the TAVI procedure [17]. Thereafter, patients remain most vulnerable for approximately 30 days (associated with the procedure) before transitioning to a late, constant hazard phase (associated with the co-morbidities).

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**MECHANISMS OF CVEs**

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**CEREBRAL INJURY DUE TO DEBRIS EMBOLIZATION**

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post-dilation occurring immediately after or within the first 24 hours after the TAVI procedure [29]. Evidence for debris embolization during positioning and implantation of the valve prosthesis was brought by a study performed...
by van Mieghem, et al. [30]. In their study macroscopic material liberated during the TAVI procedure was captured in a filter-based embolic protection device and subsequently analyzed. The debris consisted of fibrin, or amorphous calcium and connective tissue, which were most likely derived from either the native aortic valve leaflets or aortic wall.

The impact of the access route (transfemoral or transapical) and the valve type (balloon- or self-expandable) on the occurrence of CVEs has not been clearly elucidated yet [18, 19]. Yet, we and others were not surprised that passing the semi-rigid, large-bore delivery catheter containing the folded bioprosthesis using a catheter-based approach led to silent and apparent symptomatic cerebral embolism in 73-84% and 3-10%, respectively [31-33]. Interestingly, CVE-risk was not related to the route of implantation (ante-grade-transapical versus retrograde-transvascular).

**CEREBRAL INJURY DUE TO THROMBOTIC EMBOLIZATION**

New-onset atrial fibrillation (NOAF) frequently develops after cardiovascular interventions and is associated with peri-procedural CVEs [34, 35]. The incidence of NOAF after TAVI has been reported as high as 31.9% in patients with no prior history of atrial fibrillation (AF), while NOAF was defined as any episode of atrial fibrillation lasting more than 30 seconds. NOAF occurred in about half of all events within 24 hours and in >80% of cases within 3 days after TAVI [36]. The pathogenesis of NOAF after TAVI procedure is not well understood. What is known is that pre-procedural left atrial enlargement and placement of the artificial valve by transapical approach are associated with an increased risk of NOAF [36, 37]. The impact of NOAF on delayed CVEs after TAVI was shown by Amat-Santos and colleagues. In their study, NOAF was associated with a higher rate of stroke and systemic embolism following the TAVI procedure, especially the late (>24 h) events. On the contrary, the prevalence of NOAF was only 25% in patients who experienced an acute CVE during TAVI. In conclusion, NOAF increases the risk of early and subacute CVEs by 4.4 fold [25].

**CEREBRAL INJURY DUE TO COMORBIDITIES**

By analyzing data of a multi-center registry encompassing 1061 patients, Nombela-Franc o, et al. demonstrated that both a history of peripheral as well as cerebrovascular disease (carotid stenosis, prior endarterectomy, prior CVE) each independently doubled the risk of late CVEs after TAVI. Besides, it was shown that chronic atrial fibrillation independently increases the risk of late CVEs (more than 30 days after TAVI) almost three fold [11]. Likewise, Fairbairn, et al. demonstrated that the severity of aortic arch atheroma was an independent risk factor for the development of new CVEs after TAVI [38]. Hence, with respect to comorbidities, chronic atrial fibrillation and presence of atherosclerotic disease burden are key independent risk factors for TAVI related CVEs.

**CEREBRAL INJURY DUE TO INSUFFICIENT CEREBRAL PERFUSION PRESSURE**

Several clinical settings may lead to hemodynamic instability and impair cerebral perfusion pressure beyond cerebral autoregulatory capacity, namely general anesthesia, paravalvular leakage, aortic regurgitation, vascular complications, as well as major bleeding. Besides, rapid ventricular pacing, which is used to decrease cardiac output during balloon valvuloplasty and valve deployment in an attempt to reduce the risk of valve malpositioning, causes systemic hypotension. In a recent study, a time-dependent effect of rapid ventricular pacing on microflow was demonstrated, leading to 50 and 25% of baseline microflow at 8 and 18 seconds of rapid ventricular pacing, respectively. Besides, in a substantial proportion of patients, rapid ventricular pacing is associated with microcirculatory arrest and a delayed recovery of microflow [39].

All of the above mentioned non-embolic mechanisms may cause malperfusion and consecutive brain dysfunction. Depending on the duration and severity of cerebral hypoperfusion, patients may suffer from postoperative alternating states of consciousness, transient or irreversible neurologic impairment after TAVI. Nuis, et al. demonstrated that moderate aortic regurgitation was associated with an approximately 3-fold increase of risk of non-embolic cerebral ischemia in computed tomography. In this study, lacunar strokes and watershed infarction occurred in 26% and 2% of patients, respectively [25].

In conclusion, embolic as well as non-embolic mechanisms may lead to cerebral injury following TAVI. Hence, the underlying mechanisms are to be considered with respect to read-outs and prevention of TAVI-related CVEs (see Table 2).

**MECHANISMS OF TAVI-RELATED CEREBROVASCULAR EVENTS**

Clinical parameters of cerebrovascular events

Among TAVI related complications, cerebrovascular events causing focal or global neurologic deficit are dreaded because of their excessive morbidity and mortality [40]. Yet, postoperative stroke may also cause subtle clinical symptoms (e.g. cognitive decline or impairment in activities of daily living), which are not diagnosed until a neuropsychological exam, e.g. the Mini-mental State Exam (MMSE) or the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), is used.
Table 2. Embolic and non-embolic mechanisms leading to CVEs following TAVI.

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<th>Embolic origin</th>
<th>Non-embolic origin</th>
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<tr>
<td>Acute onset</td>
<td>Debris embolization due to device manipulation in the aortic arch and valvular ring.</td>
<td>Bleeding / vascular complications</td>
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<td></td>
<td>- Thrombotic embolization due to thrombus formation on the device.</td>
<td>- Pericardial tamponade</td>
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<tr>
<td></td>
<td>- NOAF</td>
<td>- Rapid ventricular pacing</td>
</tr>
<tr>
<td>Chronic onset</td>
<td>Atrial fibrillation</td>
<td>Low output / heart failure</td>
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<td></td>
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<td>- Paravalvular leakage</td>
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NOAF: New-onset of atrial fibrillation, SIRS: Systemic inflammatory response syndrome

The Valve Academic Research Consortium limits the diagnostic criteria of perioperative cerebrovascular events to clinically apparent acute neurologic signs or symptoms consistent with stroke. For standardized assessment of a patient’s neurologic status, use of the National Institutes of Health Stroke Scale (NIHSS) is recommended. While clinical findings like changes in the level of consciousness, unilateral neurologic deficits, or aphasia are easily diagnosed, other neurologic signs or symptoms like hemianopsia, amaurosis fugax, or spinal cord dysfunction can only be diagnosed if a more detailed history is taken and a dedicated neurologic exam is performed.

In order to assess cognitive performance or the degree of disability or dependence in the daily activities of patients who have suffered from stroke, the MMSE and the modified Rankin Scale (mRS) can be used. Several investigators examined cognitive function after TAVI utilizing the MMSE, and found stable cognitive performance for up to 24 months after TAVI [31, 33, 41]. In our experience, no sub-clinical parameter of brain injury was related to lifestyle or to activities of daily living one year after TAVI [42].

In conclusion, NIHSS and mRS are the basic clinical characteristics defining procedure-related CVEs. Available data on sustained cognitive performance, improved quality of life, and activities of daily living after TAVI are encouraging and should be considered in the individual decision-making of the heart team [43, 44]. It is indeed very interesting, that clinical measures of neurological deficits are up to 4-fold higher in trials with clinical assessment by a board-certified neurologist as compared to trials with neurological assessments performed by a surgeon, cardiologist or intensivist [22]. This important observation should be of interest for future comparative trials in lower risk patient subsets.

Imaging modalities of cerebral injury

Different imaging modalities have been used to detect cerebrovascular events after TAVI, namely computed tomography (CT), transcranial Doppler (TCD) and diffusion-weighted (DW)-MRI. Although new ischemic events have been documented in as many as 93% of patients after the TAVI procedure [45, 46], most of these events are silent infarctions with no clinical apparent neurologic deficit [31-33] and have no effect on self-sufficiency in lifestyle, health-related quality of life and mortality [38, 42]. Cerebral imaging has yielded mechanistical insights into an alternative origin of cerebral injury after TAVI, displaying non-embolic, cortical watershed infarction as indirect sign of non-embolic, hemodynamic impairment in 10.5% of patients undergoing TAVI [25].

In contrast to the tomographic modalities, TCD identified critical intra-procedural steps with respect to cerebral embolism by recognition and quantification of high-intensity transient signals and microembolic signals [47]. Microemboli have been detected during all stages of the TAVI procedure but are most frequent during the stages of valve positioning and valve implantation. In the largest and most comprehensive study to date investigating TCD-detected emboli, Kuhlert, et al. demonstrated a high number of high-intensity transient signals during the stage of valve implantation, suggesting release of calcific debris and valve tissue from the native aortic valve during release of the prosthesis [48]. Long-term follow-up studies are needed to elucidate the consequences of cerebral embolism in regards to neurocognitive decline, mild cognitive impairment and vascular dementia [49, 50].

Serological parameters of cerebral injury

Over the last two decades, different serologic markers have been assessed as surrogates for neurologic injury after traumatic brain injury or cerebral ischemia. The concentrations of the serologic markers S-100 B and neuron-specific enolase (NSE) have been shown to predict infarct volume and the long-term neurologic outcome of patients after ischemic brain infarction [51]. In small studies, a correlation between infarct volume and the degree of post-procedural release of S-100B was demonstrated [52, 53]. In contrast, studies could not demonstrate a correlation between the post-procedural increase in serum concentration of NSE neither in relation to cerebral injury in DW-MRI nor to neurological and cardiovascular outcome up to 1 year after TAVI [32, 42].

“e-RIFLE” Criteria and the prognostic value of cerebral injury

Analogous to the RIFLE criteria [54], which consist of three graded levels of kidney dysfunction (Risk, Injury, and Failure), based upon either the magnitude of increase in serum creatinine or urine output, and two outcome measures (Loss and End-stage renal disease) conceptual analogies can be found for myocardial injury (see Table 3):

Table 3. Cerebral RIFLE criteria (e-RIFLE) - in analogy to the RIFLE criteria.

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<tr>
<td>Risk:</td>
<td>asymptomatic patients at increased risk of developing stroke after TAVI, e.g. due to NOAF</td>
</tr>
<tr>
<td>Injury:</td>
<td>postprocedural increase of biomarkers or evidence of new ischemic stroke on MRI imaging in patients without focal or global neurologic deficit</td>
</tr>
<tr>
<td>Failure:</td>
<td>postprocedural clinical evidence of temporary focal or global neurologic deficit lasting less than 24 hours (TIA)</td>
</tr>
<tr>
<td>Loss:</td>
<td>postprocedural clinical evidence of persistent focal or global neurologic deficit lasting longer than 24 hours with evidence of cerebral injury in specific tomographic imaging modalities (stroke)</td>
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Patients suffering from early CVEs after TAVI demonstrated a significantly higher mortality rate as compared to patients who did not suffer from stroke [17]. Major, disabling stroke was associated with higher 30-day (7.4-fold) and late (1.75-fold) mortality [11]. A meta-analysis including more than 10,000 patients reported on a 3.5-fold increase of mortality after CVE [18]. Several measures of subclinical cerebral injury have been reported to be associated with TAVI, but only apparent CVEs seem to have an adverse impact on prognosis [42]. Long-term studies are needed to assess if the subclinical emboli which many patients are exposed to during TAVI procedure will ultimately cause mental impairment or effect. Interestingly, the lack of silent ischemic events does not lead to improvement of cognitive outcome [42].

Prevention of cerebrovascular events

Because of the increased risk of CVE associated with TAVI, adjunctive pharmacotherapy to prevent thrombosis, periprocedural measures to prevent non-embolic cerebral injury, and use of neuroprotection devices may be discussed. Scientific evidence, especially randomized trials on neuroprotection during TAVI is scarce. Most of the few studies that have been conducted have focused on use of antiplatelet therapy and anticoagulation during an after TAVI. In the following we discuss several preventive strategies in regard to the timing and underlying mechanisms CVE and propose interventional measures.

Prevention of acute procedural embolic cerebral injury

In one of the few published clinical trials to date, Ussia, et al. randomized 79 patients undergoing TAVI to receive a 300-mg loading dose of clopidogrel on the day of procedure plus post-procedural maintenance therapy consisting of 3 months of 75 mg of clopidogrel daily plus aspirin 100 mg lifetime or aspirin 100 mg alone. The study did not show a benefit of adding clopidogrel to aspirin for 3 months after TAVI to be superior to aspirin alone at 30 days and after 6 months [55].

In analogy to the aforementioned trial, Durand et. al. compared use of dual antiplatelet therapy (DAPT) in patients undergoing TAVI to monoaantiplatelet therapy alone [56]. The results demonstrated a reduced risk of life-threatening and major bleeding but no reduction of risk in regards to stroke and myocardial infarction by using monoaantiplatelet therapy versus DAPT. The ongoing randomized multicenter “BRAVO 2/3 trial” will assess the safety and efficacy of using bivalirudin instead of unfractionated heparin in TAVI with the hypothesis that bivalirudin reduces bleeding rates and improves clinical outcomes relative to heparin (NCT01651780).

Although prevention of acute CVEs can be tackled in the pre-procedural setting, several preventive measures can be implemented during the intervention. On the one hand improvements in the design of delivery catheters, such as smaller size or steerability, can reduce contact with vulnerable lesions [12]. On the other hand, transcranial Doppler studies have demonstrated that cerebral embolism occurs throughout the multi-step TAVI procedure, but cumulate predominantly during valve positioning and deployment within the calcified native valve [48]. Therefore, the ‘no contact’, ‘minimal contact’, or ‘direct’ TAVI approach, without preparatory balloon valvuloplasty to minimize the dislodgement of calcified atherosclerotic emboli, have been proposed to reduce the risk of peri-procedural stroke [57]. In this regard precise sizing of the annulus and the correct valve-selection is essential to avoid valve dislodgement, valve malposition, post-dilatation or deployment of a second valve, each of which might increase the risk of CVEs. Therefore, a meticulous planning and rapid performance of the procedure is of paramount importance.

In addition, patients undergoing TAVI may also benefit from the use of distal cerebral embolic protection devices. The rational for their use relies on the reduction of cerebral embolic debris by either deflecting or capturing embolized material from entering the supraaortic-cerebral arteries. Distal cerebral embolic protection devices consist of a filter membrane placed either in the aortic arch to deflect debris toward the descending aorta (TriGuard™ Cerebral Protection Device, Keystone Heart Ltd., Embrella™ Edwards Inc.) or placed in the anonymous and common carotid arteries (Montage™, Claret Medical Inc., Lumen Biomedical) to either deflect (TriGuard™, Embrella™) or capture (Montage™) embolic debris during the procedure. Proof of efficacy for cerebral protection devices was demonstrated in a few pilot studies in patients with severe aortic stenosis undergoing TAVI in 2010 and 2012 [58-60]. In the recently published PROTAVI-C trial (n=41), Rodés-Cabau, et al. demonstrated that deployment of the Embrella Embolic Deflector system did not prevent the occurrence of cerebral microemboli during TAVI or new transient ischemic lesions as evaluated by DW-MRI, but that its use was associated with a reduction in cerebral lesion volume [33].

In a recent randomized controlled trial Linke, et al. could demonstrate that in patients with severe aortic stenosis who are at increased surgical risk, the use of Claret MontageTM dual filter cerebral protection system during TAVI significantly reduced the number and volume of cerebral lesions as determined by DW-MRI subtraction at 2 and 7 days after TAVI (Linke, et al., „Oral presentation at TCT 2014“).

Future larger outcomes studies are needed in order to validate the observed beneficial effects of routine cerebral protection during TAVI in improving acute neurological outcome and reducing stroke rate.

Prevention of acute procedural non-embolic cerebral injury

Intraoperative arterial hypotension and transient decay of unil- or bilateral cerebral perfusion pressure can lead to non-embolic mechanisms of cerebral injury. In a study by Nuis, et al. watershed infarction could be demonstrated in 10.5% of patients by means of computer tomography. Different mechanism can lead to inproto- and cerebrovascular disease. Future neuroprotective trials should evaluate if near infrared spectroscopy (NIRS) can contribute to the management of patients in terms of preoperative risk stratification as well as intraoperative decision making [61, 62].

Prevention of subacute post-procedural embolic cerebral injury

Stroke is an independent predictor of morbidity and mortality after surgical aortic valve replacement and TAVI. Prevention of subacute post-procedural embolic cerebral injury is of paramount interest, since more than half of the TAVI-related CVEs occur later than 24 hours after implantation. Evidence regarding the optimal treatment strategy is scarce and unequivocal. In small-scale trials no change in clinical status was detected in patients treated with monoaantiplatelet therapy (MAPT), as compared to dual-antiplatelet therapy (DAPT) [55, 63]. Based on current available data the intensity of antiplatelet therapy does not seem to change the incidence of subacute CVEs. Ongoing large multicenter randomized trials will clarify whether MAPT after TAVI is safe enough with respect to prevention of subacute CVEs (NCT02247128).

New onset atrial fibrillation occurs in approximately one-third of patients after TAVI, and its onset significantly increases the risk of subacute CVEs [36]. Based on the compelling data of the recent ASSERT Trial [64] even very short time periods of atrial fibrillation (6 minutes) are indicative for future strokes. Hypothetically, the combination of MAPT and limited-dosage of oral anticoagulants could be a compromise between excessive bleeding risk of transient “triple therapy”. On-going trials are investigating the syn-
ergistic effects of Aspirin, Clopidogrel or newer anti-thrombotic agents, as well as direct thrombin-inhibitors and their combinations with APT to decrease bleeding risk utilizing combination of APT and OAC following the principle “as low as reasonably achievable”, weighting out embolic and bleeding risk (REDUAL-PCI: NCT02164864, Pioneer AF-PCI: NCT01830543). Hence, we assume that future studies will concentrate on synergistic effects of APT and OAC in adapted dosage after TAVI, to address the underlying complex pathophysiological mechanisms of subacute stroke.

**Prevention of subacute post-procedural non-embolic cerebral injury**

The mechanism of late cerebral embolism beyond the high-risk period (first week to 30 days after TAVI) appear to be mainly related to thrombotic origin and are associated with the underlying comorbidities of the aged TAVI patient. Atrial fibrillation, carotid stenosis, arterial hypertension, and peripheral vascular disease, among other known predictors of late cardiovascular events, need to be treated in order to prevent late CVEs. With respect to patients at high risk of bleeding, use of new anticoagulants could be of help to prevent this major challenge [11, 17].

**ABBREVIATIONS**

- AF = atrial fibrillation
- AVR = aortic valve replacement
- CT = computed tomography
- CVEs = cerebrovascular events
- DAPT = dual antiplatelet therapy
- DW-MRI = Diffusion weighted Magnetic Resonance Imaging
- LBBB = left bundle branch block
- mRS = modified Rankin Scale
- MASP = mono-antiplatelet therapy
- MMSE = Mini-mental State Exam
- NIHSS = National Institutes of Health Stroke Scale
- NOAF = new-onset atrial fibrillation
- NSE = neuron-specific enolase
- RBANS = repeatable Battery for the Assessment of Neuropsychological Status
- SAVR = surgical aortic valve replacement
- TCD = transcranial Doppler
- TAVI = transcatheter aortic valve implantation
- VARC = Valve Academic Research Consortium

**CONFLICT OF INTEREST**

The authors confirm that this article content has no conflict of interest.

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Declared none.

**REFERENCES**


