Transcatheter aortic valve replacement and stroke: a comprehensive review

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Abstract

Transcatheter aortic valve implantation (TAVR) has emerged as an alternative, rapidly evolving treatment option for patients with severe aortic stenosis and high surgical risk. Stroke is a devastating complication being confined mainly in the periprocedural and 30-day period following TAVR, with a lower and relatively constant frequency thereafter. Early stroke is mainly due to debris embolization during the procedure, whereas later events are associated with patient specific factors. Despite the fact that the rate of clinical stroke has been constantly decreasing compared to initial TAVR experience, modern neuro-imaging with MRI suggests that new ischemic lesions post-TAVR are almost universal. The impact of the latter is largely unknown. However, they seem to correlate with a reduction in neurocognitive function. Because TAVR is set to expand its indication to lower surgical-risk patients, stroke prophylaxis during and after TAVR becomes of paramount importance. Based on clinical and pathophysiological evidence, three lines of research are actively employed towards this direction: improvement in valve and delivery system technology with an aim to reduce manipulations and contact with the calcified aortic arch and native valve, antithrombotic therapy, and embolic protection devices. Careful patient selection, design of the procedure, and tailored anti-thrombotic strategies respecting the bleeding risks of this fragile population constitute the main defense against stroke following TAVR.

Keywords: Aortic stenosis; Stroke; Transcatheter aortic valve replacement

1 Introduction

Degenerative aortic stenosis (AS), is the most frequently encountered valvular heart disorder, as its incidence approaches 2.5%–7% in elderly patients. In 2013, 50,222 deaths were related to valvular heart disease in USA. Of those, 67.5% were due to aortic valve disorders. Indeed, after symptoms’ onset, AS carries a poor prognosis if left untreated. Surgical aortic valve replacement (SAVR) has been the standard treatment for symptomatic aortic stenosis in patients at low and intermediate surgical risk. Hence, more than 200,000 TAVR procedures have been performed worldwide since 2002. More importantly, some recent randomized trials and observational studies have reported similar, or even superior results with TAVR compared to SAVR in lower risk patients. Therefore, an expansion of the use of this procedure might be anticipated in the near future. One of the most feared complications of TAVR is stroke because of its associated severe disability and high mortality, being also one of the most feared complications by patients. With the expected broadening of the indications for TAVR in the future, the aim of this review is to enlighten the incidence, predictors, clinical impact, and potential strategies to avoid stroke following TAVR.

2 Stroke incidence following TAVR (Figure 1)

In an effort to adjust for discrepancies in the definitions of stroke used in various studies, the Valve Academic Research Consortium has provided definitions of transient ischemic attack (TIA) and stroke. TIA is defined as a new neurological deficit that resolves rapidly, in less than 24 h (usually within 1–2 h), without evidence of tissue injury in neuroimaging. Stroke is defined as new focal or global neurological deficit that persists for more than 24 h and is thought to be embolic, ischemic or hemorrhagic.
As will be discussed, the procedure of TAVR carries an inherent risk of stroke, which however continues to accrue with extended follow-up. Therefore, we should evaluate stroke risk with TAVR relative to the stroke risk of a similar patient population treated either medically, or with conventional SAVR, during the same follow-up period. Data from PARTNER 1B, study showed that medically treated patients had a 30-days stroke/TIA risk of 1.7%, and a 1-year risk of 4.5%, compared with corresponding risks of 6.7% and 10.6% in high risk TAVR patients. Early experience with TAVR was associated with stroke rates nearly twice as high compared to SAVR. Data from the PARTNER 1A study showed a risk of neurologic events with SAVR of 2.4% at 30 days and 4.3% at one year, with corresponding rates for TAVR of 5.5% and 8.3%, respectively. Generally, in high risk patients, the risk of stroke following SAVR is approximately 2%–4%. Hence, it is reasonable to speculate that violent manipulation of a calcified aorta and stenotic aortic valve with TAVR results in a higher frequency of cerebral events, through debris embolization, compared to SAVR during which debris removal and cross-clamping of the aorta is involved. On the contrary, the long-term risk of stroke following TAVR is somewhat similar to that of medically and/or surgically treated patients, and depends on their profile. In a much larger analysis of PARTNER trial including the continued access registry with 2621 patients, the 30-days, 1-year and 3-year stroke rate were 3.3% (85% of them within one week), 5.4% and 6.9%, respectively. In the randomized controlled trial of the self-expandable valve bioprosthesis (CoreValve, Medtronic, Minneapolis, MN) vs. SAVR in relatively high surgical risk patients (STS score 7.4%), the rates of stroke at 30 days and 1 year did not differ significantly between the two groups (4.9% vs. 6.2%, \( P = 0.46 \), and 8.8% vs. 12.6%, \( P = 0.1 \), respectively). A recent report including 3687 patients from the CoreValve US Extreme Risk and High Risk Pivotal Trials or Continued Access Study, the 1-year stroke rate after TAVR was 8.4%, with a frequency of major stroke 2.8% at 30 days, and 5% at 1 year. The frequency of TIA within 30 days was 0.5%, and within the first year 2.1%. Following initial experience with TAVR, various studies reported a range of stroke of 0–3.9% vs. 0.5%–5.7% with SAVR. Similarly, according to published registries, the overall incidence rate of stroke in high-risk patients after TAVR varied from 1.7% to 4.8%. An earlier meta-analysis including 10,037 patients subjected to TAVR in various studies published between 2004/01 and 2011/11 reported a total 30-days stroke rate of 3.3% ± 1.8% (nearly all major strokes), which increased at 1-year to 5.2% ± 3.4%. Two recent meta-analyses, one including seven European TAVR registries (9786 patients), and another including 29,034 patients, treated with both SAPIEN and CoreValve bioprostheses and involving both transfemoral (TF) and transapical (TA) approaches, reported a 1-year incidence of stroke of approximately 3%. Additionally, a recent report from 299 US hospitals (12,182 patients), reported a stroke rate of 4.1% at 1 year following TAVR. Finally, in a review of studies comparing TAVI vs. SAVR in patients with severe aortic stenosis and a mean risk score of 8% or less, the hazard for stroke was lower with TAVI (20 fewer per 1000 patients), however with a broad confidence interval (HR: 0.81, 95% CI: 0.63–1.01). Additionally, an analysis of patients with an STS PROM risk score < 7 revealed lower albeit not statistically significant stroke rates after TAVR compared with SAVR at 30 days (4.9% vs. 6.3%, \( P = 0.46 \)).
Thus, following the initial observation of a higher stroke rate with TAVR when compared to SAVR, latest studies, registries, and meta-analysis repetitively and constantly confirm that the incidence of stroke after TAVR decreased to rates comparable with those with SAVR.[15,19,23–28] This may be due to inclusion of lower risk patients compared to initial study cohorts, and to evolution of valve technology and implantation technique.

3 Timing and predictors of stroke following TAVR

The occurrence of TAVR related stroke demonstrates a bimodal pattern of distribution, which was evident in studies of the two most frequently implanted valves, namely the balloon expandable Edwards Sapien, and the self-expandable CorValve.[11,13,16] Indeed, in the CoreValve US Extreme Risk and High Risk Pivotal Trials, and the Continued Access Study, with the self-expanding CoreValve bioprosthesis, strokes clustered in an early phase (0–10 days; 4.1% of strokes), and a late phase (11–365 days; 4.3% of strokes), for a total stroke rate at 1 year of 8.4%.[16] As mentioned, in the PARTNER trial, 3.3% of patients experienced a stroke within the first 30 days, the vast majority within the first week (85%), whereas the corresponding rate of TIA within 30 days was much less (0.5%).[11] More specifically, in the PARTNER trial, the stroke rate demonstrated a very early peak on the second day post-procedure, dropping thereafter to a low constant rate of 0.8% at 1 to 2 weeks.[11] A meta-analysis of 10,037 patients reported an incidence of stroke manifesting in < 24 h post TAVR of 1.5% ± 1.4%.[15]

The bimodal distribution of stroke post TAVR implies that different mechanisms and potential contributing factors are involved in its pathophysiology. Indeed, predictors of early stroke include patients’ demographics, clinical characteristics, and procedural factors.[11,16] The former two probably reflect the degree of patients’ illness, whereas the latter mainly refer to the duration and complexity of the procedure. On the other hand, predictors of late stroke seem to be principally related to patients’ frailty.[11,16]

4 Early stroke predictors (Table 1)

In general, early stroke (within the first seven days) is broadly considered to be related to the procedure due to particle embolization. These particles are comprised of tissue fragments from the aortic valve, aorta, and left ventricular myocardium, and thrombus, as shown in studies using embolic protection devices during TAVR.[29] A potential explanation for a delayed (up to 7 days) diagnosis of a stroke causally related to the procedure, might be lack of early imaging, and the requirement of additional time for thrombus formation on the embolized material and subsequent clinical presentation.[11] Indeed, the high rate of peri-procedural stroke which seems to stabilize thereafter, highlights the paramount significance of procedural factors in stroke causality post TAVR.[11] However, it is also reasonable to assume that specific patient characteristics may relate with a higher predisposition for embolic events. However, despite the inherent complexity of analyzing and identifying two interrelated different groups of potential predictors of early stroke (i.e., procedural and baseline patient characteristics), it is important to realize that the former group of predictors (procedural) may be modifiable, whereas identification of the latter (patient characteristics), although theoretically not modifiable, could help us to avoid or improve certain procedural details which may confer a higher risk of stroke in specific patient subsets.

In the CoreValve trials, patient related multivariable predictors of stroke were a total NIHSS score > 0, history of stroke, or TIA, peripheral vascular disease, absence of prior coronary artery bypass surgery, presence of angina, low body mass index, and falls within the past six months.[16] Interestingly, there were no significant imaging predictors of early stroke (echocardiographic, or computerized tomographic).[16] In a recent meta-analysis by Krassopoulos, et al.,[23] the mean Logistic EuroSCORE was not associated with the incidence of stroke.

Procedural related multivariable predictors of stroke in the CoreValve trials were the total time in the catheteriza-

Table 1. Early and late stroke predictors.

| Patient related | Procedure related |
|----------------|-------------------|
| Female gender | AV annulus size |
| CKD           | Pure AS           |
| History of stroke | Total time in the Cathlab |
| PVD           | Time of delivery catheter in |
| Low BMI       | patient’s body    |
| History of falls | Rapid pacing     |
| NOAF          | Balloon predilation |
| Angina        | Valve repositioning |
| Absence of CABG | Balloon postdilatation (debatable) |

Early phase (0–10 days)

AF: atrial fibrillation; AS: aortic stenosis; AV: aortic valve; BMI: body mass index; BSA: body surface area; CABG: coronary artery bypass surgery; CKD: chronic kidney disease; PVD: peripheral vascular disease; NOAF: new onset atrial fibrillation.

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tion laboratory, the total time that the delivery catheter time in the patient’s body, rapid pacing during valvuloplasty, and repositioning of the CoreValve with a snare. In the PARTNER trial, predictors of stroke were stratified according to the access strategy, namely TF vs. TA. A higher aortic valve leaflet gradient pre-TAVR was a predictor of early strokes in TF access, and pure aortic stenosis without regurgitation, along with more valve post-dilatations for the TA approach. More rapid pacing during valvuloplasty was also a weak predictor of early stroke in the TA approach, whereas longer procedure time was weakly associated with an increasing number of late strokes in the TF approach.

At first glance, TA-TAVR might confer a lower risk of stroke compared to TF-TAVR, as it involves minimal manipulation of the ascending aorta and arch, which in elderly patients with severe atherosclerosis may be a source of embolic material. However, in the PARTNER trial, a slightly higher rate of stroke was noted in the transapical group of patients, potentially related to the higher vascular risk of the latter. On the other hand, in the meta-analysis by Eggebretch, et al., stroke rates at 30-days were significantly lower with the TA approach using the Edwards SAPIEN valve (2.7% ± 1.4%), compared to the retrograde transarterial (TF and subclavian) implantation of the same valve (4.2% ± 2.2%). However, retrograde transarterial implantation of the 18 Fr Medtronic/ CoreValve prosthesis compared to the bulkier 22–24 Fr Edwards SAPIEN valve was associated with a lower 30-days stroke rate (3.1% ± 2.2% vs. 4.2% ± 2.2%). Hence, it may be that the valve type and the bulkiness of the delivery system play a significant role in determining stroke risk when it comes to TF access. In the meta-analysis of seven European TAVR registries, the pooled estimate for the incidence of stroke was 0.03 [95% CI: 0.03–0.04], 0.03 [95% CI: 0.02–0.05] and 0.03 [0.02–0.04] for TF implanted SAPIEN™, TA implanted SAPIEN and CoreValve, respectively (test for subgroup difference, P = 0.79). In general, the majority of evidence does not verify an association between type of access (TA vs. retrograde TF) and stroke. Despite lack of significant differences in stroke rates between the two types of access, stroke predictors seem to differ between them as pointed above. The potential risk of stroke with new approaches like transcarotid has not been studied in detail.

Although balloon valvuloplasty with valve pre-dilatation has been associated with a higher risk for stroke, balloon post-dilatation of the prosthesis used to reduce severe paravalvular leak, is not universally recognized as predictor of stroke post TAVR. It has been proposed that this probably relates to the different design of valves used for TAVR. For example, the CoreValve prosthesis is surrounded by a relatively large metal scaffold, which may prevent particle embolization from the ascending aorta during post-dilatation. Additionally, balloon post-dilatation may actually reflect more extensive vascular disease, leading to the decision for the need of further valve dilatation. On the other hand, the type of valve per se seems to be not crucial as there was a similar stroke risk between them across a broad spectrum of studies.

The potential relationship of the aortic valve area with stroke post-TAVR is also debated. In the PARTNER trial, a higher rate of stroke was demonstrated in patients with smaller aortic valve area (6.3% vs. 2.8%). It has been shown that women demonstrate smaller aortic annuli dimensions than men, irrespective of age or body surface area. It may be that a smaller aortic anulus may increase the mechanical interaction between the native valve and the prosthesis, and this may partly explain the higher risk of early stroke demonstrated by women in some studies.

It would appear reasonable that operator, and center experience may also be predictors of stroke post TAVR. This was suggested by the meta-analysis by Athappan, et al., who found a 1.5% drop in stroke risk between early and late experience within high-volume centers, and this has been reproduced in a later meta-analysis. However, in the CoreValve trials, this was not evident. The latter observation may relate to the “sterile” environment of a clinical study, but the concept that the risk of stroke due to instrumentation of the aorta, arch, and aortic valve, may not be centre/operator dependent cannot be excluded. In the PARTNER trial, valve implantation during the “earlier date” of TAVR experience, had a weak and unreliable association with early stroke only in the TA group of patients. In essence, analyses based on chronology may be influenced by numerous patient and procedure related factors like patient selection, and procedural and device evolution, which make difficult to reach to definite conclusions regarding any potential relationship between stroke and the TAVR learning curve.

A recent meta-analysis of sixty-four studies involving 72,318 patients suggested that female sex, chronic kidney disease (CKD), performance of TAVR during the first half of centers’ experience, and post-procedural new onset of atrial fibrillation (AF), are associated with an increased risk of early stroke following TAVR. Most importantly, in this study, no association was found between early stroke following TAVR and other baseline risk factors, valve type and implantation approach. In contrast to other datasets, only CKD and not other markers of advanced atherosclero-
sics such as peripheral vascular disease, or cardiovascular disease (CAD), was associated with stroke post-TAVR in this analysis.[32] This may suggest the existence of a “renal factor” leading to an excess risk of stroke regardless of the existence of other traditional risk factors. This includes advanced atherosclerosis and calcification demonstrated by CKD patients, and the administration of suboptimal antithrombotic treatment due to bleeding risks. Finally, the strongest predictor of early stroke in this analysis was new onset AF, which happens in up to 30% TAVR patients, especially with the TA approach.[32] The pivotal role of new onset AF in predicting subacute (1–30 days), stroke following TAVR has also been pointed by earlier studies.[38]

5 Late stroke predictors (Table 1)

Predictors of late stroke seem to be principally related to patients’ atherosclerotic risk and frailty.[11,16] In the CoreValve trials, predictors of late strokes (between 11 days and 1 year) were small body surface area, severe aortic calcification, and falls within the past six months, with the latter being the only significant predictor of major stroke.[16] The degree of aortic calcification, however, is rather considered a marker of a severely diseased vascular system, with the potential for aorto-arterial embolism.[16] Predictors of late stroke in the PARTNER trial were dementia, and a smaller prosthetic valve size (23 vs. 26 mm) for the TF approach, and race (non-white), lower left ventricular ejection fraction (LVEF), and atrial fibrillation (AF), for the TA approach.[11] Markers of patients’ atherosclerotic risk and frailty such as prior cerebrovascular disease, peripheral vascular disease, and chronic AF, have also been shown to predict late stroke risk by others.[38]

In general, it seems that the baseline predictors of early stroke post-TAVR including both clinical and procedural factors, whereas after the first 10 days or so, post TAVR, stroke risk is mainly dependent on patient characteristics and not to specific valvular anatomic features.[16,39]

6 Clinical implications of stroke following TAVR

The occurrence of major stroke following TAVR is associated with increased early and late mortality.[11,38] However, mortality from stroke does not seem to differ between TAVR and SAVR.[28] In the CoreValve studies, the one-year mortality following a stroke was quite high and similar for patients who sustained the primary event either during the early or late phase of stroke distribution post TAVR (46.2% and 44.6% for all strokes).[16] The highest mortality was confined in patients with a major stroke. An alarming observation was that 7% of patients with a stroke within the first year experienced a recurrent stroke during the first year of follow-up.[16] In the PARTNER trial, both TIA and stroke had a major impact compared to expect one year survival rates (64% and 47% vs. 83% and 82%, respectively).[31] In the meta-analysis by Eggebrecht, et al,[15] (10,037 patients, 81.5 ± 1.8-years, mean logistic EuroSCORE 24.77% ± 5.60%), the average 30-day mortality was more than 3.5-fold higher in patients with stroke (25.5% ± 21.9% vs. 6.9% ± 4.2%). Similarly, in a recent meta-analysis of 29,034 patients with a mean age 81.37 years, mortality following a stroke within the first 30-days of implantation was 12.27%, and stroke related mortality was 28.22%, compared to 6.4% for patients without a stroke.[9] This fourfold increase in mortality corresponded to an OR of 6.45 (95% CI: 3.9–10.66, P < 0.0001).[9]

7 Silent stroke

There is a growing body of evidence that the real stroke rate following TAVR is underestimated.[40] This is due to the fact that the clinical definition of stroke and TIA, may be a low sensitivity measure. With increasing use of neuroimaging (CT and MRI), the definition of stroke has changed over time. Hence, the 2013 AHA/ASA expert consensus document proposed an “Updated Definition of Stroke for the 21st Century”, which updated the definition of cerebral infarction (based on imaging, and/or pathology), but also proposing a definition for “silent” central nervous system (CNS) infarction.[41] The latter constitutes imaging or pathological evidence of CNS infarction without acute clinical neurological dysfunction.[41] Subsequently, studies that used brain imaging with MRI [diffusion weighted imaging (DWI)] early post TAVR, found a more than tenfold increase in the rate of “silent infarction” compared to the rate of clinical evident ischemic stroke as reported in the PARTNER trial.[42,43] However, even with such sensitive contemporary brain imaging, different acquisition protocols, post-processing, and interpretation, may lead to a wide variation in the reported incidence of “silent infarction”, underlining the need for standardization of brain imaging protocols post TAVR.[40]

Inherent to the “silent” nature of such findings, is their largely unknown long-term implications. It may be that such brain lesions detected with MRI have an impact on patients’ neurocognitive function, which in one study not involving imaging was shown to decline in 5% of patients post TAVR.[44] In the well designed, albeit small neuro-TAVI trial, DWI-MRI imaging was used with serial systematic
neurologic and cognitive assessments in 44 consecutive patients.[45] Brain lesions were detected in 94% of patients, with worsening of NIHSS score in 22.6% at discharge and 14.8% at 30-days, whereas cognitive deviation from baseline using the Montreal cognitive assessment was shown in 33% and 41% of patients, respectively.[45] This study implies that cerebral insult may be much more frequent than reported, and it may be associated with neurological impairment not routinely evaluated with current scoring systems. A similar high rate (84%), of new brain lesions on DWI-MRI was reported in an earlier study of 32 patients undergoing TAVR, which is much higher compared to a 48% incidence in control patients undergoing surgical AVR.[42] However, no TAVR patient in this study developed clinical neurological events, or a measurable impairment of neurocognitive function at 3-months follow-up. Hence, the potential implications of this nearly universal imaging finding post TAVR needs clarification in larger scale studies.

Despite all these uncertainties, DWI-MRI may prove a useful research tool for evaluation of embolic protection devices, as a clearly smaller number of patients will be needed in such studies.[40]

8 Stroke prophylaxis (Figure 2)

It is evident that a strategy to reduce the probability of stroke following TAVI should include modification of procedural factors associated with the former, development of protection devices against debris embolization, and antithrombotic treatment during the procedure and thereafter. Unfractionated heparin (UFH) administration is the current standard of treatment during TAVR. The latter, is administered as a parenteral bolus, followed by additional doses until an activated clotting time (ACT) of ≥ 300 s is achieved, with complete reversal of anticoagulation by administration of protamine sulphate (milligram-to-milligram neutralisation dose), being available but not always necessary with the TF approach.[46] As major bleeding has a reported incidence of up to 17% post TAVR,[45] administration of bivalirudin could be an attractive alternative to UFH due to its lower incidence of major bleeding in coronary stenting trials.[47] An equal rate and type of early stroke with administration of bivalirudin instead of UFH during TAVR has been shown.[48] However, the effect of Bivalirudin on Aortic Valve Intervention Outcomes 2/3 (BRAVO 2/3) study, in which 802 patients undergoing TF-TAVR were randomized to bivalirudin versus UFH, failed to demonstrate superiority of bivalirudin as the latter did not result in significantly less major bleeding episodes 48 h [6.9% vs. 9.0%; relative risk: 0.77; 95% confidence interval (CI): 0.48–1.23; P = 0.27], with similar net adverse clinical events at 30 days.[49] Despite the fact that the noninferiority hypothesis was met regarding effectiveness, the authors pointed that due to cost

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**TAVR: Stroke Prophylaxis Strategies During and After the Procedure**

|                     | Anticoagulation (UFH) | VKA-Anticoagulation (?) |
|---------------------|-----------------------|-------------------------|
| **Procedural Details**<br>(Avoid: pre/post balloon dilatation, rapid pacing) |                       |                         |
| **Embolic Protection Devices (?)** |                       |                         |
| **Without AF**      | Antiplatelets (DAPT)  | DAPT                    | DAPT vs. MAPT?          |
| **Chronic AF**      | ASA + UFH             | DAPT + VKA              | VKA                     |
| **NOAF**            | DAPT + UFH            | DAPT + VKA              | VKA                     |
| **Procedure**       | 6 months              | 6-12 months             |

*Figure 2. Stroke prophylaxis strategies.* During TAVR, antithrombotic treatment includes anticoagulation with UFH, and antiplatelets. DAPT with low dose ASA and Clop is administered thereafter for six months, although the exact time needed is not known. Certain procedural details like avoiding balloon pre-dilatation and rapid pacing, minimal contact with the aortic arch etc, may contribute to stroke prophylaxis. For patients with chronic AF low dose ASA and UFH is administered during the procedure, whereas VKA with low dose ASA or Clopidogrel are administered for 6 months, and VKA thereafter. Similarly, for NOAF, switching from DAPT to ASA/clopidogrel plus VKA is preferred instead of triple antithrombotic treatment. The role of extended DAPT or MAPT, or VKA-anticoagulation treatment is not known. AF: atrial fibrillation; ASA: aspirin; Clop: clopidogrel; DAPT: dual antiplatelet therapy; MAPT: monoantiplatelet; NOAF: new onset atrial fibrillation; TAVR: transcatheter aortic valve replacement; UFH: unfractionated heparin; VKA: vitamin-k antagonists.

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issues, UFH should remain the standard of care, with bivalirudin reserved for patients unable to receive the former.

There is no consensus regarding the best antithrombotic treatment strategy post TAVR regarding both the antithrombotic regimen, and the duration of such treatment due to lack of properly designed and powered studies thus far.\[50\] In the CoreValve trials, approximately 95% of patients were discharged on aspirin, 85% on aspirin with a P2Y12 inhibitor, and 61% on anticoagulants.\[10\] The antithrombotic regimen did not differ between patients with or without stroke. Current AHA/ACC guideline recommendations suggest empirical therapy with ASA and clopidogrel for 6 months after TAVI (class IIb, level of evidence C).\[51\] Surprisingly a systematic review and meta-analysis of studies comparing dual antiplatelet (DAPT) with mono-antiplatelet (MAPT) therapy following TAVR, showed a trend toward an increase in 30-day stroke, spontaneous MI, all-cause mortality, and combined lethal and major bleeding with DAPT.\[52\] However, the authors pointed that this was driven by increased events in observational studies, with no difference in randomized studies. Nevertheless, despite current recommendations, there is no robust evidence that DAPT may be superior to MAPT in preventing ischemic complications post-TAVR, whereas it may increase bleeding complications.\[52\] MAPT with clopidogrel may be equally efficacious to aspirin, and clopidogrel 300 mg loading before the procedure, may increase periprocedural bleeding complications.\[52\] More importantly, data from the PARTNER trial showed a rate of 5.9% major late bleeding (≥ 30 days) post-TAVR at a median time 132 days.\[53\] These included gastrointestinal (40.8%), intracranial (15.5%), and traumatic fall (7.8%) bleedings. These late bleeding events were strong predictors of mortality between 30 days and 1 year (adjusted hazard ratio: 3.91; 95% CI: 2.67–5.71; \(P < 0.001\)).\[53\] Data from the CoreValve US Extreme Risk and High Risk Pivotal Trials or Continued Access Study, designate 8.9% of strokes post-TAVR as hemorrhagic.\[16\] These occurred solely in patients on double antiplatelet therapy (aspirin and clopidogrel), aspirin and anticoagulant, and patients on triple antithrombotic therapy, with nearly half of hemorrhagic strokes occurring in the latter, highlighting the bleeding risk with combination of antithrombotic therapies in this fragile population. However, frequent comorbidities in this patient population may require addition of anticoagulation to antiplatelet therapy, with a history of, or new onset AF being the most frequent indication for the latter. New onset AF may happen in up to 30% of patients early post-TAVR as mentioned above.\[52,53\] In patients with a history of AF, an older expert opinion document suggests continuing anticoagulation and adding low dose aspirin without clopidogrel post-TAVR.\[46\] The recent ACC/AHA guidelines do not comment specifically on anticoagulation post-TAVR.\[51\] The Canadian perspective is against triple antithrombotic therapy post-TAVR unless definite need exists.\[54\] Finally, European Guidelines suggest use of vitamin-K antagonists with either aspirin, or clopidogrel, weighting the risk of bleeding.\[55\]

Procedural improvements (smaller size and better flexibility of delivery catheters, avoidance of balloon pre-dilatation), may have contributed to the decrease in the incidence of stroke following TAVR, as already mentioned. Although the role of balloon post-dilatation in early stroke post TAVR is still debated,\[11,16,32,33\] proper imaging of the aortic annulus for valvular size selection, and emphasis on device features which may reduce paravalvular leak (external skirt of the Sapien 3 valve, or repositionable prostheses), are advised so as to avoid the former.\[32\] Continuous in hospital and Holter outpatient monitoring for capturing new onset AF may also be important in TAVR patients as the latter seems to be a significant predictor of stroke.\[32\]

Finally, the use of cerebral protection devices has not shown any positive clinical results yet.\[30,50\] These devices usually employ a filter membrane used to either capture, or deflect debris away from cerebral circulation during the procedure. However, a significant reduction of total ischemic lesion volume, and number of new ischemic cerebral lesions has been reported with some devices.\[45-57\]

### 9 Conclusions

Stroke is a devastating complication being confined mainly in the periprocedural and 30-day period following TAVR, with a lower and relatively constant frequency thereafter. Early stroke is mainly due to debris embolization during the procedure, whereas later events are associated with patient specific factors. Despite the fact that the rate of clinical stroke has been constantly decreasing compared to initial TAVR experience, modern neuro-imaging with MRI suggests that new ischemic lesions post-TAVR are almost universal. The impact of the latter is largely unknown, however they seem to correlate with a reduction in neurocognitive function. Because TAVR is set to expand its indication to lower surgical-risk patients, stroke prophylaxis during and after TAVR becomes of paramount importance. Based on clinical and pathophysiological evidence, three lines of research are actively employed towards this direction: improvement in valve and delivery system technology with an aim to reduce manipulations and contact with the calcified aortic arch and native valve, antithrombotic therapy, and embolic protection devices. Careful patient selec-
tion, design of the procedure, and tailored antithrombotic strategies respecting the bleeding risks of this fragile population appear crucial in further reducing stroke rate following TAVR.

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This article is part of “Transcatheter aortic valve implantation” Special Issue. Guest Editors: Ioanna Koniari, George Hahalis