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Review

Incidence and Prevention of Strokes in TAVI

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Abstract: Transcatheter aortic valve implantation (TAVI) is now a widely adopted option for many inoperable and high risk patients with severe aortic valve stenosis, and clinical trials continue to show great benefit with regards to mortality and major cardiovascular endpoints. As the technology continues to expand and possibly grow to include intermediate and low risk populations, investigators have remained focused on efforts to reduce the risk of peri-procedural complications, of which neurologic events remain some of the most feared. Fortunately, contemporary studies have shown a significant decline in the risk of stroke with TAVI as compared to early clinical trials, and no difference when compared to surgical aortic valve replacement in the most recent trials. This review will focus on current methods for diagnosing, defining, and quantifying the effect of stroke after TAVI, explore the evidence with regards to stroke risk in various populations undergoing these procedures, discuss possible mechanisms for both early and late neurologic events after TAVI, and discuss strategies for both pharmacologic and device based embolic protection during these procedures.

Keywords: TAVI; TAVR; transcatheter aortic valve implantation; stroke; embolic protection device; anti-platelet; anti-coagulation

1. Introduction

Transcatheter aortic valve implantation (TAVI) provides a significant mortality benefit for patients with severe aortic stenosis who are at prohibitive surgical risk [1,2]. It is also an effective alternative to surgical aortic valve replacement (SAVR) for patients at high surgical risk, with some studies showing superiority [3,4]. It continues to be studied in intermediate risk populations and the results from large clinical trials are eagerly awaited.

Early clinical trials suggested a higher incidence of neurologic events in patients undergoing TAVI as compared to surgical AVR and/or non-operative control groups, but more recent studies

have shown a significant decrease in the incidence of stroke and TIA in these populations. Stroke is associated with significant long-term morbidity, mortality, and decreased quality of life, making it one of the most feared complications of any procedure. Thus, great effort has been placed on gaining a better understanding of the mechanisms that underlie these neurologic events and developing strategies to reduce their incidence.

In this review we will explore the data regarding the diagnosis, definition, and incidence of these events, discuss the possible mechanisms for neurologic events that occur both during and after TAVI, and focus on pharmacologic and procedural based strategies to reduce strokes associated with TAVI including the utilization of intra-procedural, embolic protection devices.

2. Diagnosis of neurologic events

Neurologic events after TAVI have been diagnosed and quantified by a wide variety of clinical, functional, and radiographic methods in both clinical practice and throughout the literature. It is important to understand the strengths and weaknesses of each of these approaches to understand their utility as surrogate endpoints for patients, and how they are utilized in clinical trials to compare various strategies for managing aortic valve disease. In the past, there was little consistency between studies with regards to how neurologic events were diagnosed and defined. This has sometimes led to misguided comparisons between contemporary clinical trials and historical literature or surgical databases that have not been developed using the same definitions. For example, the 2008 Society of Thoracic Surgeons report estimated a 1.5% risk of stroke with isolated, surgical aortic valve replacement, but these events were classified based on site reported events which may be inaccurate [5]. Demonstrating this point, a prospective study showed that when strokes were classified based on pre- and post-surgical evaluation by a neurologist, 34 clinical strokes were identified among 196 patients ≥ 65 years old undergoing SAVR, but ultimately, only 13 of these 34 cases were found to be reported in the STS database [6].

Thus, in effort to establish consistency in the valve-disease related literature, there is wide agreement that the diagnosis of stroke or TIA in the setting of clinical trials should be made based on current guidelines published by the Valve Academic Research Consortium, referred to in their second iteration as the "VARC-2" criteria [7,8]. These criteria require a clinical definition of stroke, defined as the detection of a focal or global neurological deficit in the absence of another identifiable cause, and necessitate that the diagnosis be confirmed by a neurologist, neurosurgical specialist, or neuroimaging procedure. The VARC-2 criteria further differentiate neurologic events into TIA, stroke, or disabling stroke based on the duration of the deficit. While the establishment and utilization of the VARC-2 criteria has led to improved consistency in large clinical trials, more sensitive ways to determine sub-clinical events continue to be important. This is particularly true when developing and testing new techniques aimed at reducing neurologic events, considering how infrequent clinical strokes have become.

One of the most sensitive ways to identify sub-clinical micro-emboli during a procedure is by detection of transcranial Doppler (TCD) signals from the intracranial arterial circulation. The presence of high-intensity transient signals (HITS) can be quantified as either present, absent, or by the total number of signals recorded. It is not clear what truly causes these Doppler signals however, and HITS have been hypothesized to represent solid microemboli, cavitation, gaseous bubbles, or even artifacts, and various artifact elimination algorithms have been used in studies [9]. TCD signals

have been studied in both surgical and trans-catheter aortic valve replacement cohorts. One study evaluated 24 patients undergoing surgical AVR with or without an embolic protection filter, and surprisingly found that there were more HITS in patients who had a filter in place compared to those without, although there were no differences in clinical events, diffusion weighted MRI, or neuropsychological findings between groups [10]. In studies comparing surgical AVR and TAVI, one group reported fewer total HITS with TAVI, with the highest incidence of HITS in the surgical group occurring while coming off of cardiopulmonary bypass, but showed no differences in clinical events [11]. Another group showed similarly higher HITS with surgical AVR but interestingly there were fewer lesions detected by MRI in the surgical group as compared to the TAVI cohort [9]. Thus, TCD as a clinical tool has largely been abandoned due to the lack of a clear association with either radiographic or clinical endpoints.

Diffusion weighted magnetic resonance imaging (DW-MRI) is another highly sensitive method for identifying acute ischemia in the brain, and has been employed extensively both as a clinical and research tool for evaluating neurologic events associated with aortic valve procedures (Figure 1). DW-MRI is able to detect sub-clinical events in up to 47% of patients undergoing surgical AVR, and up to two thirds of patients undergoing TAVI in some studies [9]. While the relationship between sub-clinical findings on DW-MRI and long-term neurologic sequela is still unclear, the technique has become especially useful in early clinical trials involving embolic protection devices where sub-clinical events can be quantified based on both the number and volume of new DW-MRI findings.

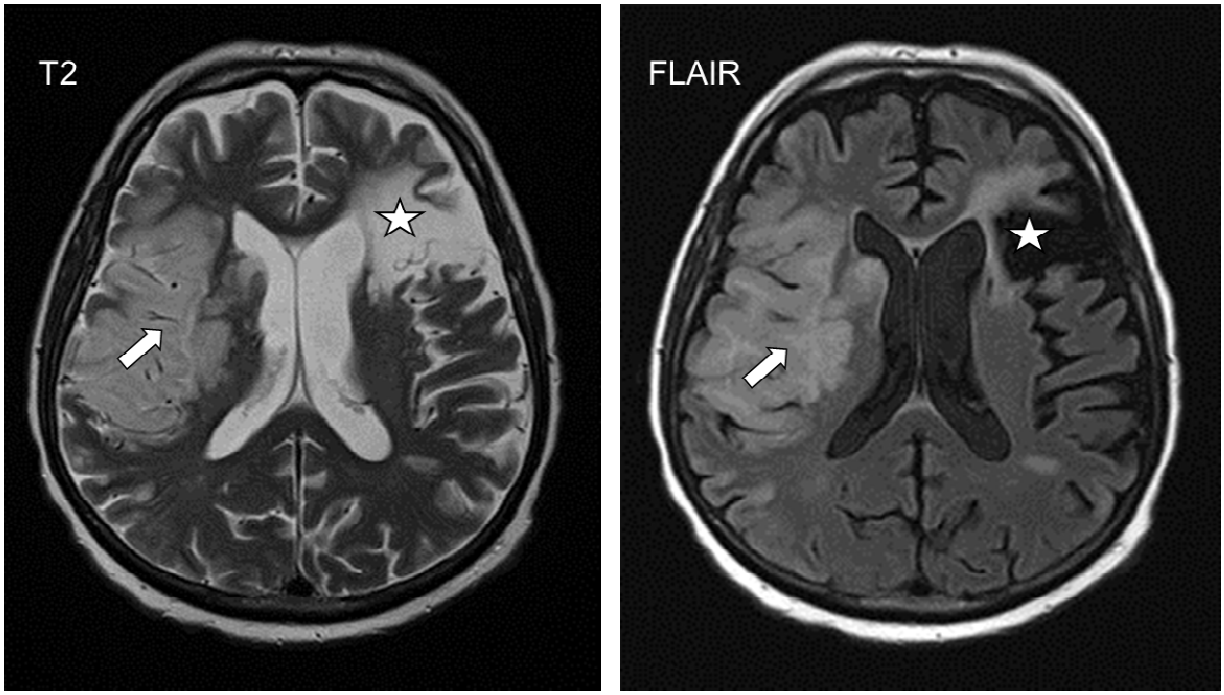

Figure 1. Embolic stroke after TAVI. Embolic stroke involving the right middle cerebral artery (R-MCA) distribution (arrow) after TAVI, seen on T2 and Flair MRI images. Superimposed is an old, transcortical infarct in the left frontal and parietal lobe (star). *(Reproduced from Intervent Cardiology Clinics, Jones et al. 2015;4(1):83-93 with permission from Elsevier)[12]*

Finally, in attempts to find more sensitive ways to detect clinically relevant events, some have used neurocognitive testing to identify subtle neurologic changes in cerebral function. The most well known of these methods is the Mini-Mental State Examination, but many others exist and have been looked at in a variety of studies [9]. Generally, these tests attempt to identify changes with regards to memory, attention, language, or other cognitive functions, but often require specific expertise to apply, and results can vary greatly based on a patient's baseline visual acuity, hearing ability, or educational background.

3. The incidence and predictors of stroke in surgical AVR and TAVI

As stated above, the estimated stroke risk for isolated aortic valve surgery based on the 2008 report from the STS database is 1.5%. Older age, female gender, prior cerebrovascular or peripheral vascular disease, diabetes mellitus, hypertension, and previous cardiac surgery were all identified as clinical risk factors associated with a higher risk of stroke [5]. Procedural variables that increased stroke rate included urgent surgeries, longer cardio-pulmonary bypass times, use of hemofiltration, and high blood transfusion requirements [5]. Other reports have given estimates that range from 0.7–5.0% risk of stroke with isolated valve surgery, and when AVR is combined with coronary artery bypass grafting, the risk is increased [13,14]. Thus, in patients who are being evaluated for high-risk AVR or TAVI, the risk of stroke with surgery is likely to be significantly higher than the 1.5% estimate from the STS database. Representative of this fact, one study of 159 high-risk patients undergoing surgical AVR as defined by an STS score > 10 showed a 4.4% rate of permanent neurological deficit and a 2.5% rate of transient events after surgery [15].

Similarly, the risk of stroke in patients undergoing TAVI has been estimated based on a large meta-analysis of 10,037 patients showing that the overall incidence of 30-day stroke or TIA was 3.3 ± 1.8% with most events representing major stroke (2.9 ± 1.8%), although this data is vulnerable to the same inaccuracies that plague the STS database, as it combines multiple definitions of stroke and represents a heterogeneous group of studies [16]. Data from the PARTNER trial showed that having a smaller aortic valve area was an independent predictor for early stroke after TAVI, and late strokes (after 30 days) were more common among patients with a history of stroke between 6–12 months prior to the procedure, those who were not a candidate for trans-femoral access (perhaps reflecting higher atherosclerotic burden), and patients who had higher NYHA functional class symptoms [17]. Other studies have shown that a prior history of cerebrovascular disease, severe aortic regurgitation at baseline, chronic obstructive pulmonary disease, or a body mass index < 25 kg/m were independent, patient-related predictors for events after TAVI [18–20]. The first major randomized control study to report outcomes with transcatheter aortic valve replacement as compared to surgical or non-operative control groups was the Placement of Aortic Transcatheter Valves (PARTNER) trial using the Edwards SAPIEN balloon-expandable, bovine pericardial valve (Edwards Lifesciences, Irvine, CA; USA). In the PARTNER IB cohort that compared transfermoral (TF)-TAVI vs. non-operative therapy for patients at extreme surgical risk, there was a 6.7% incidence of ischemic stroke within 30-days with TAVI as compared to 1.7% in the control group ($p = 0.02$) [2]. In the PARTNER IA cohort that compared TAVI to surgical AVR for patients at high surgical risk, there was a 2-fold increased risk of the composite of stroke or TIA within 30-days in the TAVI group (5.5% vs. 2.4%, $p = 0.04$), though the rate of major stroke was similar (3.8 vs. 2.1%, $p = 0.20$) [4]. Thus, these initial results led many to conclude that TAVI carried a higher risk of neurologic events

as compared to surgical AVR.

Subsequent studies however did not substantiate these initial concerns. The more contemporary PARTNER II trial involved the next-generation SAPIEN XT device, which features a lower-profile delivery system, improved valve frame, and leaflet geometry enhancements. In PARTNER II, inoperable patients who received the SAPIEN XT device had a 3.2% risk of disabling stroke, much lower than the 6.7% rate in the initial trials (Leon, ACC 2013). Furthermore, after FDA approval of the first-generation SAPIEN valve, the US commercial experience among 7,710 cases from November 2011–May 2013 was reported by the STS/ACC Transcatheter Valve Therapy (TVT) Registry, and demonstrated a site-reported, in-hospital and 30 day stroke risk of 2% and 2.8% respectively (based on standardized VARC-2 criteria) [21].

Finally, the results of the self-expanding, porcine-pericardial CoreValve ReValving System (Medtronic Inc., Minneapolis, MN; USA) pivotal trial were recently published. In patients at extreme-risk for SAVR, the rate of major stroke at 30-days was 2.3% after TAVI [3]. For patients at high-risk for surgery, there was no difference in the rate of stroke at 30-days with TAVI as compared to surgical AVR (4.9% with TAVI vs. 6.2% with surgery, $p = 0.46$) [1]. Thus, while the initial literature led to concerns for an elevated risk of stroke with TAVI as compared to surgical AVR, ensuing randomized control trials and registry data have shown that these conclusions were premature, and that the risk of neurologic events with TAVI continues to decline (Table 1).

Table 1. Reported stroke rates from the pivotal trials studying the Edwards SAPIEN (PARTNER) and Medtronic CoreValve.

Study	30-days			1-year		
	TAVI	Control*	*p*-value	TAVI	Control*	*p*-value
PARTNER cohort B, (inoperable):	7.3%	1.7%	0.010	11.2%	5.5%	0.06
CoreValve, Extreme surgical risk:	4.0%	N/A	N/A	7.0%	N/A	N/A
PARTNER cohort A, (high surgical risk):	5.5%	2.4%	0.04	8.3%	4.3%	0.04
CoreValve, high surgical risk:	4.9%	6.2%	0.46	8.8%	12.6%	0.10

*Control group for high surgical risk studies = surgical AVR, control group for PARTNER cohort B = medical management, the CoreValve Extreme surgical risk study was compared to historical controls only.

4. Possible mechanisms for neurologic events complicating TAVI

There are a number of procedural and non-procedural factors that could be implicated in causing neurologic events during and after TAVI (Table 2). Peri-procedural events are likely to be caused by emboli that are elaborated during manipulation of catheters, wires, or valve delivery devices in the aorta, aortic root, or across the aortic valve. These risks are not unique to TAVI procedures, and are present even during routine, diagnostic coronary angiography, where stroke is reported to occur in approximately 0.2–0.4% of cases [22]. Elderly patients with multiple comorbidities are known to be at an even higher risk of procedure related neurologic events [22].

Crossing a severely calcified aortic valve has been shown to add to the risk of neurologic events and performing balloon aortic valvuloplasty (BAV), which is often a preparatory step prior to valve implantation, can itself carry a risk of stroke that approaches 2% [23,24]. Finally, unique to TAVI, positioning of the rigid device across the native valve, subsequent valve deployment, or post-dilation of an under-expanded prosthesis all provide additional opportunities for embolic particles to be liberated [25].

Table 2. Mechanisms of stroke complicating TAVI.

Timing	Mechanism of Stroke	Potential Associated Factors
Peri-procedural	Embolic:	• Wire and catheter manipulation in the aortic arch, ascending aorta, or aortic root. • Balloon aortic valvuloplasty. • Device positioning in the aortic root and annulus. • Valve deployment. • Post-dilation of an under-expanded valve.
	Hemorrhagic:	• Bolus dose heparin use during procedure. • Severe hypertension during procedure.
	Global ischemia:	• Severe hypotension during procedure. • Anesthetic complications. • Rapid RV pacing during valve deployment.
Post-procedural	Thrombo-embolic:	• New onset atrial fibrillation. • Other cardio-embolic phenomena.
	Hemorrhagic:	• Typical risk factors associated with long-term anti-platelet and/or anti-coagulant medication use.

Although embolism is thought to be the predominant mechanism, non-embolic events might result from global ischemia in vulnerable patients. This could occur during periods of relative cerebral hypoperfusion (either extreme hypotension or hypertension), due to complications of general anesthesia, or from rapid pacing of the right ventricle during valve deployment. Hemorrhagic stroke is significantly less common TAVI patients as compared to ischemic stroke, but does rarely occur. Finally, thrombo-embolic phenomena from new or pre-existing atrial fibrillation can lead to cardio-embolic events when inadequately diagnosed or pharmacologically managed, and is a significant factor to consider in patients suffering more delayed events. In one study, new onset atrial fibrillation was found in 31.9% of patients following TAVI, and was associated with a higher rate of stroke or systemic embolism (13.6% vs. 3.2%, adjusted p-value = 0.047) at 30-days, with no difference in mortality at 30-days or 1 year follow-up [26].

5. Procedural variables that impact stroke risk

Given that most neurologic events are thought to be due to embolic phenomena, many authors have compared the data from different device designs, vascular access approaches, or other

procedural variables that may impact the incidence of stroke with TAVI. For example, it has been hypothesized that the transapical (TA) approach may carry a lower risk of stroke as compared to the transfemoral (TF) approach given that the latter requires the passage of a bulky device over the aortic arch, requires crossing of the stenotic valve in a retrograde fashion, and may be associated with a higher incidence of paravalvular leak [27]. One early meta-analysis of 7,564 patients gave further support to this theory showing a trend toward a lower rate of 30-day stroke/TIA with the TA SAPIEN valve (2.7 ± 1.4%) as compared to the TF SAPIEN (4.2 ± 2.2%) or TF CoreValve (3.1 ± 2.2%) approach (not statistically significant) [16]. A larger, more recent meta-analysis did not substantiate these early hypotheses however, and showed a pooled 30-day stroke rate after TF-TAVI of 2.8% (95% CI: 2.4–3.4) among 18,712 patients and an identical 2.8% (95% CI: 2.0–3.9) among 5,650 TA patients, comparing data from large multicenter registries [28]. There was also no difference in stroke rates when combining data from single-center studies (3.8% vs. 3.4%) which included an additional 4,556 TF and 2,588 TA patients [28]. The fact that both the TF and TA approach have shown low and equivalent rates of stroke in this large meta-analysis likely represents better patient selection as the technology has advanced, and the complementary role of both TF and TA approaches.

Authors have also looked to device design to identify differences in stroke risk considering the initial concern for elevated stroke rates in the PARTNER trial, and comparatively promising data from the CoreValve registries. The CHOICE trial randomized high-risk patients to receive either the SAPIEN XT (121 patients) or the CoreValve (120 patients), and reported a 30-day risk of stroke of 5.8% (3 major, 4 minor) vs. 2.6% (3 major), respectively, which was not a statistically significant difference (p = 0.33) [29]. Similarly, a large meta-analysis showed no difference in pooled 30-day stroke risk, 3.0% [95% CI 2.4–3.7] vs. 2.4% [95% CI 1.9–3.2] with the SAPIEN and CoreValve devices respectively [28].

As device technology continues to advance, authors have further considered whether low-profile delivery devices are a driving factor in the observed reduction in stroke rates between first and second-generation devices. The SAPIEN valve which was studied in the initial PARTNER I trial requires a 22- or 24-F delivery sheath as compared to the SAPIEN XT and CoreValve systems which both use an 18-F sheath. Newer, device designs have even smaller diameter systems. While it is logical to think that a less bulky device might cause fewer traumas to the aortic arch and annulus, direct comparisons in the literature are difficult to find. Most compelling perhaps are the initial results from the PARNTER II trial (Leon, ACC 2013, unpublished) showing a 3.2% incidence of disabling stroke at 30 days among 284 inoperable patients randomized to the SAPIEN XT device and a similar 3.0% risk in 276 patients undergoing first-generation SAPIEN valve implantation, much reduced from the 6.7% risk of stroke in the inoperable cohort of the PARTNER I trial. This data would suggest that other factors aside from the device design may be playing a larger role in the reduction of neurologic events over time such as greater operator experience, better patient selection, or perhaps more precise valve-sizing using 3-dimensional imaging.

Precise valve-sizing is important due to the potential, added risk of stroke in patients who require balloon post-dilation of the deployed valve or placement of more than one valve due to paravalvular leak. One study showed an 11.9% risk of 30-day stroke for patients requiring post-dilation as compared to 2.0% (p = 0.006) for patients who did not [30]. Subsequent studies however have not demonstrated such dramatic differences in stroke or TIA between these groups [25].

6. Pharmacologic strategies to reduce stroke with TAVI

Currently, pharmacologic strategies regarding TAVI are largely based on expert opinion and are extrapolated from the surgical and PCI literature. Large studies comparing different anticoagulant or antiplatelet strategies are unfortunately lacking. Adding to the confusion, strategies with surgical AVR are not uniform either, and currently many surgeons recommend use of oral vitamin K antagonist therapy for 3 months after traditional bioprosthetic AVR. The most recent 2012 ACCP guidelines do not support this practice however (Grade 2C), and it has been largely abandoned in favor of aspirin monotherapy in many centers [31]. With regards to TAVI, the ACCP guidelines, as well as current 2012 ACCF/AATS/SCAI/STS joint guidelines specific to transcatheter AVR both recommend use of aspirin (50-100 mg daily) plus clopidogrel (75 mg daily) for 3 months after TAVI followed by aspirin alone (Grade 2C) [31,32]. Oral anticoagulants (including warfarin or new oral anticoagulants) are not recommended unless indicated for other reasons such as treating atrial fibrillation or venous thromboembolism. Weight-based heparin has been used for intra-procedural anticoagulation in both the PARTNER and CoreValve study protocols, with a goal of achieving an activated clotting time of >250 seconds after arterial access is obtained.

Several clinical trials comparing different antiplatelet or anticoagulant strategies in TAVI are currently ongoing. The ARTE trial (aspirin versus aspirin and clopidogrel following transcatheter aortic valve implantation) is underway and plans to randomize 200 patients after SAPIEN XT valve implantation (clinicaltrials.gov: NCT01559298). This builds off a smaller single-center study showing similar MACCE, mortality, and bleeding rates, with no significant difference in major stroke (3% vs. 5%, $p = 0.49$) among 79 patients treated with dual anti-platelet therapy vs. aspirin alone [33]. The BRAVO 2/3 trial is a randomized control trial of bivalirudin vs. heparin for patients undergoing TAVI (clinicaltrials.gov: NCT01651780). This trial builds off the results of BRAVO 1, which studied patients undergoing elective balloon aortic valvuloplasty (BAV) with bivalirudin as compared to unfractionated heparin, and indicated lower rates of in-hospital major bleeding and similar rates of ischemic stroke in the bivalirudin group [34]. Finally, the AUREA trial compares dual antiplatelet therapy to oral anticoagulation with the vitamin K antagonist acenocoumarol after TAVI, and is also ongoing (clinicaltrials.gov: NCT01642134).

7. Embolic protection strategies:

As most events are thought to be embolic in nature, the utilization of filters and embolic deflection devices during TAVI has become an exciting strategy to potentially reduce the incidence of peri-procedural stroke [35]. There are currently four devices that have been, or are currently under investigation for their potential applications in TAVI (Table 3 and Figure 2).

The Embrella Embolic Deflector Device (Edwards Lifesciences, Irvine, CA), is inserted through a 6-Fr sheath in the right arm (radial or brachial artery), and consists of two, oval-shaped petals that cover the ostium of the innominate and left common carotid arteries. The petals are made from a nitinol frame with a polyurethane membrane that allows blood flow to the branch vessels, but deflects particles larger than 100μm in diameter. The device covers a length of 58 mm with a width of 25 mm, which means the petals are unable to cover the left subclavian artery in approximately 50% of patients, leaving the left vertebral artery vulnerable. First-in-human experience showed feasibility in three patients undergoing TAVI and one patient undergoing BAV [36]. Subsequently, the

"Prospective Outcome study in patients undergoing TAVI to Examine Cerebral Ischemia and Bleeding Complications" (PROTAVI-C) trial enrolled 54 trans-femoral TAVI patients in a phase 1 pilot study. Initial results (presented by Rodes-Cabau et al.; EuroPCI, 2013, unpublished) unfortunately showed that cerebral microembolization (as assessed by trans-cranial Doppler) occurred during each step of the procedure including Embrella insertion, valve positioning, and valve deployment. Furthermore, all but one patient had some new diffusion abnormality on MRI after the procedure, although there was suggestion that the total lesion volume was decreased compared to historical reports. Phase 2 of the PROTAVI-C trial is a randomized, control trial of the Embrella deflection device among patients undergoing TAVI, and is ongoing.

Table 3. Summary of clinical trials regarding embolic protection devices in TAVI.

Device	Arterial access	Initial clinical trial results	Ongoing trials.
Embrella Embolic Deflector	6Fr R-radial or brachial artery.	• First-in-human (4 patients): Showed safety. • PROTAVI-C Trial (54 patients): All but 1 patient had some new diffusion abnormality on MRI after the procedure. There was suggestion however that the lesion volume was decreased compared to historical reports	Phase II of PROTAVI-C, randomized control trial, ongoing.
Claret Montage Device	6Fr R-radial or brachial artery.	• First-in-human (40 patients) • 4 vascular injuries, 3 requiring surgical repair. • 2 major strokes (occurring at 4 hours and 27 days after procedure). • 1 minor stroke (occurring at 30 days after procedure.	SENTINEL study, randomized control trial, projected enrollment 359 patients.
Triguard Cerebral Protection Device	9Fr Femoral arterial sheath which allows concomitant use of a 6 French pigtail catheter.	• First-in-human (15 patients vs. 20 retrospective controls): Showed safety, 3.2 new cerebral lesions per patient on MRI with device compared to 7.2 per patient in the retrospective control group. • DEFLECT I trial (28 patients vs. 150 retrospective controls): 70% of patients had one or more new lesions on MRI with the device vs. 76% without. New lesions per patient (5.1 (0–28) with device vs. 4.4 (0–39)). Average volume of new lesions (0.70 (0–3.94) cm^3 with device vs. 1.64 (0–70.3) cm^3).	DEFLECT II: Pilot study, 12 patients. DEFLECT III: Randomized control trial, projected enrollment 86 patients.
Embol-X intraaortic filtration system	17Fr direct aortic introducer sheath.	• Case reports (3 patients): Showed safety, technical success, and all filters recovered embolic debris.	TAo-EmbolX study, randomized control trial, projected enrollment 50 trans-aortic TAVI patients.

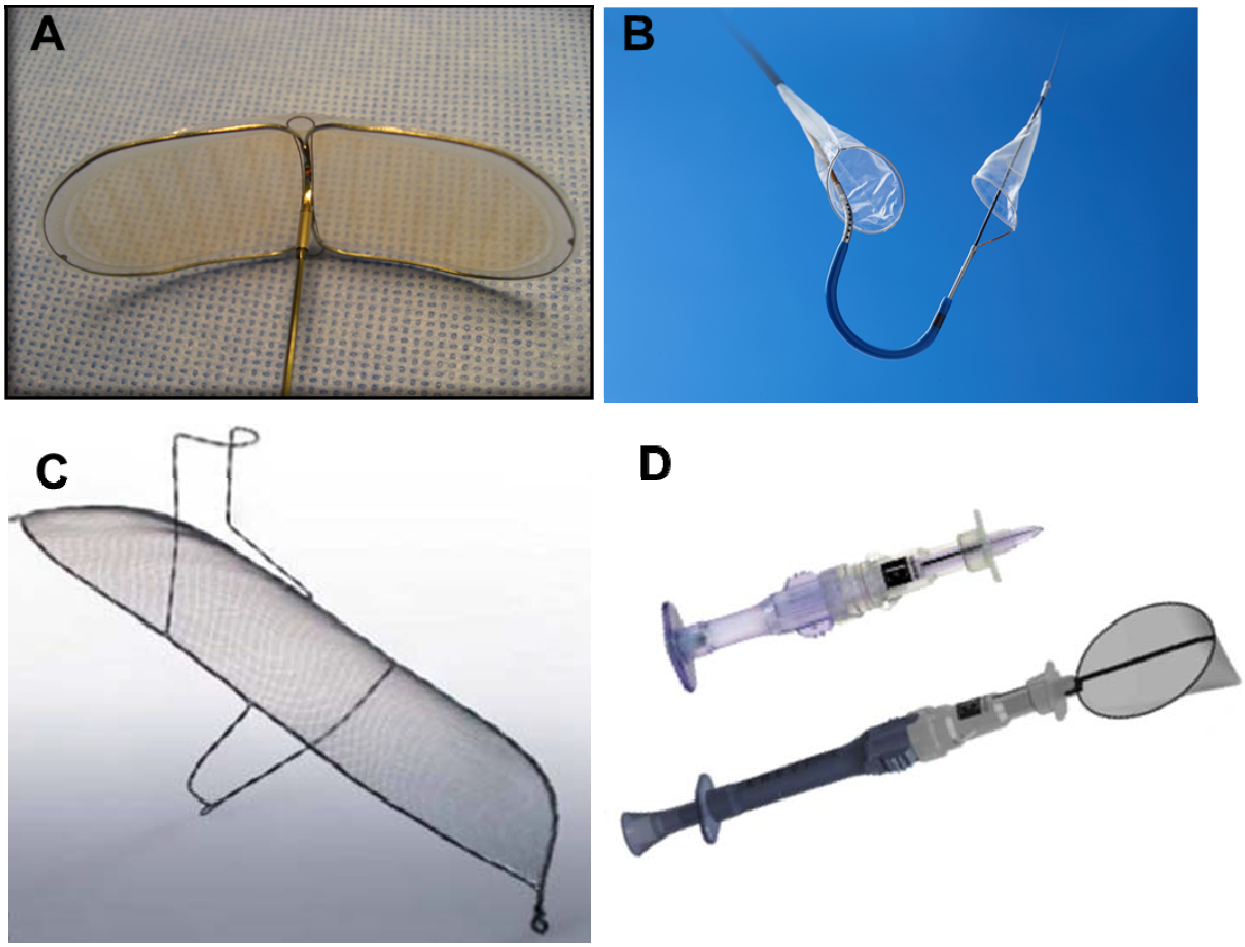

Figure 2. Embolic protection devices used in TAVI. Embolic protection devices that are under investigation for use during TAVI. A: The Embrella Embolic Deflector. B: The Claret Montage Device. C: The Triguard Cerebral Protection Device. D: The Embol-X intraaortic filtration system. (*Courtesy of [A, D] Edwards Lifesciences, Irvine, CA; [B] Claret Medical, Santa Rosa, CA; and [C] Keystone heart, Herzliya Pituach, Israel.)*

The Triguard Cerebral Protection Device (Keystone Heart, Herzliya Pituach, Israel) is also a deflection device. In contrast to the Embrella, it is placed via a 9-Fr femoral arterial sheath, although the sheath allows for concomitant use of a 6-Fr pigtail catheter, which would otherwise require separate arterial access. The device is designed to cover all of the branch vessels in the aortic arch, and deflects particles > 140 μm with a semi-permeable nitinol mesh. First-in-human experience reported safety and efficacy among 15 patients undergoing TAVI with the Triguard device compared to 20 retrospective control patients, and showed 3.2 new cerebral lesions per patient by DW-MRI compared to 7.2 per patient in the control group [37]. Next, the DEFLECT I trial (presented by Mullen et al. at euro PCI 2013, unpublished) compared diffusion weighted MRI findings in 28 consecutive patients who underwent TAVI using the Triguard device to 150 historical control patients. Trial investigators reported 100% technical success in device placement and retrieval, without filter-associated complications. Comparing DW-MRI before and after TAVI, the device failed to decrease the proportion of patients with new lesions (70% with device vs. 76% without), or the number of new lesions per patient (5.1 (0–28) vs. 4.4 (0–39)), but did show a significant reduction in the volume of new lesions (0.70 (0–3.94) cm^3 vs. 1.64 (0–70.3) cm^3) respectively. The randomized

DEFLECT III trial with a projected enrollment of 86 patients is currently underway and preliminary results (presented by Lansky et al. ACC 2015) show good in-hospital safety and a possible improvement in neurocognitive function, with longer term results expected soon.

The Claret Montage Device (Claret Medical, CA) is a duel filter system, advanced from a 6-Fr sheath in the right upper extremity. The proximal filter is attached to a 100 cm long catheter, and is positioned at the ostium of the innominate artery where a second filter is advanced through the catheter lumen and into the left common carotid artery. Unlike the Embrella and Triguard devices, the Claret has the presumed advantage of catching embolic particles rather than just deflecting them to the mesenteric or lower extremity circulation, but shares the potential disadvantage of leaving the left vertebral circulation unprotected. The polyurethane filters have 140 μm pores and accommodate vessels between 9 and 15 mm in diameter. The first-in-man experience included 40 patients, and exposed significant challenges with successful device placement specific to the first generation device which was used in the initial 7 patients [38]. A second-generation device was utilized in the remaining 33 patients, which incorporated a central 0.014 guide wire lumen and a modified curve on the distal catheter to improve access to the left common carotid artery. Of the 33 attempted placements, 30 (91%) were successful in delivering the device to the aortic arch, and 26/30 (87%) had successful positioning of both proximal and distal filters. Filters were examined after the procedure, and 19 of 35 devices captured significant debris (5 first-generation and 30 second-generation devices). With regards to safety, there were two radial artery injuries with the first generation device (one requiring surgical repair), and two brachial artery pseudo-aneurysms after removal of the second-generation device (both requiring surgical repair). There were no intra-procedural cerebrovascular events (TIA, minor, or major stroke), although two major strokes were reported post-procedurally (one at 4 hours and one at 27 days after the procedure), and one minor stroke was reported 30 days after the procedure. Currently, the SENTINEL study is enrolling patients in a randomized fashion with a target enrollment of 359 patients (clinicaltrials.gov: NCT02214277).

Finally, the Embol-X Intraaortic Filtration System (Edwards Lifesciences, Irvine, CA) is a system that was initially developed for use during open-heart surgery, and requires direct access to the ascending aorta, where the collapsible filter is deployed through a side-port in a 24-Fr aortic bypass cannula. Safe use of the device was documented in 1,289 randomized patients undergoing cardiac surgery with or without the filter, and showed recovery of particulate emboli in 96.8% of the filters that were successfully deployed, but failed to show significant differences in clinical endpoints such as mortality, stroke, TIA, renal insufficiency, myocardial infarction, GI complications, or limb threatening ischemia [39]. On post-hoc analysis however, the authors showed a reduction in events among patients with moderate or high preoperative risk scores, mostly driven by a reduction in renal complications (17/124 (14%) vs. 28/117 (24%), $p = 0.04$). A modified version of the Embol-x filter with a smaller 17 French sheath has been subsequently used in trans-aortic TAVI with three initial case reports indicating technical success and safety [40,41]. The device is currently being studied in the trans-aortic TAVI population.

8. Conclusion

Neurologic events remain some of the most feared complications of trans-catheter aortic valve procedures, and are associated with significant morbidity and mortality. Fortunately, recent data

suggests that rates are declining, whether due to technological advances, increased operator experience, or improved patient selection. The utilization of the VARC-2 criteria as a clear and uniform guideline for diagnosing stroke in the context of current clinical trials provides much needed consistency to the literature as we study these events. As most events seem to be peri-procedural, much of the current focus has been on comparing different pharmacologic strategies and protecting the cerebral circulation via embolic protection devices, with randomized clinical trial results eagerly awaited. Until then, it is important for operators to continue to minimize the risk of neurologic events to their patients by following the established steps of careful patient selection, ensuring appropriate procedural anticoagulation, and appropriate management of post-procedural atrial fibrillation. Hopefully with these efforts, neurologic events will continue to become even less frequent in patients who undergo trans-catheter aortic valve implantation.

Conflict of Interest

The authors have no conflict of interest to disclose.

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