Embolic protection devices for transcatheter aortic valve replacement

Michele Gallo, Alessandro Putzu, Michele Conti, Giovanni Pedrazzini, Stefanos Demertzis and Enrico Ferrari

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) is performed in elderly high-risk patients with severe aortic stenosis [1, 2]. During TAVR, cerebrovascular accidents can occur at any time. The Valve Academic Research Consortium (VARC) published a report on standardized definitions of cerebrovascular events during TAVR categorized as major/disabling stroke, minor/non-disabling stroke, transient ischaemic attack (TIA) and silent brain infarction [3]. The occurrence of microembolization with silent brain lesions may play a substantial role in long-term cognitive function [4]. The rate of clinical neurological events after TAVR ranges from 3% to 7%. The majority of patients (50–70%) experience a stroke within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within the first 24 h [5–7], with considerable worsening of the patients’ quality of life and a mortality rate that increases 3.5-fold within

to further reduce the risk of perioperative stroke during the procedure. Therefore, identifying risk factors and predictors of procedural stroke and developing new solutions and devices to prevent this complication are crucial steps for quality improvement in modern TAVR.

What we know is that a published meta-analysis showed no differences in stroke rate associated with a stent valve model or the TAVR access route [11], despite a trend towards fewer cerebrovascular events with the transapical route at the 30-day follow-up [8]. Balloon aortic valvuloplasty and postimplant balloononing can mobilize calcium debris as well; the manipulation of large-sized delivery catheters into diseased aortas can also contribute to the increased risk [12, 13].

Recently, embolic protection devices (EPDs) have been developed to reduce the risk of stroke during TAVR. These systems are deployed in the aortic arch and protect the cerebral arteries. The Claret Sentinel (Claret Medical, Inc., Santa Rosa, CA, USA), the Embrella (Edwards Lifesciences, Irvine, CA, USA), the TriGuard (Keystone Heart, Herzliya, Israel) and the Embol-X (Edwards Lifesciences) are commercially available but, to the best of our knowledge, are not widely used in clinical practice. Therefore, in...
73% of treated patients [17]. Similarly, a recent study reported per- shown new ischaemic brain lesions within 3 days after TAVR in up to 

clinical practice. Moreover, stroke and TIA are clinically evident, but 

graphic scans [14, 15] using the Agatston score. However, there are 

raphy and quantify the amount of calcium from computed tomo-

eutrographic phase or, rarely, during postoperative recovery after TAVR

Cerebrovascular complications can occur in the early postopera-
tive phase or, rarely, during postoperative recovery after TAVR [7]. Nombela-Franco et al. [7] showed that 50% of postoperative 
cerebrovascular complications occur within the first 24 h, whereas the remaining 50% happen between 24 h and 2 months after TAVR. The pathophysiology of intraprocedural stroke is likely a multifactorial event where embolization is the leading mechanism [20]. Embolization could arise from particulate material (valve tissue, wall tissue or atherosclerotic plaques) dislodged during the manipulation of catheters or wires into the aorta and from the valve during stent valve deployment [20]. In particular, large transvascular delivery systems navigating into diseased aortic arches can generate micro- and macroembolization. Moreover, re-ballooning and valve dislodgement or migration is described as independent predictors of stroke in a recent report [7]. A meta-analysis showed that predictors of stroke after TAVR are female gender, chronic renal failure, new onset of atrial fibril-
ation (AF) after TAVR and lower site experience [21].

Different kinds of debris found in EPDs have been analysed. The most common types of captured debris were thrombus (91%), material from the arterial wall (68%), valve tissue (53%), calcium (46%) and foreign material (30%) [22]. The thrombus was the most common type of debris; it is conceivable that it can develop at any time and in any part of the delivery catheter including the guidewires. The management of intraprocedural anticoagulation with an activated clotting time above 250 s is highly recommended during the entire procedure. Thrombus generation during TAVR can also originate from the interaction between the native valve and the transcatheter valve or it can be triggered by chronic or new-onset AF (Table 1) [23].

On the other hand, the aetiology of a delayed stroke after TAVR is poorly understood and mainly involves patient-related risk factors and comorbidities. Nevertheless, factors related to the presence of an implanted transcatheter valve should also be considered. Before a complete endothelialization, the metal frame may be thrombogenic, and the crimping of the stent valve can play a role in damaging the leaflet tissue, exposing thrombogenic xenonantigens [24]. Microthrombosis on the surface of the leaflets has recently been associated with cusp hypomobility, and its role in late stroke requires further investigation [25].

Table 1: Mechanisms of cerebrovascular events during and after TAVR

<table>
<thead>
<tr>
<th>Source</th>
<th>Acute cerebrovascular complications</th>
<th>Late cerebrovascular complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcific aortic cusps</td>
<td>Delivery system navigation within the aortic arch</td>
<td>Calcific aortic cusps</td>
</tr>
<tr>
<td>Atherosclerotic aortic wall</td>
<td>Interaction between the native valve and the transcatheter valve</td>
<td>Atherosclerotic aortic wall</td>
</tr>
<tr>
<td>Thrombotic apposition valve cusps, catheters, delivery systems and guidewires</td>
<td>Rapid ventricular pacing</td>
<td>Left appendage in chronic or new-onset atrial fibrillation</td>
</tr>
<tr>
<td>Left appendage in new-onset atrial fibrillation</td>
<td>Long procedural time and imprecise anticoagulation control</td>
<td>Thrombotic apposition on transcatheter valve leaflets</td>
</tr>
</tbody>
</table>

Mechanisms of cerebrovascular events during and after TAVR | Patient risk factors for stroke | Microthrombosis on the leaflet surface due to imprecise anticoagulation control or tissue valve damage |

Cerebrovascular events | Aortic wall damage and late embolization |

Silent brain lesions

Postoperative stroke and TIA have been the end-points of most registry studies on TAVR. However, these clinical events probably represent only a percentage of the total number of new neurological lesions in the brain after TAVR. Some studies have recently confirmed the presence of silent brain lesions using transcranial Doppler or diffusion-weighted brain magnetic resonance imaging (DW-MRI) [16, 17]. Transcranial Doppler was used to identify high-intensity transient signals during balloon aortic valvuloplasty, stent valve positioning and valve deployment [16]. Similarly, DW-MRI studies have shown new ischaemic brain lesions within 3 days after TAVR in up to 73% of treated patients [17]. Similarly, a recent study reported percentages of 45% and 41% in new DW-MRI-detectable silent brain lesions after TAVR and standard aortic valve replacement, respectively [18]. However, silent lesions seem not to be correlated with a lower rate of late survival, cognitive dysfunction, impaired self-sufficiency and impaired quality of life during follow-up [19].

This review, we analysed the real need for protection from stroke during TAVR, including an in-depth analysis of possible origins of the intraprocedural stroke, and we provide an overview of neuro- logical results with the available EPDs in order to better under- stand the advantages or disadvantages related to their use.

NEUROLOGICAL COMPLICATIONS

Preoperative quantification of the amount of calcium in the sten-
otic calcified aortic valve with last-generation cardiac imaging can be useful to assess the risk of stroke during TAVR. One can identify floating calcium on the cusps using transoesophageal echocardiog- raphy and quantify the amount of calcium from computed tomo-

graphic scans [14, 15] using the Agatston score. However, there are no stroke scores or calcific predictive factors that can be used in clinical practice. Moreover, stroke and TIA are clinically evident, but many patients can have silent brain lesions after TAVR.

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Cerebrovascular events

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Anticoagulation and antiplatelet therapy

A comprehensive strategy for reducing the stroke rate during TAVR also requires correct anticoagulation and antiplatelet therapy. During TAVR, current practice generally recommends intravenous
injection of heparin (activated clotting time >250–300 s) to reduce the thrombogenicity of catheters, wires, delivery systems and stent valves [26]. Longer procedural time and additional thrombogenic surfaces given by EPD use require even more accurate intraprocedural anticoagulation management. Interestingly, there is a wide inter-hospital variability in antiplatelet treatment during TAVR because some centres use different loading doses of clopidogrel (300 mg or 600 mg).

After TAVR, recommendations about antiplatelet therapy in patients in sinus rhythm are essentially based on a consensus of experts who assumed that a stent requires dual antiplatelet therapy for at least 6 months. Consequently, a wide difference in antiplatelet management is seen across available studies/registries with an inconsistent duration of treatment with clopidogrel (75 mg/day) ranging from 1 to 6 months. Aspirin dosage also varies from 81 to 325 mg/day, although it is usually continued indefinitely [27].

Additionally, AF is likely the most common reason to start anticoagulation after TAVR in association with 1 antiplatelet drug. In 2012, another consensus of experts supported by the American College of Cardiology and the American Heart Association suggested the use of an anticoagulation therapy coupled with low-dose aspirin without clopidogrel for patients having TAVR [26].

Future studies should focus on a correct anticoagulation/antiplatelet strategy because some evidence supports the resolution of subclinical and clinical leaflet hypomobility/thrombosis with warfarin [28–30]. However, warfarin and aspirin therapy for AF in TAVR appear not to reduce the incidence of stroke, major cardiovascular events or death but rather increase the risk of major bleeding [31].

EMBOLIC PROTECTION DEVICES

In Table 2, we report the main features of commercially available EPDs. The Sentinel, the Embrella and the TriGuard are percutaneous devices designed for transfemoral or transradial/transbrachial implantation; the Embol-X is a device conceived for use in arterial canulans during standard surgery that was also used (off-label) during transcatheter TAVR with direct placement in the ascending aorta.

### Edwards Embrella

The Embrella Deflector Device (Edwards Lifesciences) (Fig. 1A) is an umbrella-like device with 2 heparin-coated polyurethane membranes (100-μm-sized pores) mounted on an oval-shaped nitinol frame. This device deflects rather than captures embolic material. The pores are the smallest in size of any of the currently available EPDs, and the device can be loaded into a 6-Fr sheath inserted in the right arm through the radial or the brachial artery. Three markers guide the deployment under fluoroscopy: 1 at the outer point of each petal and 1 on the distal shaft [32]. When deployed, the petals extend over a length of 58 mm with a width of 25 mm covering the greater curvature of the arch (protecting the brachiocephalic trunk and the left carotid artery). In some patients, it further covers (sometimes partially) the left subclavian artery. The Embrella received the CE-mark in 2010. No additional trials are ongoing, and it has been withdrawn from the market by the manufacturer.

### Clinical results

The first Embrella implants were reported in 2010 in 4 cases: in 1 patient undergoing stand-alone balloon aortic valvuloplasty, a cerebral infarction was detected by postoperative MRI [32] (Table 3). In 2014, the PROTAVI-C trial, a non-randomized pilot study, compared 41 patients who had TAVR protected with the Embrella to 11 patients who had TAVR performed without the device [33]. The authors showed the safety of the device with complete deployment into the arch and no procedural complications. However, this study failed to show a reduction in the number of cerebral embolic events when transcranial Doppler and DW-MRI scans were viewed, and, at the 30-day follow-up, 3 patients in the study group had a stroke/TIA compared with 0 in the control group [33]. Nevertheless, the use of the Embrella was associated with smaller brain lesions evident on DW-MRI scans compared with the control group [33].

In a more recent analysis, Samim et al. [34] (Table 3) compared 15 patients who had TAVR with the Embrella to 37 patients who had historical TAVR and found a significant increase in DW-MRI-detectable cerebral embolic events using the Embrella. However, they also reported significantly smaller lesion volumes in the study group. The Embrella group also showed an increased number of embolic events in the right cerebral vessels. It has been suggested that the right radial/brachial artery access point may be the origin of the mobilized atheromatous plaques, which are more prone to migrate into the right carotid artery. In conclusion, the Embrella appears to be protective against large cerebral emboli and showed no adverse effects or interference during valve deployment [33, 34].

### Claret Sentinel

The Sentinel (Claret Medical) (Fig. 1B and 1C) is placed through a 6-Fr introducer sheath in the right radial or brachial artery.

### Table 2: Commercially available EPDs

<table>
<thead>
<tr>
<th>Mesh pore size (μm)</th>
<th>Mesh material</th>
<th>Delivery sheath (Fr)</th>
<th>Access site</th>
<th>Mechanism of cerebral protection</th>
<th>Targeted protected arteries</th>
<th>Protection system</th>
<th>Embol-X filter</th>
</tr>
</thead>
<tbody>
<tr>
<td>130</td>
<td>Nitinol</td>
<td>9</td>
<td>Transfemoral</td>
<td>Deflection</td>
<td>Brachiocephalic trunk and LCC and LSC arteries</td>
<td>Claret Medical</td>
<td>Edwards Lifesciences</td>
</tr>
<tr>
<td>140</td>
<td>Polymer</td>
<td>6</td>
<td>Radial/brachial</td>
<td>Debris capture and retrieval</td>
<td>Brachiocephalic trunk and LCC artery</td>
<td>Edwards Lifesciences</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>Polymer</td>
<td>6</td>
<td>Radial/brachial</td>
<td>Debris capture and retrieval</td>
<td>Brachiocephalic trunk and LCC artery</td>
<td>Edwards Lifesciences</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>Polyester</td>
<td>17</td>
<td>Direct transaortic</td>
<td>Debris capture and retrieval</td>
<td>Brachiocephalic trunk and LCC and LSC arteries</td>
<td>Edwards Lifesciences</td>
<td></td>
</tr>
</tbody>
</table>

EPD: embolic protection device; LCC: left common carotid; LSC: left subclavian.
The device consists of 2 polyurethane filters with 140-μm diameter pores placed in a flexible nitinol radiopaque frame attached to a 100-cm long delivery catheter. The Sentinel is deployed before the insertion of the valve delivery system and is removed after its removal.

The first generation was the CE Pro System, which featured a commercially available third-party single embolic filter (ev3 SpiderFX, Covidien) as the distal filter to insert during the procedure. The second generation was the Montage system: It was the result of integrating a Claret-designed distal filter into the CE Pro System. The third generation is the actual Sentinel. This version employs the same working end of the Montage system; the innovation is a new ergonomic device handle and an additional 5-cm catheter working length. The Sentinel received the CE-mark in 2013 and Food and Drug Administration (FDA) approval in 2017.

Clinical results. Naber et al. [35] published the first study in humans using the first-generation CE Pro System in 40 patients undergoing TAVR (Table 3). The technical success rate during the deployment was suboptimal (60%) and was related to the anatomical variations of epiaortic vessels and the aortic arch. The second-generation device, the Montage, presented an improved success rate during deployment with 75% and 86% of documented captured debris [36] (Table 3). In the randomized CLEAN-TAVI trial, 50 patients received TAVR with the Montage and 50 controls did not [38]. In this study, the device was deployed successfully in 96% of cases: The main cause of unsuccessful deployment was the tortuosity of the epiaortic vessels. The incidence of any neurological symptom up to 30 days after TAVR was the same in both groups (12% vs 12%). The incidence of new brain lesions detected with DW-MRI was similar, but patients with a filter presented a significant reduction in volume of cerebral lesions [38].

The third generation, the Sentinel (Table 3), was evaluated in a multicentre double-blinded randomized trial (MISTRAL-C) that enrolled 65 patients who had TAVR [39]. Compared with the control group, patients with the Sentinel had fewer new cerebral lesions and smaller total lesion volume evident on DW-MRI scans. Neurocognitive deterioration was present in 4% of patients with the Sentinel compared with 27% of the control patients. The limitations of the study were a DW-MRI follow-up of 57% and neurocognitive tests performed in 80% of patients [39].

Recently, the Sentinel was evaluated in a blinded, randomized clinical trial, the SENTINEL study, which is the first randomized trial on EPD in the USA (Table 3) [40]. In the study, 99% of patients had captured embolic debris, and the incidence of stroke at 30 days was 9.1% in the control group and 5.6% in the protected group (P = 0.25). Reduction in new lesion volume on MRI was not statistically significant (P = 0.33) [40].

Keystone TriGuard

The TriGuard embolic protection device (Keystone Heart) (Fig. 2A) deflects emboli. It is the only available device designed to cover all arteries in the arch. The device is delivered through a 9-Fr 75-cm long femoral sheath and features a nitinol mesh coated with chemical and physical substances (Applause™ Heparin Coating SurModics, Inc., Eden Prairie, MN, USA), thereby reducing the possibility of thrombus formation. An upper stabilizer is anchored to the ostium of the innominate artery, whereas a lower stabilizer is placed in the inner curvature of the arch to maintain a stable filter position.
Table 3: Clinical studies evaluating EPDs in TAVR

<table>
<thead>
<tr>
<th>Study design</th>
<th>Patients</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Edwards EMBRELLA</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nietlisplach et al. [32]</td>
<td>Single centre</td>
<td>Treatment: 1 BAV; 3 TAVR</td>
</tr>
<tr>
<td>Rodés-Cabau et al. [33]</td>
<td>PROTAVI-C study</td>
<td>Multicentre Prospective Non-randomized Controls: 11 TAVR</td>
</tr>
<tr>
<td>Samim et al. [34]</td>
<td>Single centre Retrospective</td>
<td>Treatment: 15 TAVR Historic cohort as controls: 37 TAVR</td>
</tr>
<tr>
<td><strong>Claret SENTINEL</strong></td>
<td></td>
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<tr>
<td>Naber et al. [35]</td>
<td>CE PRO Single-arm study Multicentre (Germany, Brazil)</td>
<td>Treatment: 40 TAVR 30-day outcome: 1 patient had a minor stroke 1 stroke and 1 TIA Patients with EPD had fewer new silent cerebral lesions and a smaller total lesion volume (95 mm³ [IQR 10–257] vs 197 mm³ [95–525]) Neurocognitive deterioration in 4% of patients with EPD vs 27% of the controls (P = 0.017) 30-day outcome: Stroke rate of 9.1% among the controls and 5.6% in patients with EPD (P = 0.25)</td>
</tr>
<tr>
<td>Van Mieghem et al. [36]</td>
<td>Montage Single-arm study</td>
<td>Treatment: 40 TAVR Single centre 1 patient with TIA and 2 patients with disabling stroke 1 life-threatening bleed in 1 patient with filter 1 life-threatening bleed in the control group</td>
</tr>
<tr>
<td>Van Mieghem et al. [37]</td>
<td>Montage Single-arm study Single centre CLEAN-TAVI trial Single centre Prospective Blind Randomized 1:1 (protection vs no protection)</td>
<td>Treatment: 50 TAVR Controls: 50 TAVR</td>
</tr>
<tr>
<td>Haussig et al. [38]</td>
<td>Montage SENTINEL trial Randomized 1:1 (Safety arm vs device imaging arm vs control imaging arm)</td>
<td>Safety arm: 123 TAVR Device imaging arm: 121 TAVR Control imaging arm: 119 TAVR</td>
</tr>
<tr>
<td><strong>Keystone Heart TriGuard</strong></td>
<td></td>
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</tr>
<tr>
<td>Onsea et al. [41]</td>
<td>Triguide Single centre</td>
<td>Treatment: 15 TAVR Controls: historic TAVR cohort 3.2% new silent cerebral lesions evident on DW-MRI scan per patient compared with 7.2% in the retrospective control group 70% of patients with EPD have one or more new silent brain lesions vs 76% of patients without the device 30-day outcome: No strokes observed Decrease in mean brain lesion volume per patient evident on DW-MRI scans (median 13.8 mm³ vs 25.1 mm³, P = 0.049) Greater freedom from new silent brain lesions evident on DW-MRI scans (26.9% vs 11.5%) at 30 days</td>
</tr>
<tr>
<td>Baumbach et al. [42]</td>
<td>TriGuard DEFLECT-I trial Multicentre Prospective Pilot study Single centre 'DEFLECT-II' trial Single centre Prospective Randomized 1:1</td>
<td>Treatment: 37 TAVR</td>
</tr>
<tr>
<td>Campelo-Parada et al. [43]</td>
<td>SENTINEL trial Randomized 1:1 (Safety arm vs device imaging arm vs control imaging arm)</td>
<td>Safety arm: 123 TAVR Device imaging arm: 121 TAVR Control imaging arm: 119 TAVR</td>
</tr>
<tr>
<td>Van Mieghem et al. [39]</td>
<td>Sentinel MISTRAL-C trial Randomized 1:1 (protection vs no protection)</td>
<td>Treatment: 32 TAVR Controls: 33 TAVR</td>
</tr>
<tr>
<td>Kapadia et al. [40]</td>
<td>Sentinel SENTINEL trial Randomized 1:1 (Safety arm vs device imaging arm vs control imaging arm)</td>
<td>Safety arm: 123 TAVR Device imaging arm: 121 TAVR Control imaging arm: 119 TAVR</td>
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<td><strong>Edwards EMBOL-X</strong></td>
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<tr>
<td>Etienne et al. [46]</td>
<td>Case report Case series Single centre Prospective Single-blinded Randomized</td>
<td>Treatment: 1 TAVR Treatment: 2 TAVR Treatment: 14 TAVR Controls: 16 TAVR</td>
</tr>
<tr>
<td>Ye and Webb [47]</td>
<td></td>
<td>No neurological events No neurological events New silent brain lesions evident on DW-MRI scans in 50% of patients with EPD vs 69% of controls Decrease in mean brain lesion volume per patient evident on DW-MRI scans (median: 33 mm³ vs 76 mm³, P = 0.04) No neurological events after transaortic TAVR</td>
</tr>
<tr>
<td>Wendlt et al. [48]</td>
<td></td>
<td>No neurological events No neurological events</td>
</tr>
</tbody>
</table>

BAV: balloon aortic valvuloplasty; DW-MRI: diffusion-weighted magnetic resonance imaging; EPD: embolic protection device; IQR: interquartile range; TAVR: transcatheter aortic valve replacement; TIA: transient ischaemic attack.
The TriGuard HDH is the second generation of the device employed in the DEFLECT-II and III trials. Compared with the first-generation device, the actual device features an improved nitinol mesh with a pore size of 130 μm, 4 new radiopaque markers to facilitate the positioning of the device and a new delivery system with improved manoeuvrability [43, 44]. The TriGuard received the CE-mark in 2013 and is available in the USA as an investigational device.

**Clinical results.** The first successful placement of the TriGuard was reported by Dr Onsea in 15 patients who had TAVR (Table 3) [41]. The DEFLECT-I trial was a prospective, multicentre, single-arm study enrolling 37 patients (Table 3) [42]. The success rate of device implantation was 80%; major adverse cardiovascular and cerebrovascular events occurred in 16% of patients. The per-patient total brain lesion volume detected by DW-MRI was 34% smaller than that reported from the previous control data [42]. The DEFLECT-II trial is a prospective, single-centre, single-arm safety study with 14 enrolled patients (Table 3) [44]. The device did not reduce the number of new DW-MRI-detectable brain lesions but was associated with a decreased volume [44]. Campelo-Parada et al. [43] used the TriGuard in a single-arm study enrolling 10 patients who had TAVR: in 6 asymptomatic patients undergoing DW-MRI, new brain ischaemic lesions were detected in 5 (83.3%).

The DEFLECT-III trial is a prospective, multicentre, single-blinded randomized trial evaluating the safety and efficacy of the TriGuard HDH in patients having TAVR (Table 3) [45]. The study enrolled 85 patients of whom 46 were randomized to the TriGuard and 39 to the control group. Complete cerebral vessel coverage was achieved in 89% of subjects in the protected arm. Patients who underwent TAVR with the TriGuard had fewer ischaemic brain lesions evident on DW-MRI scans (11.5% vs 26.9%) and a lower per-patient lesion volume [45]. Neurocognitive outcome was assessed for all patients included in the study: Fewer neurological deficits and improved cognitive function were noted in the protected group [45]. Another study, the REFLECT-Trial (ClinicalTrials.gov NCT02536196), is an ongoing randomized trial aiming to assess the safety and efficacy of the TriGuard in comparison with a control group of patients having unprotected TAVR.

**Edwards Embol-X**

The Embol-X EPD (Edwards Life Sciences) (Fig. 2B) is an aortic filter designed to be inserted, during standard surgery, in an aortic arterial cannula for cardiopulmonary bypass. However, the device was used in transaortic TAVR (off-label use). The filter is self-expandable and sits across the ascending aorta. The Embol-X can be deployed in the ascending aorta during transaortic TAVR through a short 17-Fr sheath and consists of a heparin-coated, 120-μm polyester mesh in a flexible nitinol frame. The Embol-X is available in 5 sizes covering all aortic diameters (22–40 mm).

**Clinical results.** The first reports of the Embol-X used in patients having transaortic TAVR are 3 cases showing the technical success and the safety of the device (Table 3) [46, 47]. Wendt et al. [48] reported the results of a prospective, single-blinded, randomized trial that assigned 30 patients to either transaortic TAVR with the Embol-X (n = 14) or transaortic TAVR without protection (n = 16) (Table 3). Cerebral lesions were assessed by DW-MRI: New brain lesions of restricted diffusion were reported in 69% of patients in the control group and in 50% of patients in the Embol-X group. Lesion volume was smaller with the Embol-X and was statistically significant in the area of the middle cerebral artery (33 ± 29 mm³ vs 76 ± 67 mm³, P = 0.04) [48].
New EPDs

The following promising new devices are under investigation. The ‘Emblok system’ (Innovative Cardiovascular Solutions, Grand Rapids, MI, USA) (Fig. 3A) is a protection device designed to offer full circumferential aortic protection from embolic debris. The Emblok is deployed through an 11-Fr femoral sheath and incorporates a 4-Fr radiopaque pigtail catheter. Mesh pore size is 125 μm, and the company has recently announced the first in-human implantation (http://www.emblok.com/wp-content/uploads/ICS_Press-Release_1st-Milan-Procedures-FINAL.pdf). A small non-randomized trial is ongoing to assess performance and safety end-points (NCT03130491). The ‘Emboliner’ embolic protection catheter (Emboline Inc., Santa Cruz, CA, USA) (Fig. 3B) is a dual filter designed to capture and remove all emboli, providing full-body protection. Studies of the Emboliner in humans began in 2017.

DISCUSSION

A stroke after TAVR is a serious neurological event that has an impact on the patient’s morbidity and mortality. The risk of clinical neurological events after TAVR ranges from 3% to 7% with the majority of the patients (50–70%) experiencing stroke within the first 24 h [5–7]. Most ischaemic strokes that occur as a complication of invasive percutaneous cardiac procedures are thought to be caused by embolic events: Atherosclerotic aortic walls and heavily calcified aortic leaflets are the source of embolic debris when catheters, wires and large delivery systems navigate into the aorta. Preoperative computed tomographic scans are widely used to assess the quality and the size of the vessels (to better define the strategy for the easiest and the safest access route), and many efforts have been made to decrease the size of the delivery catheters (less traumatic for the vascular walls). However, the risk of neurological complications during TAVR still exists; therefore, EPDs have been designed. Growing evidence indicates that using an EPD during TAVR reduces the volume of silent cerebral lesions, but results from ongoing large clinical trials are pending and only relatively small studies have been published so far.

Because some randomized controlled trials (RCTs) investigating the efficacy and safety of EPDs have been underpowered for clinical end-points, some aggregate data meta-analyses have been conducted. Giustino et al. [49, 50] performed a meta-analysis of randomized trials that comprised a total of 5 trials with 625 patients allocated to an embolic protection device group or a control group. They found that patients in the EPD group had a lower risk of death or stroke (6.4% vs 10.8%; relative risk 0.57; 95% confidence interval 0.33–0.98) [49, 50]. A larger meta-analysis including non-randomized studies found no difference in stroke and mortality rates. On the other hand, the authors suggest that TAVR procedures with EPD might be associated with a smaller volume of silent ischaemic brain lesions without reducing the number of new single, multiple and total number of brain lesions [51]. Given the substantial limitations of the present RCTs, the results of meta-analyses should be interpreted with caution and interpreted only as hypothesis generating. Limitations of the published RCTs are the use of surrogate disease markers (e.g. DW-MRI-detected lesions) and different definitions for the disease (e.g. neurocognitive evaluation). Further RCTs adequately powered for clinically relevant outcomes such as stroke or death are needed to establish the real role of EPSs during TAVR.

A recent study found that EPD failed to prevent either imaging-based cerebral infarction or clinically relevant stroke among patients undergoing standard aortic valve replacement [52]. However, a potential benefit of EPD was found in the reduction of postoperative delirium, a common and harmful postoperative event linked to worse outcome after TAVR [53, 54].

Another important point of discussion is that the physiopathology of stroke during TAVR needs more investigation to better understand the preferred direction of debris (brachiocephalic trunk, left carotid artery) and the clinical relationship between the timing, frequency and volume of emboli. Improved knowledge about the mechanism of stroke during TAVR will help ameliorate the design of new EPD to further mitigate the risk of
periprocedural stroke. An ideal EPD requires a small introducer sheath for different route accesses and a mesh material for the filter that is biocompatible with blood (there is no basic science study proving the superiority of the manufactured meshes on the market: nitinol, polymer and polyester). The same argument can be made about different manufactured pore sizes (100 μm, 120 μm, 130 μm and 140 μm). Moreover, it is crucial to be able to ascertain the completeness of the sealing of the aortic lumen by the filter to exclude "paralifer" embolization.

CONCLUSION

In view of the younger patients and the lower risk patients who will soon be having transcatheter aortic procedures, the increasing demand to reduce cerebral complications after TAVR has pushed companies and physicians to develop improved EPDs. Preliminary studies evaluating the role of EPD during TAVR have confirmed the safety of the available systems. However, clinical results show that EPD may help to reduce the size and volume of periprocedural silent cerebral ischaemic lesions without reducing the number of new cerebral lesions and strokes [50]. The clinical impact of EPD in reducing cerebral adverse events needs to be further investigated with randomized trials and new devices.

Conflict of interest: none declared.

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[10] Alpert J, Al-Saidi S, Lock J, Dangas G, Patel H, Swift P, Wendl D et al. Preliminary studies evaluating the role of EPD during TAVR have confirmed the safety of the available systems. However, clinical results show that EPD may help to reduce the size and volume of periprocedural silent cerebral ischaemic lesions without reducing the number of new cerebral lesions and strokes [50]. The clinical impact of EPD in reducing cerebral adverse events needs to be further investigated with randomized trials and new devices.

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