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Debate. Cerebral embolic protection systems in TAVI: there is not enough evidence available

A debate. Sistemas de protección cerebral en procedimientos de TAVI: no existen evidencias suficientes

Pedro Luis Martín Lorenzo*

Unidad de Hemodinámica, Servicio de Cardiología, Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas de Gran Canaria, Spain

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Question: Is there, currently, enough clinical evidence to recommend the use of cerebral protection in transcatheter aortic valve implantation (TAVI)?

Answer: Transcatheter aortic valve implantation (TAVI) has become the treatment of choice of severe aortic stenosis in patients with some degree of surgical risk involved. Perioperative stroke is a serious complication associated with a dramatic reduction of the patient's quality of life and, occasionally, with a lower mid-term survival rate. Although the rate of clinical stroke is relatively low (between 2% and 7%, according to the different series published)[1], rates of silent cerebral infarction after TAVI of up to 70% have been described, which has been associated with the appearance of progressive cognitive decline at follow-up[2]. To prevent these adverse events from happening, different cerebral embolic protection devices (CEPD) have been created over the past few years. However, despite several randomized clinical trials conducted, no proven net clinical benefit has been confirmed regarding lower rates of clinical stroke. In the DEFLECT III trial[3] using the Triguard device (Keystone Heart Ltd., Israel), Lansky et al. obtained a successful CEPD implantation rate of 88.9% without any differences being reported regarding the safety endpoint, and a tendency towards more new-onset brain injuries (26.9% vs 11.5%) but with less neurological deficit (3.1% vs 15.4%) in the device group. The MISTRAL-C4 trial[4] on the Sentinel device (Claret Medical Inc., United States) did not achieve its primary endpoint and found no significant differences in the percentage of patients with new-onset brain injuries in both groups. That same year, the CLEANTAVI trial[5] on imaging modality-guided Sentinel devices before and after the procedure, confirmed the presence of fewer and smaller brain injuries in the CEPD group (242 mm^2 vs 527 mm^2; $P < .001$). However, no significant differences were found regarding fewer clinical strokes. The SENTINEL IDE trial[6] published back in 2017 met its safety endpoint (100% technical success rate). However, no significant differences were found regarding clinical events (major adverse cardiovascular and cerebrovascular events: 7.3% vs 9.9%; $P = .40$) or volume of new-onset brain injuries (103 mm^2 vs 178 mm^2; $P = .33$). However, a lower rate of early stroke (3% vs 8.2%; $P = .05$) was reported in the CEPD group. More recently, the REFLECT II trial[7] on the Triguard 3 device showed a non-significant higher rate of bleeding and major vascular complications associated with TAVI in the CEPD group. Also, no significant differences were found in the efficacy endpoint between both groups (30-day rate of mortality or stroke, worsening of the NIHSS score, and presence of new-onset brain injuries on diffusion-weighted magnetic resonance imaging between the second and fifth days). Finally, in the anticipated PROTECTED TAVR trial[8] the authors concluded that the use of the Sentinel device (Boston Scientific, United States) during TAVI via femoral approach did not have a significant impact on the rate of perioperative stroke. Therefore, in light of the results obtained from different studies published so far, there is not enough clinical evidence to support the routine use of CEPD during TAVI.

Q.: What do you make of the PROTECTED TAVR trial?

A.: Although the SENTINEL IDE trial[6] showed a secondary endpoint of fewer clinical strokes within the first 72 hours after the procedure (3% vs 8.2%; $P = .05$), it lacked the statistical power needed to assess this variable. To confirm this hypothesis, the PROTECTED TAVR clinical trial[8] was conducted. This is a prospective and multicenter study that randomized 3000 patients with severe aortic stenosis who were going to be treated with TAVI via femoral accees into 2 groups: the Sentinel CEPD group or the control group. The primary efficacy endpoint was the occurrence of a clinical stroke within the first 72 hours after the procedure or until hospital discharge whatever came first. Cerebral imaging modalities were spared only for patients with neurological deficits after TAVI. The rate of clinical stroke was 2.6% (2.3% in the CEPD group vs 2.9% in the control group; $P = .30$). The rate of non-disabling stroke was 1.7% in the CEPD group compared to 1.5% in the control group ($P = .67$) while the rate of disabling stroke was 0.5% of the CEPD group vs 1.3% in the control group ($P = .02$). The device efficacy and safety rates were 94.4% and 99.9%, respectively. Therefore, after a detailed analysis of the study, we can conclude that there is no significant benefit associated with the use of CEPD to reduce the rate of clinical stroke after TAVI. No subgroups of patients were identified either who could benefit from their use. Although the

* **Corresponding author.**
E-mail address: pemarlor@hotmail.com (P.L. Martín Lorenzo).
@pemarlor08

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safety profile of the device appears excellent, the associated financial cost and the low benefit derived from it with a number needed to treat regarding total stroke and disabling stroke of 166 and 125 patients, respectively, make the routine use of CEPD in TAVI ill-advised. It seems obvious that both the etiology and pathophysiology of stroke in this context are multifactorial. Therefore, we should not expect that devices that only act as a barrier mechanism will significantly reduce these types of events that occur not only during TAVI but also within the next 72 hours following the procedure. Additionally, the greater experience gained by interventional cardiology units, the precision of imaging techniques, the thorough analysis of each case before the procedure, the progressive reduction of device profiles, and the decreasing complexity of the implantation technique are all factors that could contribute to reduce the rate of stroke associated with TAVI.

Q.: Do you consider the use of cerebral protection devices in some kind of patients or in no patients at all?

A.: To this date, scientific evidence has not yet been able to establish which subgroup of patients eligible for TAVI may have a higher risk of having a stroke and, therefore, would benefit more from the use of CEPD. Although factors associated with the procedure that could increase the risk of stroke during TAVI have been described (pre- or postdilatation maneuvers, valve-in-valve procedures, smaller native aortic valve areas, higher valve gradients, severe valve calcification, bicuspid valve morphology, aortic atheromatous disease)[9], it remains controversial since former studies have shown that several of these factors don't seem to predispose to having a stroke after TAVI. Makkar et al.[10] found no statistically significant differences regarding the morphology of bicuspid or tricuspid valve between the rates of mortality (0.9% vs 0.8%; $P = .55$) and stroke (1.4% vs 1.2%; $P = .55$) at 30 days in a series of low surgical risk patients. In the PROTECTED TAVR trial[8] no significant differences were seen either regarding the use of CEPD in the subgroup analyses including the variables age, sex, STS-PROM (Society of Thoracic Surgeons Predicted Risk Of Mortality) surgical risk score, surgical risk assessed by the heart team, bicuspid or non-bicuspid morphology of the aortic valve, degree of aortic annular calcification, past medical history of coronary artery disease, peripheral arterial disease, stroke, previous valve-in-valve procedure, use of balloon-expandable valves, pre- and postdilatation.

Personally, I would say that patients with significant atheromatous disease in the ascending and thoracic aorta, and those undergoing valve-in-valve procedures with aggressive postdilatation maneuvers (annular fracture) could be subgroups where the use of DPEC could reduce the rate of perioperative stroke. It seems necessary to keep on conducting in-depth retrospective studies on potential predisposing factors thoroughly in patients who have suffered a stroke with or without clinical implications after TAVI before establishing subgroups of higher risk of stroke during implantation.

Q.: Are there any evidence-based differences regarding the type of devices used?

A.: Currently, we have 2 DPEC available with CE marking: the Sentinel and the Triguard 3. The former, on which we have more clinical experience, consists of 2 connected nitinol filters that independently seal the brachiocephalic trunk and the left carotid artery for particles ≥ 140 µm. The system is advanced from the right radial artery using a 6-Fr delivery catheter mounted over a 0.014 in guidewire. The Triguard 3 consists of a self-positioning nitinol structure arranged as a net that is advanced over a 0.035 in exchange guidewire via femoral artery using an 8-Fr delivery catheter. As a potential advantage over its competitor, it protects all 3 vessels (including the left subclavian artery too), thus preventing the passage of particles ≥ 145 µm. Similarly, its design allows us to advance a pigtail catheter through the same introducer without having to cannulate additional vascular accesses. Recently, the results of the PROTEMBO C trial[11] on the ProtEmbo device (Protembis GmbH, Germany) have been published. This device consists of a 38 mm × 70 mm self-expanding nitinol mesh inserted via left radial or brachial artery through a 6-Fr catheter mounted over a 0.014 in guidewire. With it we can protect all 3 cerebral vessels by capturing particles ≥ 60 µm. In the 37 patients finally included in the study, the device implantation success rate was 94.5%. Only 1 thalamic stroke was documented in a patient in whom the DPEC was removed prematurely due to significant interaction while TAVI was being performed. Regarding subclinical strokes, diffusion-weighted magnetic resonance imaging found a mean volume of new-onset lesions of 210 mm^3 (undetected in 97% of the patients with lesions with volumes > 350 mm^3). Currently, no studies comparing the different DPEC available today have been conducted so there is no evidence to recommend the use of 1 device to the detriment of the others. Perhaps the emergence of DPEC with high device implantation success rates, no associated vascular complications, and protection of all 3 major cerebral vessels, preventing the passage of smaller particles could contribute to reducing the rate of perioperative stroke.

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CONFLICTS OF INTEREST

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