Cardiovascular Revascularization Medicine 50 (2023) 8–12

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Clinical Outcome of Transcatheter Aortic Valve Replacement With TriGUARD 3™ Cerebral Embolic Protection Device

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ARTICLE INFO

Article history:
Received 8 August 2022
Received in revised form 11 January 2023
Accepted 11 January 2023
Available online 16 January 2023

Keywords:
Transcatheter aortic valve replacement
Cerebral embolic protection device
Stroke prevention
TriGUARD 3

ABSTRACT

Objective: Periprocedural stroke during transcatheter aortic valve replacement (TAVR) is a highly feared adverse event. The TriGUARD 3 cerebral embolic protection device (CEPD) may have the potential benefit of reduction of embolic events, but it still remains unclear whether it reduces the incidence of periprocedural stroke or transient ischemic attack (TIA).
We aimed to investigate whether the latest TriGUARD 3 CEPD reduces the incidence of clinically overt stroke within 72 h or at discharge after TAVR.
Methods: In this prospective single-center study 117 patients (mean age 80.3 years, 53.8 % male) were included from July 2020 to December 2021.
Results: The primary efficacy endpoint of this study, periprocedural clinically overt stroke or TIA, within 72 h or at discharge after TAVR with the TriGUARD 3 CEPD occurred in 1/117 pts (0.8 %). Secondary endpoints (device related issues such as life-threatening or disabling bleeding, acute kidney injury, major vascular complications) were reported in 4/117 pts (3.4 %).
Conclusions: This study suggests that the use of the latest TriGUARD 3™ CEPD in transfemoral TAVR seems to be associated with a low rate of clinically overt stroke and a low rate of device related adverse events, reflecting "real world" TAVR practice. However these results should be hypothesis generating and confirmed in a large RCT.

1. Introduction

Over the last 20 years there has been a rapid rise in transcatheter aortic valve replacement (TAVR) as treatment for high-risk patients with severe aortic stenosis (AS). Although a lot of improvements have been achieved, the rate of stroke related to TAVR remains a devastating complication with an overall 30-day incidence between 2 and 6% [1–8].

It is apparent that embolization of debris from the native aortic valve, thrombi and other material due to TAVR deployment could contribute to this stroke or transient ischemic attack (TIA) risk [2,8,9]. Studies have shown that post TAVR strokes and TIA's are clinically evident within 48 hours [10,11]. According to a retrospective cohort study including 101,430 patients, post TAVR stroke is associated with a 6-fold increased risk of mortality [12]. Thus, efforts to reduce strokes and TIA's have focused on the capture or deflection of embolic material with cerebral embolic protection devices (CEPDs) during TAVR, preventing their migration to the brain.

A recent study of 36,220 patients showed that CEPDs were associated with a significantly lower incidence of stroke and in-hospital mortality, without an increased risk of procedural complications [10]. In current practice, however, evidence for the efficacy of CEPDs in stroke prevention, is limited by the number of underpowered studies and small differences in clinical outcome. A clear advantage for the standard use of CEPD's has not yet been consistently demonstrated.

At the Utrecht University Medical Center (UMCU), we have >10 years of experience with TriGUARD [13–16]. The latest TriGUARD 3™

Abbreviations: AS, aortic stenosis; AVR, aortic valve replacement; CEPD, cerebral embolic protection device; TAVR, transcatheter aortic valve replacement; TG3, TriGUARD 3; TIA, transient ischemic attack.

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https://doi.org/10.1016/j.carrev.2023.01.008
1553-8389/

(TG3) CEPD (Keystone Heart) was designed to provide complete coverage of all cerebral arteries with easier handling and positioning compared to its previous generation [17]. During the REFLECT study, Keystone Heart became aware of the importance of improving the percentage of complete 3 vessel coverage, throughout the index procedure and therefore made effective steps to improve device stability and ease of use.

The objective of this study is to evaluate the neurological outcome of patients undergoing TAVR with European TG3 CEPD.

2. Methods

2.1. Study design

In-hospital data of all consecutive patients who underwent a transfemoral TAVR procedure with the use of a TG3 CEPD between July 28th 2020 and December 21th 2021 were collected and analyzed. All patients with adequate anatomy for the use of TG3 CEPD were eligible for inclusion. Anatomical exclusion criteria were severe peripheral vascular disease that might preclude appropriate vascular access of the TG3 CEPD (iliofemoral minimal luminal diameter < than 3.5 mm according to computer tomographic angiogram (CTA)), severe tortuosity and severe calcification at the femoral puncture site (all puncture sites were ultrasound guided). There were 187 TAVR procedures performed during the study duration. A total of 67 patients were excluded either due to anatomical exclusion criteria or due to operator preference and in 3 patients a Sentinel CEPD was used. Of this exclusion cohort, 21 patients (11 %) were excluded due to anatomical exclusion criteria as mentioned above.

The ACURATE neo2™ Aortic Valve System (Boston Scientific Corporation) and the SAPIEN 3 Ultra Transcatheter Heart Valve (Edwards Lifesciences) were the two implanted valves in this study. The procedure was performed via the transfemoral approach according to standard institutional practice by five different experienced operators. Single-antiplatelet therapy with aspirin, clopidogrel or anticoagulation was recommended post-procedure according to indications for anticoagulation, such as atrial fibrillation.

2.2. Device description

The TG3 CEPD is a temporary, retrievable, single-use, self-expanding deflection filter composed of a radiopaque Nitinol frame and a polymer mesh (nominal pore size 115–145 mm) capable of covering all three major aortic arch vessels (the right brachiocephalic, left common carotid and left subclavian arteries) upon deployment (Fig. 1A and B). The device is advanced into the aortic arch under fluoroscopic guidance through the contralateral 8Fr femoral artery sheath and has an additional port to advance a 5Fr pigtail catheter. The filter mesh features of the TG3 CEPD result in maintenance of optimal cerebral blood flow by deflecting debris while maintaining flow towards the brain.

Since all patients already provided written informed consent for data collection within the scope of scientific research and for quality control within the Dutch Heart Registration database (NHR) (http://nederlandsehartregistratie.nl), local ethics approval for this study was waived. Patients were not involved in study design at this point, however from 2021 onwards, patients/public are part of our institutional ethics review committee.

2.3. Endpoints and outcomes

The primary endpoint was the absence of clinically overt stroke or TIA at 72 h or at discharge. The definition of clinically overt stroke in our study was face or arm weakness, speech difficulty or other sudden-onset indicators. In case of clinical suspicion on stroke symptoms all patients were examined by a certified neurologist and additional imaging and testing was performed. Secondary endpoints were the absence of any life-threatening or disabling bleeding, stage 2 and 3 acute kidney injury or any major vascular complication. Other outcomes were complete cerebral coverage with the TG3 CEPD, in-hospital VARC-3 outcomes such as coronary artery obstruction, valve-related dysfunction, pacemaker implantation, and at 30 days all-cause mortality.

2.4. Statistical analysis

The data analyses were performed with statistical and computing program R (R Foundation for Statistical Computing, Vienna, Austria. Version 3.6.1). Normally distributed continuous variables were presented as mean ± standard deviation. Skewed continuous variables were presented as median and interquartile range. Normality of the distributions was tested using the Kolmogorov-Smirnov test. Categorical variables were presented as counts and percentages.

3. Results

3.1. Patient demographics

Baseline characteristics all of the 117 patients who underwent a transfemoral TAVR procedure with the TG3 CEPD are shown in

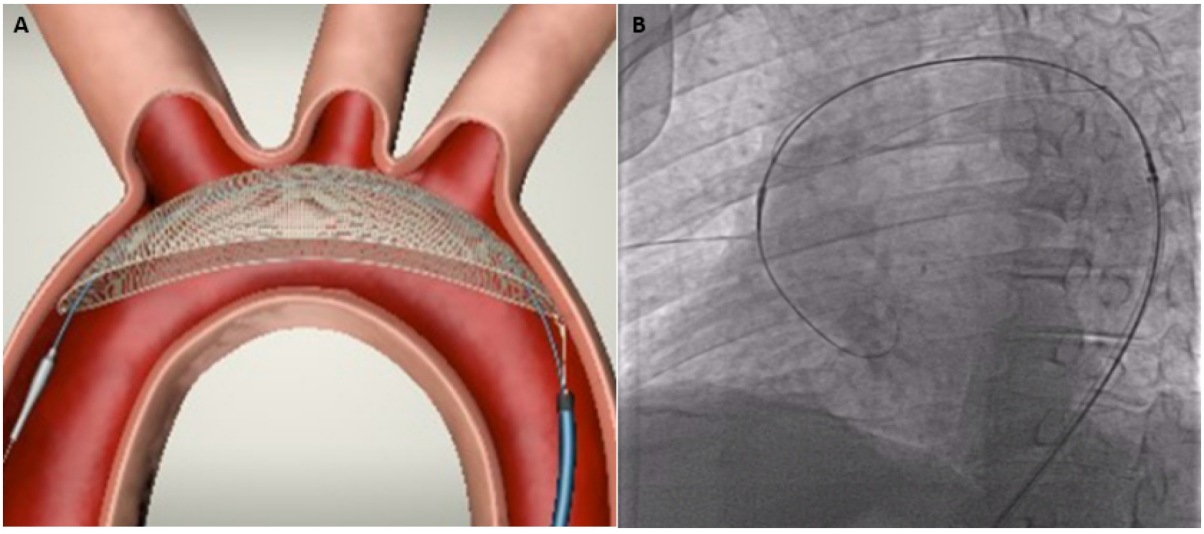

Fig. 1. (A) The TriGUARD 3™ CEPD positioned in the aortic arch providing full coverage of all three major branches.
(B) Real life experience of the device with angiographic positioning.

Table 1
Baseline demographics and clinical presentation.

Variables	Overall (n = 117)
Age (years)	80.3 ± 6.2
Male patients	63 (53.8)
Diabetes mellitus	33 (28.2)
Hypertension	74 (63.2)
Dyslipidemia	77 (65.8)
Atrial Fibrillation	41 (35.0)
Prior MI	9 (7.7)
Prior PCI	27 (23.0)
Prior CABG	6 (5.1)
NYHA class	
I	0 (0)
II	71 (60.8)
III	45 (38.4)
IV	1 (0.8)
PVD	14 (11.9)
Previous stroke/TIA	20 (17.0)
COPD	14 (11.9)
CKD	15 (12.8)
Porcelain aorta	4 (3.4)
EuroScore II	
<4	97 (82.9)
>4	20 (17.0)
Frailty (Edmonton)	29 (24.7)

Values are presented as mean ± standard deviation or number (%).
MI, myocardial infarction; CABG, coronary artery bypass graft surgery; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and PVD, peripheral vascular disease.

Table 3
In-hospital VARC-3 endpoints.

Adverse events	Overall (n = 117)
All cause mortality at 30 days	0 (0)
Neurologic events	
Stroke	0 (0)
TIA	1 (0.8)
Valve related re-hospitalization at 30 days	0 (0)
Major bleeding (≥BARC-3a)	0 (0)
Major vascular complications	4 (3.4)
Major cardiac structural complications	1 (0.8)
Other procedural and valve-related complications	0 (0)
New conduction disturbances and arrhythmias	
New onset LBBB	22 (18.8)
New PM	6 (5.1)
New onset AF	1 (0.9)
Acute kidney injury	
Stage 1	4 (3.4)
Stage 2	0 (0)
Stage 3	0 (0)
Stage 4	0 (0)
Myocardial infarction	0 (0)
Bioprosthetic valve dysfunction	0 (0)
Leaflet thickening and reduced motion	0 (0)
Clinically significant valve thrombosis	0 (0)
Patient-reported outcomes and health status	0 (0)
Composite endpoints, technical success and device success	117 (100)

Values are presented as number (%).
AF, atrial fibrillation; AKI, acute kidney injury; BARC, Bleeding Academic Research Consortium; LBBB, left bundle branch block; TIA, transient ischemic attack; PM, pacemaker, and VARC-3, Valve Academic Research Consortium 3.

Table 1. Mean age was 80.3 ± 6.2 years and 63 patients (53.8 %) were male. A total of 41 patients (35.0 %) had preexistent atrial fibrillation. Twenty patients (17.0 %) had a previous stroke or TIA before TAVR and 14 patients (11.9 %) had peripheral vascular disease. In the TAVR workup 71 patients (60.8 %) met a NYHA II classification and 29 patients (24.7 %) were frail as defined by the Edmonton criteria.

3.2. Procedural details

The two different valves that were implanted are summarized in Table 2. The SAPIEN 3 Ultra Transcatheter Heart Valve was implanted in 66 patients (56.5 %) and ACURATE neo2™ Aortic Valve System in 51 patients (43.5 %).

3.3. Outcomes

The clinical outcomes after TAVR with the TG3 CEPD are summarized in Table 3. One patient was diagnosed with a potential TIA with weakness in the right hand 5 h after the procedure. Upon review by the neurologist, an MRI was performed which showed no new defects. The temporary weakness disappeared <24 h. No other clinically overt stroke or TIA was detected by the clinical team before discharge or 72 h after TAVR in the other 116 patients (99.1 %).

Four patients (3.4 %) had a major vascular complication. These 4 patients were among the first 25 patients to undergo TAVR and TG3 CEPD.

Table 2
Procedural specifications (n = 117).

Valve size	
SAPIEN 3 Ultra	n = 66
23	15 (22.7)
26	32 (48.5)
29	19 (28.8)
ACURATE neo2™	n = 51
S	19 (37.3)
M	12 (23.5)
L	20 (39.2)

Values are presented as number (%).

Three patients (2.6 %) developed an aneurysm spurium and were successfully treated femoral with a thrombin injection. One patient (0.8 %) required surgical intervention of the superficial femoral artery by a vascular surgeon. Other secondary endpoints were not observed.

One patient (0.8 %) had a coronary obstruction which required acute PCI which was performed successfully. New pacemaker implantation was required in 6 patients (5.1 %) as a result of total AV-block after TAVR. Complete coverage of all the three cerebral arteries was achieved in all patients and verified with angiography and fluoroscopy throughout the TAVR procedure (Fig. 1A and B).

4. Discussion

The use of TG3 CEPD during TAVR in this study was associated with a very low number of clinically overt cerebral events. With the exception of 1 patient who exhibited symptoms of a TIA no neurological events were detected in our patient group undergoing TAVR.

Cerebral embolic protection devices are designed to protect the brain from adverse neurologic events, improving the safety and outcomes of the TAVR procedure. While the clinical requirement of CEPDs is increasingly recognized, research on these devices is still ongoing and the evaluation of the effectiveness remains challenging. It also demands identification of procedural confounders and necessities differentiating between CEPD and TAVR related adverse events. The early-generation TriGUARD HDH CEPD demonstrated to be safe in the DEFLECT III trial, however the trial was not sufficiently powered to establish efficacy. Safety of the TriGUARD CEPD meeting the primary endpoint was shown in the REFLECT II trial including 345 patients [17]. Although the REFLECT II trial failed to show a significant reduction of procedure-related cerebral injury, our personal experience over the past years using the same device was different and thus this registry with the latest generation TG3 was done.

In the present study, the incidence of clinically overt cerebral events was very low, compared to recently published studies with the use of CEPDs [18–21]. We considered a few possible reasons for that. First, it could reflect the improvements made on the TG3 CEPD which allows for easier deployment and stable position covering all cerebral vessels throughout the TAVR procedure, without interference with TAVR

devices. Second, it potentially reflects the TAVR team increasing experience over the past years with usage of CEPD and streamlining of the TAVR procedure using local anesthesia, short procedural times and early mobilization and discharge of the patients. And finally it may be that the standard use of the TG3 CEPD actually does result in reduced periprocedural cerebral events.

Although no routine assessment by a neurologist nor a routine MRI was performed to identify silent strokes after TAVR, we believe these results to be promising and reflecting real world practice in experienced TAVR centers. Several studies have already shown that there is no real clinical correlation between new cerebral lesions on DW-MRI and clinical symptoms, therefore we believe clinical outcome to be the most important.

Secondary endpoints were only seen in a few patients. There were 4 cases of major vascular complications, which was better compared to the REFLECT II trial (3.4 % vs. 9.5 %) [17]. Even more, these complications occurred in the first 25 patients. In order to avoid local access site complications, after the first 25 patients, the operators adjusted their approach strategy. The renewed approach in all the following patients included a standardized access preparation with preclosure with a Perclose Proglide device and predilatation with an 8 french dilator. No vascular complications were observed after these adjustments in the procedure. Furthermore, no device interaction with the TAVI device was noted. Deflection of debris might theoretically cause acute kidney injury. However we had no cases of acute kidney injury after TAVR, while 2.5 % was reported in the REFLECT II trial. The latter finding might be explained by the use of a standardized pre and post hydration protocol in patients with reduced kidney function in our center.

Performance endpoints included successful device deployment, successful device positioning (defined as complete apposition of the device against the aortic arch and complete 3-vessel coverage maintained throughout the procedure) assessed by the angiographic evaluation during the procedure (Fig. 1A and B), device interaction and successful device retrieval in the absence of device interference. In comparison to both the DEFLECT III study and the REFLECT II study (71 % vs. 59.3 %), technical success with complete cerebral coverage was accomplished in all 117 patients (100 %).

The latter findings are particularly important given the fact that all procedures were done by 5 different operators with previous experience in the use of several CEPDs.

4.1. Study limitations

The present study has several limitations. The most important limitation is the single-center registry. Because of this single center setting, there is an inherent risk of a potential selection bias. In addition, no routine assessment by a neurologist nor a routine MRI was performed to identify silent strokes after TAVR. Furthermore, this study analyzed only the in-hospital clinically overt cerebral events, whereas 30-day stroke rate was usually assessed in other studies. However due to this prolonged follow-up in others studies, it is hard to detect if a stroke is due to the TAVR procedure or correlated to other causes such as atrial fibrillation.

5. Conclusions

This registry shows that the use of the latest TriGUARD 3™ CEPD in transfemoral TAVR is associated with a low rate of clinically overt stroke and a low rate of device related adverse events. We reflected “real world” TAVR practice where not all patients are routinely tested by certified neurologists after the procedure. Therefore our results should be viewed as hypothesis generating for bigger randomized clinical trials where close monitoring of all potential adverse events should be included.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Sayonara M. Daal: Investigation, Data curation, Writing – original draft, Visualization. **Gian M.J. Jimenez-Rodriguez:** Formal analysis, Investigation, Data curation, Writing – original draft. **Michiel Voskuil:** Writing – review & editing. **Adriaan O. Kraaijeveld:** Writing – review & editing. **Thomas C. Dessing:** Writing – review & editing. **Faiz Z. Ramjankhan:** Writing – review & editing. **Mostafa M. Mokhles:** Writing – review & editing. **Pieter R. Stella:** Conceptualization, Writing – review & editing, Supervision.

Conflict of interest

PS serves on advisory board Keystone Heart, AK received consultancy fees for Boston Scientific, all other authors declare no conflict of interest.

Acknowledgments

The authors thank Nicole van Hemert and Astrid Links for careful collection of data. We thank Seema Biswas for English language assistance.

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