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A prospective randomized evaluation of the TriGuard™ HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial

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Aims To evaluate the safety, efficacy, and performance of the TriGuard™ HDH Embolic Deflection Device (TriGuard) compared with no cerebral protection in patients undergoing transcatheter aortic valve implantation (TAVI).

Methods and results From February 2014 to March 2015, 85 subjects undergoing TAVI at 13 centres in Europe and Israel were randomized to TriGuard protection vs. no protection. Subjects underwent neurologic and cognitive evaluation at baseline, pre-discharge and 30 days; cerebral diffusion-weighted magnetic resonance imaging was performed at 4 ± 2 days post-procedure and at 30 days. Technical success, which included complete 3-vessel cerebral coverage, was achieved in 88.9% (40/45) of cases. The primary in-hospital procedural safety endpoint (death, stroke, life-threatening or disabling bleeding, stage 2 or 3 acute kidney injury, or major vascular complications) occurred in 21.7% of TriGuard and 30.8% of control subjects ($P = 0.34$). In the Per Treatment population (subjects with complete three-vessel cerebral coverage), TriGuard use was associated with greater freedom from new ischaemic brain lesions (26.9 vs. 11.5%), fewer new neurologic deficits detected by the National Institutes of Health Stroke Scale (3.1 vs. 15.4%), improved Montreal Cognitive Assessment (MoCA) scores, better performance on a delayed memory task ($P = 0.028$) at discharge, and a >2-fold increase in recovery of normal cognitive function (MoCA score >26) at 30 days.

Conclusion TriGuard cerebral protection during TAVI is safe and complete cerebral vessel coverage was achieved in 89% of subjects. In this exploratory study, subjects undergoing protected TAVI had more freedom from ischaemic brain lesions, fewer neurologic deficits, and improved cognitive function in some domains at discharge and 30 days compared with controls.

Keywords Neuroprotection • Transcatheter aortic valve implantation • Diffusion-weighted imaging • Cerebral ischaemia • Stroke prevention

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Introduction

In large randomized controlled trials, clinical stroke is reported in 4–7% of patients within 30 days after transcatheter aortic valve implantation (TAVI),[1–4] with 50% occurring in the peri-procedural time frame.[5] The implications of stroke on morbidity and subsequent mortality (a 3- to 9-fold increased risk)[6,7] are well established. However, there is growing evidence that not only is overt stroke substantially underreported following cardiovascular procedures[8] but also that it represents only one extreme of a spectrum of adverse neuro-embolic outcomes. Procedural transcranial Doppler ultrasound monitoring detects cerebral embolic signals in 100% of patients undergoing TAVI (primarily during valve placement and deployment),[9] and ischaemic brain lesions on diffusion-weighted magnetic resonance imaging (DW-MRI) are detected in 68–100% of patients post-procedure.[10–12] While the clinical impact of such lesions has not been completely characterized, there is ample cause for concern: the reported total ischaemic lesion volume range of 1.5–4.3 cm^3 is equivalent to the death of at least 2 million neurons and 1 billion synapses,[13] and in various clinical contexts the presence of these 'silent' cerebral lesions has been linked to cognitive decline, a >2-fold risk of subsequent dementia,[14] and a >3-fold risk of subsequent overt stroke.[15]

The TriGuard™ HDH embolic deflection device (TriGuard) is designed to address this issue by reducing the passage of embolic material to the cerebral arteries during endovascular procedures. The results of the DEFLECT I Trial, a single-arm safety and performance evaluation of the first-generation TriGuard device that led to Conformité Européenne marking in October 2013, have previously been reported.[16] The DEFLECT III trial is the first multi-centre randomized controlled trial to evaluate patients with severe symptomatic aortic stenosis (AS) undergoing TAVI with and without cerebral embolic protection; as an exploratory study, its purpose was to evaluate potential endpoints and benchmark event rates to inform the design of a pivotal randomized trial.

Methods

Study design and patient population

The DEFLECT III trial (NCT02070731) was a prospective, multi-centre, single-blind, randomized controlled trial evaluating the safety, efficacy and performance of the TriGuard device in subjects undergoing TAVI at 13 investigational centres in five countries in the European Union and Israel. Eligible subjects were adults presenting with severe symptomatic AS referred for TAVI due to high or extreme surgical risk.[17] Exclusion criteria included recent (<72 h) acute myocardial infarction, recent (<6 months) stroke or transient ischaemic attack, cardiogenic shock, impaired renal function (glomerular filtration rate <30 mg/dL), past or pending organ transplant, active peptic ulcer or recent (<6 months) gastrointestinal bleeding, and history of bleeding diathesis or coagulopathy or contraindications to antiplatelet or anticoagulant therapy. Potential subjects were also excluded if they were undergoing TAVI via the subclavian or direct aortic route, had known hypersensitivity to device component materials or contrast that could not be adequately premedicated, had severe peripheral artery disease that precluded vascular access, had a heavily calcified or severely atheromatous aortic arch or aortic arch anatomy that could prevent positioning and stability of the device, had contraindications to cerebral MRI, or if another intervention was planned during or within 2 weeks prior to TAVI or treatment with any other investigational device or procedure was planned at any time during the study period. The study protocol was approved by the Institutional Review Board or Medical Ethics Committee at each site, all subjects provided written informed consent, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Study device

The TriGuard HDH embolic deflection device (Keystone Heart Ltd., Caesarea, IL, USA) is a temporary, single-use, biocompatible filter made of fine nitinol (nickel titanium alloy) wires, which is delivered transfemorally via a 9 French Mullins introducer sheath, positioned in the aortic arch, and anchored in position by an atraumatic stabilizer in the ostium of the innominate artery. The filter portion of the device covers all three major cerebral arteries in the aortic arch (innominate, left common carotid, and subclavian), maintaining blood flow to the cerebral vessels through 130 μm pores while deflecting larger emboli to the descending aorta. The filter is coated with an anti-thrombotic coating (SurModics, Inc. Eden Prairie, MN, USA).

Procedure

Transcatheter aortic valve implantation was performed with commercial transcatheter valve systems (primarily the SAPIEN transcatheter heart valve [Edwards Lifesciences, Irvine, CA, USA] or the CoreValve transcatheter aortic valve replacement platform [Medtronic, Inc., Minneapolis, MN, USA]) according to standard institutional procedures via the transfemoral or transapical approach under local or general anaesthesia. Standard dual antiplatelet therapy with aspirin (300–325 mg loading dose and 75–325 mg daily maintenance dose indefinitely) and clopidogrel (≥300 mg loading dose >6 h before the procedure or 600 mg peri-procedure, and 75 mg daily maintenance dose for ≥6 months) was recommended. At the start of the procedure, a 9 French arterial sheath was inserted in the contralateral femoral artery, through which the TriGuard was advanced to the aortic arch and deployed to cover the ostia of the three major cerebral vessel takeoffs. The TriGuard was withdrawn after completion of the TAVI procedure.

All subjects underwent clinical and detailed neurologic and cognitive assessment at baseline, post-procedure, and at 30 days. Neurologic and cognitive assessments included standard clinical scales (the National Institutes of Health Stroke Scale [NIHSS] and the Modified Rankin Scale [mRS]) as well as a neurocognitive battery that included the Montreal Cognitive Assessment (MoCA)[18] and select tests from the computerized Cogstate Research Test.[19,20] At baseline and 30 days, the neurocognitive battery included a supplemental Digit Symbol Substitution Test, Trail-making Test Parts A and B, and tests of category and letter fluency. Dedicated staff were identified at each centre to perform the neurological and cognitive assessments; these individuals were NIHSS certified, trained in administration of the mRS and neurocognitive tests, and blinded to DW-MRI findings and treatment allocation. Diffusion-weighted magnetic resonance imaging was performed post-procedure (at 4 ± 2 days) to define the ischaemic burden of the TAVI procedure, and at 30 days to evaluate ongoing embolic risk. Independent site monitoring was performed for 100% of clinical fields and clinical events.

Endpoints

The primary safety endpoint was in-hospital procedural safety, defined as a composite of the following Major Adverse Cardiovascular and Cerebrovascular Events (MACCE): all-cause mortality, all stroke (disabling and non-disabling), life-threatening (or disabling) bleeding, acute kidney injury (stage 2 or 3), and major vascular complications. All endpoints were defined according to Valve Academic Research Consortium-2

(VARC-2) recommendations.[21] Secondary device performance endpoints included technical success, defined as successful device deployment, positioning with complete three-vessel coverage (verified by an independent Angiographic Core Laboratory [Yale Cardiovascular Research Group, New Haven, CT, USA]), and retrieval, without interference with the TAVI procedure. Secondary efficacy endpoints included the frequency, number, and per-patient average and maximal single volume of cerebral ischaemic lesions on DW-MRI. Secondary safety endpoints included components of in-hospital MACCE and TAVI early safety at 30 days (composite and components) according to VARC-2 definitions.[21] All adverse events were adjudicated by an independent Clinical Events Committee (Yale Cardiovascular Research Group, New Haven, CT, USA), which included a cardiac surgeon, an interventional cardiologist, and a vascular neurologist.

Diffusion-weighted magnetic resonance imaging

Diffusion-weighted magnetic resonance imaging of the brain was performed at 4 $\pm$ 2 and 30 $\pm$ 7 days post-procedure according to a standardized image acquisition protocol. Diffusion-weighted magnetic resonance imaging data were analysed at an independent core laboratory (Global Institute for Research, Richmond, VA, USA) by two independent imaging physicians using validated qualitative and quantitative methods (Vitrea Version 6.3.2, Toshiba America Medical Systems, Tustin, CA, USA); details have been reported previously.[16]

Statistical analysis

The primary analysis of all endpoints was conducted in the intention-to-treat (ITT) population. For efficacy measures, we include a per treatment (PT) analysis population, defined as subjects in whom complete three-vessel cerebral coverage was maintained throughout the TAVI procedure. Continuous variables are presented as mean $\pm$ SD when the data are approximately normally distributed. Skewed data, such as those obtained via magnetic resonance imaging (MRI), are presented as median and interquartile range (IQR). Binary variables are described as frequencies and percentages. Time-to-event data are presented as Kaplan–Meier estimates to 30 days. As an exploratory study, no formal hypothesis testing was planned.

Results

Patient and procedural characteristics

From February 2014 to March 2015, a total of 85 subjects were randomized 1 : 1 to TriGuard ($n = 46$) or control ($n = 39$) at 13 centres in Europe and Israel. Patient flow and follow-up rates are detailed in *Figure 1*. Two subjects in each group withdrew consent after randomization but were included in the ITT safety analysis. Subject characteristics were well-matched between groups (*Table 1*), and the study population is representative of patients meeting current indications for TAVI, with severe functional limitations (42.2% NYHA Class III/IV) and frequent comorbidities (diabetes, hypertension, and hyperlipidaemia); 28.2% of subjects had atrial fibrillation on admission.

A total of 85 valves were implanted in 83 patients (two patients withdrew consent prior to valve implantation, and 2 underwent valve-in-prosthetic-valve implantation). The Edwards SAPIEN/XT/3 transcatheter heart valve was used in 63.5% (54/85) of cases and the Medtronic CoreValve transcatheter aortic valve was used in 31% (26/85) of cases; the remaining 3.5% of subjects (3/85) received other commercial valves. The majority of valves (82/85) were implanted via the transfemoral approach; in two subjects, the

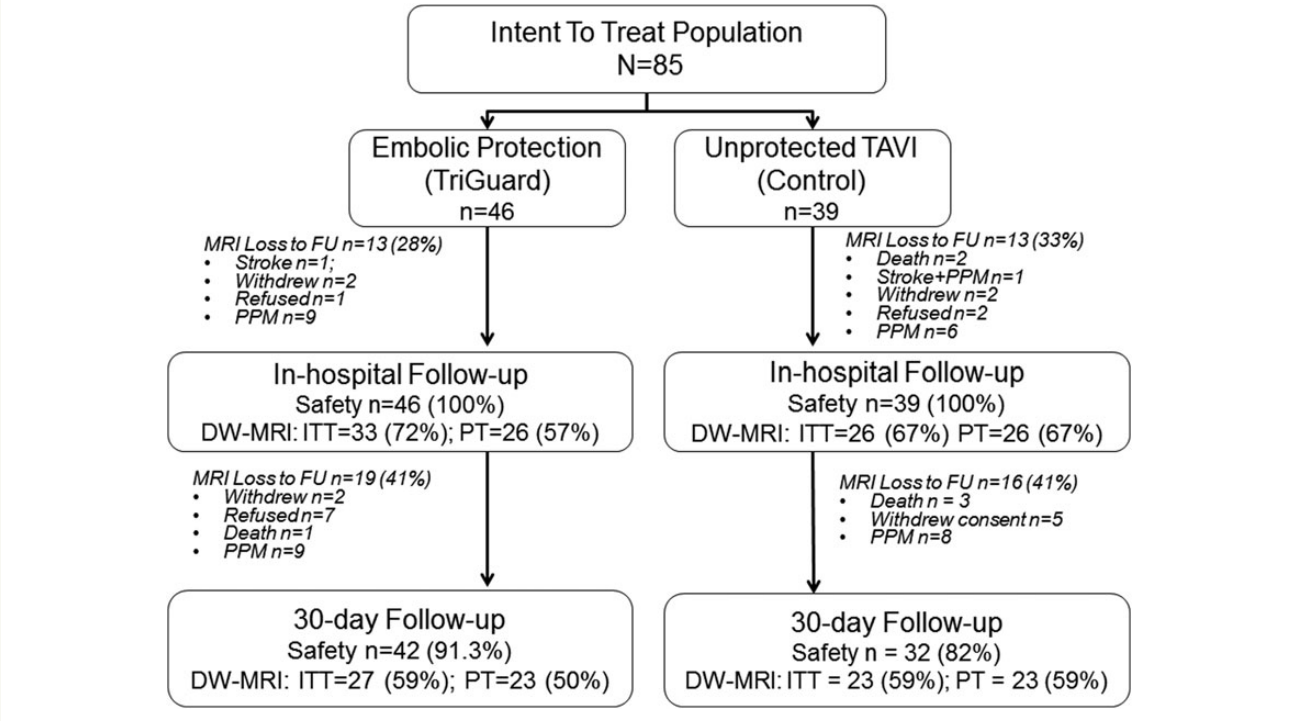

Figure 1 DEFLECT III patient disposition.

Table 1 Baseline demographic and clinical characteristics (intention-to-treat population)

Variable	TriGuard (*N* = 46)	Control (*N* = 39)	Total (*N* = 85)	*P*-value
Age (years) (mean ± SD)	82.5 ± 6.5	82.3 ± 6.0	82.4 ± 6.2	0.61
Male	43.5%	48.7%	45.9%	0.63
Diabetes	21.7%	23.1%	22.4%	0.88
Hypertension	80.4%	71.8%	76.5%	0.35
Hyperlipidaemia	67.4%	53.8%	61.2%	0.20
Atrial fibrillation	21.7%	35.9%	28.2%	0.15
Prior MI	13.0%	21.1%	16.7%	0.33
Prior CABG	10.9%	7.7%	9.4%	0.62
Prior PCI	30.4%	46.2%	37.6%	0.14
NYHA Class III/IV	45.4%	38.5%	42.2%	0.63
PVD	13.0%	12.8%	12.9%	0.98
Prior stroke/TIA	13.3%	17.9%	15.5%	0.56
COPD	30.4%	34.2%	32.1%	0.71
Home oxygen therapy	6.5%	0.0%	3.5%	0.10
Chronic renal disease	23.9%	25.6%	24.7%	0.85
Porcelain aorta	4.3%	0.0%	2.4%	0.39
Frailty	11.4%	17.9%	14.5%	0.39
EuroScore II	10.1 ± 10.1	7.2 ± 6.6	8.7 ± 8.7	0.60
STS score	6.3 ± 5.8	7.4 ± 5.5	6.8 ± 5.6	0.48

COPD, chronic obstructive pulmonary disease; CABG, coronary artery bypass grafting; ITT, intention to treat; MI, myocardial infarction; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; SD, standard deviation; TIA, transient ischemic attack.

transapical approach was employed, one of whom required a second prosthesis (valve-in-valve). Transcatheter aortic valve implantation was successful in all subjects. Mean total fluoroscopy time was 10 min longer (28.4 vs. 18.8 min, $P < 0.001$) in TriGuard subjects compared with controls. Two-thirds of patients were placed on dual antiplatelet therapy; the remainder received either aspirin or clopidogrel monotherapy (Supplementary material online, *Table S1*).

TriGuard performance

A total of 45 TriGuard devices were used in 44 subjects; two randomized subjects withdrew consent prior to device introduction, and one subject received 2 TriGuard devices over the course of a valve-in-valve procedure. The device was successfully positioned to cover all three cerebral inflow vessels prior to passage of the TAVI catheter and maintained in position throughout prosthetic-valve deployment, implantation, and retrieval in 88.9% (40/45, 95% CI [75.4%, 96.2%]) of cases. Anatomic details of the five cases are provided in Supplementary material online, *Table S2*. There was no device interference with the TAVI system and no device failures occurred.

Safety outcomes

The primary in-hospital safety endpoint occurred in 21.7% of subjects in the TriGuard group and 30.8% of controls ($P = 0.34$); no major disparity was noted in any individual endpoint component (*Table 2*). There were two strokes in each group; one death from pneumonia occurred in a stroke patient in the TriGuard arm, and two acute procedural deaths due to aortic ring rupture occurred in the control arm. The incidence of major vascular complications was similar between groups. At 30 days, the TAVI early safety endpoint was not significantly different between TriGuard and controls (26.1 vs. 31.2%, $P = 0.62$). There were no additional strokes or deaths in either group at 30-day follow-up.

Cerebral ischaemic lesions

Post-procedure DW-MRIs were available in 72% (33/46) of TriGuard subjects and 67% (26/39) of controls; at 30 days, DW-MRI data were available in 59% (27/46) of TriGuard subjects and 59% (23/39) of controls. Loss to DW-MRI follow-up was higher than anticipated: causes are detailed in *Figure 1*, and included permanent pacemaker implantation, patient refusal or withdrawal, death, and unstable clinical status due to stroke. Pre-procedure DW-MRI was not performed because pre-existing lesions are rare before TAVI (<1% of subjects[10,11,16,21,22]), and requiring subjects to undergo sequential MRIs increases patient refusal; therefore, all post-procedure lesions were considered new lesions. With TriGuard protection, complete freedom from ischaemic brain lesions was 46% higher compared with controls in the ITT population, and 57% higher than controls in the PT population (*Figure 2A*). Median per-subject single lesion volume was lower in the TriGuard group by 11% ($P = 0.3$) and 44% ($P = 0.07$) in the ITT and PT populations, respectively (*Figure 2B*), and was as high as 142 mm^3 in the TriGuard group and 202.9 mm^3 in the control group. Median per-subject maximum lesion volume was lower in the TriGuard group by 14% ($P = 0.96$) and 48% ($P = 0.17$) in the ITT and PT populations respectively, and was as high as 326 mm^3 in the TriGuard group compared with 3378 mm^3 in the control group. When per-patient total lesion volumes are categorized into zero, small, medium, or large size ranges, the proportion of subjects with medium lesions was

Table 2 Safety outcomes

Endpoint or event	TriGuard (*N* = 46)	Control (*N* = 39)	Relative risk [95% CI]	*P*-value
Hierarchical composite in-hospital MACCE	21.7%	30.8%	0.71 [0.34, 1.46]	0.34
All-cause death	2.2% (1)	5.1% (2)	0.42 [0.04,4.50]	0.46
All stroke	2.2% (1)	5.1% (2)	0.42 [0.04, 4.5]	0.46
Life-threatening bleeding	2.2% (1)	5.1% (2)	0.42 [0.04, 4.5]	0.46
AKI (Stage 2/3)	2.2% (1)	0.0% (0)	2.55 [0.11, 60.9]	0.91
Major vascular complications	15.2% (7)	15.4% (6)	0.99 [0.36, 2.7]	0.85
Non-hierarchical components				
All-cause death	2.2% (1)	5.1% (2)	0.42 [0.04,4.50]	0.46
All stroke	4.3% (2)	5.1% (2)	0.85 [0.13, 5.74]	0.87
Life-threatening bleeding	2.2% (1)	7.7% (3)	0.28 [0.03, 2,61]	0.23
AKI (Stage 2/3)	2.2% (1)	0.0% (0)	2.55 [0.11, 60.9]	0.91
Major vascular complications	17.4% (8)	20.5% (8)	0.85 [0.35, 2.05]	0.71
30 Day MACE (K–M estimates)	26.1% (12)	31.2% (12)	0.83 [0.37, 1.84]	0.62
All-cause death	2.27% (1)	5.13% (2)	0.40 [0.04,4.44]	0.44
All stroke	4.35% (2)	5.56% (2)	0.81 [0.11, 5.76]	0.83
Disabling	2.17% (1)	0.0% (0)	–	0.38
Non-disabling	2.17% (1)	5.56% (2)	0.41 [0.04, 4.50]	0.45
Life-threatening bleeding	4.5% (2)	7.84% (3)	0.54 [0.09, 3.24]	0.49
AKI (Stage 2/3)	2.17% (1)	0.0% (0)	–	0.38
Coronary obstruction with intervention	2.17% (1)	0.0% (0)	–	0.36
Major vascular complications	17.39% (8)	20.67% (8)	0.83 [0.31, 2.21]	0.69
Valve-related dysfunction	0% (0)	0% (0)	–	–

AKI, acute kidney injury; ITT, intention to treat; K–M, Kaplan–Meier; MACCE, major adverse cardiac and cerebrovascular events.

reduced by 77% (7.5 vs. 33%) indicating a shift in the distribution of total lesion volumes from medium to small or absent in the TriGuard group (*Figure 2C*). However, the proportion of subjects with large total lesion volumes was similar between groups. To better understand the comparable frequency of large lesions between groups, an exploratory analysis uncovered a TAVI device treatment effect: among subjects undergoing protected TAVI with an Edwards SAPIEN valve, 33% had no ischaemic lesions, which increased to 50% with the next-generation SAPIEN 3 valve (*Figure 3*). In contrast, all subjects undergoing protected or unprotected TAVI with the Medtronic CoreValve prosthesis had ischaemic lesions; these subjects accounted for the largest lesion volumes in the TriGuard group (Supplementary material online, *Table S3*). In addition, a *post hoc* analysis of patients presenting with vs. without atrial fibrillation—a known risk factor for embolic stroke[22]—demonstrated (i) a significant difference between groups in freedom from ischemic lesions (0 vs. 27%, $P = 0.02$) and (ii) a non-significant blunting of treatment effect for DW-MRI and neurocognitive outcome measures. No significant treatment effect interaction with atrial fibrillation was found for any endpoint measure (Supplementary material online, *Table S4*).

At 30-day follow-up, diffusion-weighted imaging revealed new ischaemic lesions that had not been present post-procedure in 11.5% (3/26) of TriGuard subjects and 9.1% (2/22) of control subjects (both mean single and maximum lesion volumes were 5.2 ± 17.9 vs. 3.3 ± 11.9 mm^3, $P = 0.78$).

Neurologic and cognitive outcomes

Paired NIHSS assessments were performed in 94% (80/85) of subjects pre-discharge (mean of 6.2 ± 2.4 days) and 74% (63/85) at 30 days. At discharge, 'new neurologic impairment' (a *post hoc* endpoint defined as a worsening in NIHSS score from baseline with DW-MRI evidence of ischaemia) was detected in 3.1% of TriGuard patients vs. 15.4% of controls ($P = 0.16$); the rate was 0% in the PT TriGuard population ($P = 0.11$ compared with controls). At 30 days, ~4% of subjects had residual deficits, with no difference between treatment groups (*Figure 4A*). Despite a substantial loss to NIHSS follow-up, all control patients with worsened NIHSS at discharge were included in the 30-day assessment.

Paired MoCA assessments were performed in 88% (75/85) of subjects pre-discharge (mean 5.6 ± 2.2 days) and 74% (63/85) at 30 days. Mean baseline MoCA scores (scale 0–30) were similar in TriGuard and Control subjects (22.6 ± 4.2 vs. 22.2 ± 4.9, $P = 0.84$). At discharge and at 30 days, fewer TriGuard subjects in both the ITT and PT populations had a worsening in MoCA scores (*Figure 4B*). Overall, controlling for age, the mean MoCA score improved from baseline to discharge and 30 days in the TriGuard group; in the control group, the mean score declined from baseline to discharge and rebounded to approximately baseline levels at 30 days (*P*-value for overall effect of treatment = NS) (*Figure 5A*). Based on an impairment threshold MoCA score of 26,[18] the proportion of unimpaired subjects improved at 30 days with TriGuard compared with controls

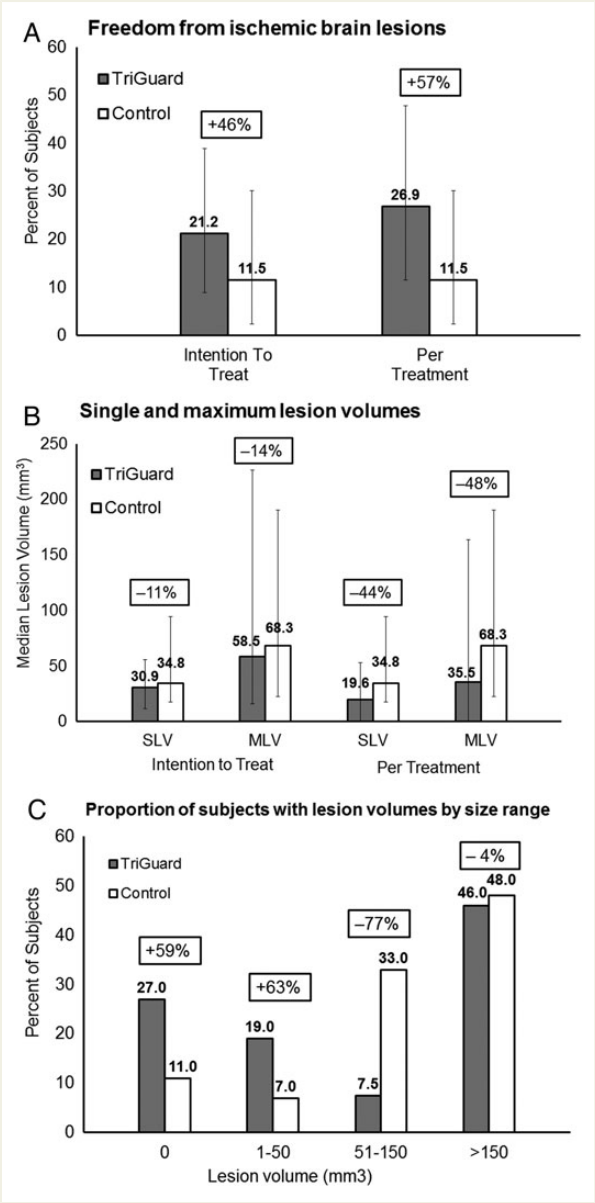

Figure 2 (*A*) Percent of patients with complete freedom from ischaemic brain lesions in the intention-to-treat and per treatment analysis populations. Error bars represent 95% confidence intervals. (*B*) Per-subject median single and maximumlesion volumes in the intention-to-treat and per-treatment analysis populations. Error bars represent the interquartile range. (*C*) Proportion of subjects experiencing a total lesion volume by diffusion-weighted magnetic resonance imaging in the given size range.

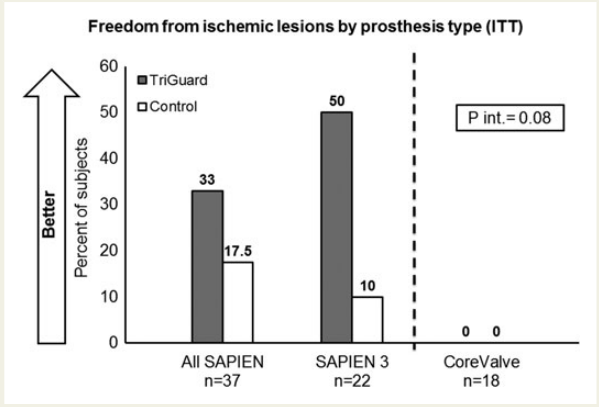

Figure 3 Variation in device efficacy (freedom from post-procedure cerebral ischaemic lesions) by valve prosthesis type.

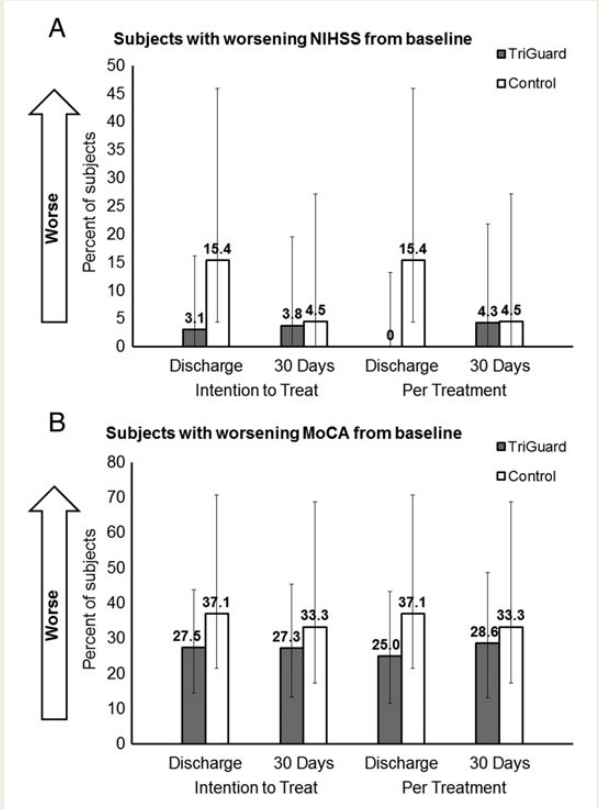

Figure 4 (*A*) Percent of patients with worsening National Institutes of Health Stroke Scale scores from baseline, evaluated pre-discharge and at 30 days in the intention-to-treat and per treatment analysis populations. Error bars represent 95% confidence intervals. (*B*) Percent of patients with worsening Montreal Cognitive Assessment scores from baseline, evaluated pre-discharge and at 30 days in the intention-to-treat and per treatment analysis populations. Error bars represent 95% confidence intervals.

(45.5% vs. 20%; RR 2.27 [95%CI, 1.01, 5.10]), whereas it was similar between groups at baseline (15.2 vs. 12.8%, $P = 0.75$) and post-procedure (20 vs. 20%, $P = 0.85$).

The Cogstate Research battery included five tests assessing a range of cognitive domains. TriGuard subjects were more likely to improve from baseline to discharge on the Identification Task, which measures visual attention and vigilance (81.5 vs. 54.5% of controls, $P = 0.06$), as well as on the International Shopping List Test (delayed recall), a measure of episodic memory (65.4 vs. 30.4%, $P = 0.022$). These differences were no longer apparent at 30 days (*Figure 5B*). No significant between-group differences were noted on other tests in the

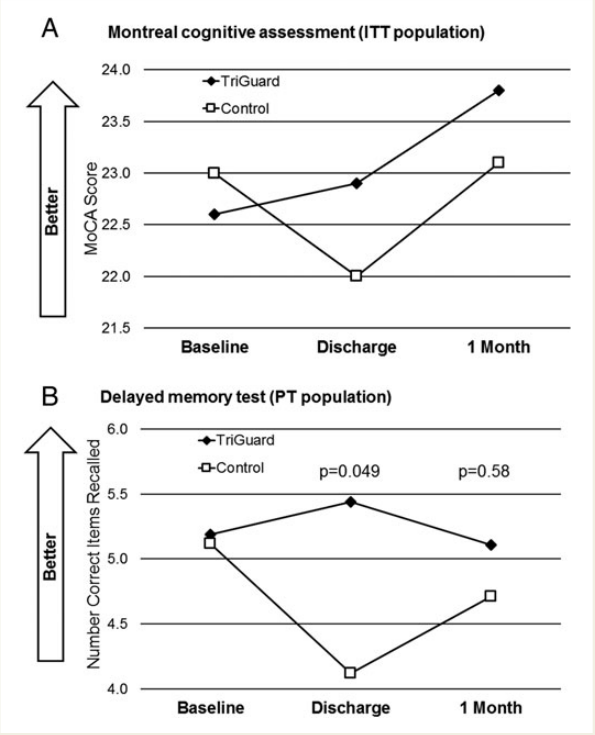

Figure 5 (*A*) Mean Montreal Cognitive Assessment score at baseline, discharge, and 30 days in the intention-to-treat analysis population. (*B*) Mean international shopping list test (delayed) scores, a measure of delayed recall, at baseline, discharge, and 30 days in the intention-to-treat analysis population.

Cogstate battery (at discharge and 30 days) or paper-and-pencil tests (30 days).

Discussion

DEFLECT III is the first multi-centre randomized clinical trial evaluating the safety, efficacy, and performance of neuroprotection during TAVI. The results demonstrate that the TriGuard device is safe and performs well, achieving complete cerebral vessel coverage in 89% (95% CI [75.4, 96.2]) of subjects. For the first time, it has been demonstrated that filter protection of the cerebral vessel takeoffs in the aortic arch is capable of increasing freedom from cerebral ischaemic lesions on DW-MRI. Compared with controls, use of the TriGuard device during TAVI numerically reduced single and maximum lesion volumes.

Importantly, systematic NIHSS and cerebral imaging assessments revealed that 15.4% of unprotected subjects had new neurologic deficits, indicating that clinically evident neurological events have been underreported in prior TAVI studies. The comparable rate in TriGuard protected patients was only 3.1%, providing preliminary evidence for clinically meaningful efficacy. Furthermore, TriGuard appears to mitigate post-procedure neurocognitive decline and was associated with improved memory at discharge and restoration of normal cognitive function in a greater proportion of patients at 30 days.

Device performance

The TriGuard HDH device used in this trial substantially outperformed the first-generation device evaluated in the DEFLECT I study (technical success 88.9 vs. 64%).[16] We attribute this improvement to iterative design changes, which include (i) an improved filter-tether connector with 180° free rotation along its axis, allowing more predictable and stable positioning; (ii) a stainless steel coil added to the tail of the filter frame for improved support and more precise positioning; and (iii) improved device visualization due to the addition of four radiopaque markers to the filter frame. A reduction in pore size from 250 to 130 μm may also have contributed to the observed efficacy outcomes. Additional device design changes are planned to further improve stability and optimize performance with all TAVI systems.

Safety measures and outcomes

DEFLECT III established the safety of the TriGuard device as an adjunct to TAVI, with similar in-hospital and 30-day composite safety endpoints compared with controls. There were two strokes in each group, commensurate with published rates from randomized clinical trials.[1–4] In the TriGuard arm, the single disabling stroke occurred in a patient who did not have full cerebral protection during the procedure; an additional non-disabling stroke occurred in a subject who appeared to have full coverage. While cerebral protection is expected to reduce procedural stroke rates, the range of stroke aetiologies in this high-risk patient population (e.g. haemorrhage, atrial fibrillation, valve thrombus, and delayed plaque embolization) likely make complete elimination of in-hospital stroke an unrealistic goal. The incidence of bleeding and vascular complications were similar between groups; although one case (2.2%) of acute kidney injury meeting stage 2/3 criteria did occur in the TriGuard group, this is well below published rates reported after unprotected TAVI[4,23,24] – providing reassurance that deflected emboli do not pose a hazard.

Efficacy measures and outcomes

DEFLECT III provides preliminary evidence for the efficacy of neuroprotection with the TriGuard device. The results of DEFLECT III also provide valuable information regarding the most sensitive measures for evaluation of the neurologic and cognitive effects of neuroprotection devices in future trials.

Diffusion-weighted magnetic resonance imaging

Our study again confirms that embolic insult to the brain occurs in the majority of patients undergoing TAVI: 88.5% of control subjects had ischemic lesions on post-procedure cerebral DW-MRI. In addition to demonstrating reductions in single and maximum lesion volumes, a new gold standard has been established with the TriGuard device: for the first time, a substantial proportion of patients undergoing TAVI with cerebral protection were found to have complete freedom of new embolic lesions, with a 45–55% improvement in this metric compared with no protection. This is in contrast to the recent CLEAN-TAVI single-centre randomized study of the Claret Montage™ dual-filter cerebral protection system, in which 98% of subjects, with or without protection, had ischaemic brain lesions.[25]

Despite the potential benefits of the TriGuard device, a sizable proportion of protected subjects in our trial (46%) still experienced relatively large cerebral lesion volumes, primarily subjects who underwent implantation with the non-steerable self-expanding Medtronic CoreValve platform. The TriGuard device appeared to be more effective in conjunction with the balloon-expandable Edwards SAPIEN/XT/3 systems, in which the nose cone of the TAVI delivery system can be steered to avoid the upper wall of the aortic arch, facilitating maintenance of complete TriGuard apposition. It is likely that with further improvements in operator technique, the proportion of patients without any peri-procedural lesions can be improved for all prosthetic-valve delivery systems.

New neurologic impairment

Recent consensus stroke definitions endorsed by the American Stroke Association and the American Academy of Neurology emphasize the role of imaging evidence of cerebral infarction, supported by clinical signs of neurological dysfunction, in the diagnosis of stroke.[26] In contrast, the traditional approach to stroke used in studies of interventional cardiology procedures (including VARC-2) has typically relied on overt symptoms to trigger further examination by a neurologist and/or confirmation by neuroimaging. It is not surprising, therefore, that the lack of systematic interrogation of subjects for subtle neurological deficits in trials of cardiovascular interventions have resulted in the under-reporting of episodes that meet the definition of acute peri-procedural stroke. In contrast to the low stroke rates reported in contemporary randomized trials of transcatheter or surgical aortic valve replacement (SAVR), a recent study that conducted systematic brain imaging and serial neurologic examinations after SAVR reported a 17% stroke rate.[8] Similarly, the recent CLEAN-TAVI trial reported new strokes in 28% of controls and 16% of protected patients undergoing TAVI.[25] The DEFLECT III findings are consistent with these results: using the updated stroke criteria reported above, we found new neurologic deficits (new deficits on NIHSS stroke scale combined with new ischemic lesions on DW-MRI) in 15.4% of controls and 3.1% of protected subjects. Though the between-group difference was not statistically significant in this trial ($P = 0.16$), larger prospective studies should confirm a reduction in clinical neurological events if the observed discrepancy is maintained.

Neurocognitive assessment

Understanding of the appropriate measures of subclinical neurological function that may be impaired following cardiac interventions is critical to an evaluation of neuroprotective strategies. For the DEFLECT III trial, we designed a novel neuropsychological battery to meet the following requirements: (1) Evaluation of a broad range of cognitive domains, (2) Sensitivity to subtle changes in cognition, (3) Feasibility in an elderly and highly comorbid subject population, and (4) Applicability to the range of languages spoken in our study sample. In addition to the well-validated MoCA cognitive screening instrument, we included a selection of standardized paper-and-pencil neuropsychological tests as well as computerized tests able to discriminate subtle changes in cognitive function. Overall, the selected battery is highly weighted toward psychomotor speed and attention, which can be affected by injury to a wide range of brain areas, rather than other cognitive domains whose function is more anatomically circumscribed.

Subjects in the TriGuard group tended to display greater improvements at discharge in both general measures of cognitive function (i.e. MoCA) and evaluations of specific domains (i.e. Cogstate visual attention, vigilance, and delayed memory), whereas control subjects tended to exhibit impaired cognitive performance post-procedure compared with baseline. At 30 days, procedural neuroprotection was associated with a greater than 2-fold increase in the proportion of patients with restoration of normal cognitive function (based on MoCA scores). Longer-term cognitive effects using other metrics may have been blunted by continued loss to follow-up, selective attrition of poor performers, and confounding by ongoing embolic events (as evidenced by the incidence of new DW-MRI lesions at 30 days). Conclusive assessment of the enduring neurocognitive effects of cardiac interventions and the potential benefits of procedural neuroprotection will require extension of the most promising outcome measures to a larger cohort of patients with longer-term follow-up.

Limitations

The DEFLECT III trial was not designed to provide conclusive evidence of the benefits of embolic protection with the TriGuard device, but rather to explore mostly novel clinical and imaging efficacy endpoints and to benchmark relevant event rates to inform the design of a subsequent pivotal trial with adequate power. Therefore, this was an exploratory trial that was not powered to detect statistically significant effects on major safety or efficacy endpoints; all results should be considered hypothesis-generating and interpreted with caution. Detailed neurocognitive assessment and routine imaging were difficult in the highly comorbid and elderly patient population, resulting in higher-than-expected loss to follow-up due to patient refusal or withdrawal of consent. Finally, follow-up was limited to 30 days; the long-term neurologic and cognitive impact of procedural neuroprotection is not known.

Conclusions

In summary, use of TriGuard cerebral protection during TAVI is safe, achieves complete cerebral protection in 89% of patients, and appears to mitigate new neurologic deficits and cognitive decline at discharge and 30 days. DEFLECT III provides preliminary evidence that neuroprotection can produce measurable neurological and cognitive benefits; the magnitude, extent, and duration of these potential benefits await confirmation in a planned large-scale pivotal trial.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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S.V. is a shareholder in Keystone Heart; K.A., A.M.B., and H.P. have received personal fees or other support from Keystone Heart; P.S. has received other support from Edwards Lifesciences and D.B. has received other support from Medtronic. The other authors have nothing to disclose.

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