European Heart Journal (2021) **42**, 2670–2679
doi:10.1093/eurheartj/ehab213

CLINICAL RESEARCH
Interventional cardiology

A randomized evaluation of the TriGuard™ HDH cerebral embolic protection device to Reduce the Impact of Cerebral Embolic LEsions after TransCatheter Aortic Valve ImplanTation: the REFLECT I trial

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Received 24 November 2020; revised 12 January 2021; editorial decision 17 March 2021; online publish-ahead-of-print 17 May 2021

See page 2680 for the editorial comment on this article (doi:10.1093/eurheartj/ehab212)

Aims The REFLECT I trial investigated the safety and effectiveness of the TriGuard™ HDH (TG) cerebral embolic deflection device in patients undergoing transcatheter aortic valve replacement (TAVR).

Methods and results This prospective, multicentre, single-blind, 2:1 randomized (TG vs. no TG) study aimed to enrol up to 375 patients, including up to 90 roll-in patients. The primary combined safety endpoint (VARC-2 defined early safety) at 30 days was compared with a performance goal. The primary efficacy endpoint was a hierarchical composite of (i) all-cause mortality or any stroke at 30 days, (ii) National Institutes of Health Stroke Scale (NIHSS) worsening at 2–5 days or Montreal Cognitive Assessment worsening at 30 days, and (iii) total volume of cerebral ischaemic lesions detected by diffusion-weighted magnetic resonance imaging at 2–5 days. Cumulative scores were compared between treatment groups using the Finkelstein–Schoenfeld method. A total of 258 of the planned, 375 patients (68.8%) were enrolled (54 roll-in and 204 randomized). The primary safety outcome was met compared with the performance goal (21.8% vs. 35%, $P < 0.0001$). The primary hierarchical efficacy endpoint was not met (mean efficacy score, higher is better: -5.3 ± 99.8 TG vs. 11.8 ± 96.4 control, $P = 0.31$). Covert central nervous system injury was numerically lower with TG both in-hospital (46.1% vs. 60.3%, $P = 0.0698$) and at 5 days (61.7 vs. 76.2%, $P = 0.054$) compared with controls.

Conclusion REFLECT I demonstrated that TG cerebral protection during TAVR was safe in comparison with historical TAVR data but did not meet the predefined effectiveness endpoint compared with unprotected TAVR controls.

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Graphical Abstract

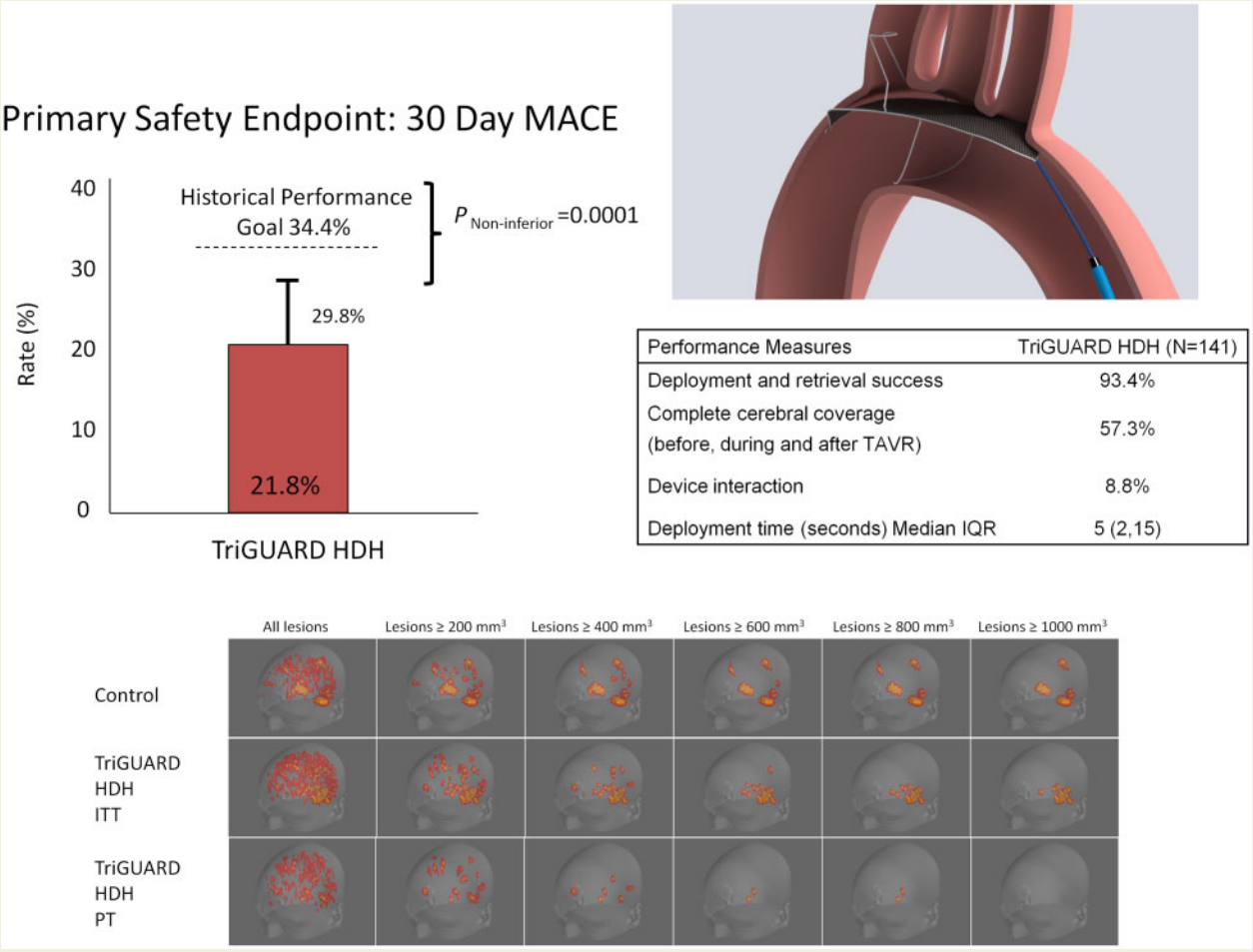

Illustration of the TriGuard HDH and performance measures (top right panels), the primary safety endpoint at 30 days (top left panel), and 3D rendering of topographical and size distribution and total new supra-threshold cerebral ischaemic lesion volume analysis across subjects by randomization group in the intention to treat (ITT) and in the full coverage per-treatment (PT) population.

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

Introduction

Transcatheter aortic valve replacement (TAVR) is a well-established alternative to surgical aortic valve replacement for patients with severe symptomatic aortic stenosis across the spectrum of surgical risk.[1,2] Beyond offering a lesser-invasive approach, an important benefit of TAVR may be lower stroke rates compared with surgical aortic valve replacement, as observed in recent randomized trials. The decline in stroke rates over time is likely related to a combination of advances in TAVR devices, operator experience, and treatment of lower-risk patients. Nevertheless, stroke remains the most common ischaemic complication following TAVR, with a roughly 2–6% peri-procedural stroke risk.[3–10] Moreover, covert or silent ischaemic brain injury detected by diffusion-weighted magnetic resonance imaging (DW-MRI) affects 85–100% of patients after TAVR[11–13] as a result of cerebral embolization during the TAVR procedure.[14,15] Balloon post-dilation, valve manipulation and migration, and longer procedure times predict procedure-related strokes,[16] suggesting that interactions between the transcatheter valve system and the aorta and calcified native valve are the primary mechanism of peri-procedural cerebral embolization and acute stroke. Stroke carries a heavy morbidity and mortality burden and significant health economic implications.[17–19] The clinical significance of acutely silent cerebral injury is poorly characterized in TAVR patients, but has been linked to cognitive decline, subsequent dementia,[20] and stroke risk in other clinical settings.[21]

Because early strokes and cerebral injury are primarily embolic and procedure-related, the use of cerebral embolic protection (CEP)

devices during TAVR may offer benefit. Previously reported studies have evaluated the safety and feasibility of the TriGuard™ embolic deflection device for preventing cerebral embolization during TAVR.[22,23] The REFLECT I trial (ClinicalTrials.gov ID: NCT02536196) was designed to prospectively evaluate the safety and efficacy of TriGuard HDH (TG) cerebral deflection during TAVR.

Methods

Trial design and oversight

The executive committee designed and oversaw the conduct and analysis of the trial in collaboration with the Sponsor (Keystone Heart, Tampa, FL, USA). The trial was conducted and reported in accordance with the protocol, FDA regulations, ICH-GCP guidelines, and the Declaration of Helsinki. The ethics committee approved the research protocol at each centre and every subject, or their legal representative, provided written informed consent prior to any study-specific procedure or assessments. The safety of patients in the trial was overseen by an independent Data Safety Monitoring Board (DSMC), and an independent Clinical Events Committee (CEC) adjudicated all potential endpoint events. Statistical analyses were performed by an independent statistician (Helen Parise LCC). The first author prepared the first draft of the manuscript. All co-authors reviewed the manuscript and provided input, vouched for the accuracy of the data, and agreed to submit the manuscript for publication. The study data is not available for public access.

Patient population

Patients with symptomatic severe aortic stenosis referred for TAVR were eligible for participation in the trial. 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 mL/min/1.73 m^2), history of bleeding diathesis or coagulopathy or contraindications to antiplatelet or anticoagulant therapy, and prior prosthetic valve implantation (including planned aortic valve-in-valve procedure). Potential subjects were also excluded if they had known hypersensitivity to device component materials or contrast that could not be adequately pre-medicated, severe peripheral artery disease that precluded vascular access, a severely atheromatous aortic arch, contraindications to cerebral MRI, planned cardiac intervention during or within 10 days prior to TAVR, or if treatment with any other investigational device or procedure was planned during the study period. An independent computed tomography core laboratory and a patient screening committee reviewed the clinical and anatomic suitability of all patients for the trial.

Trial procedures

Patients meeting eligibility criteria were randomly assigned in a 2:1 ratio to TG or control using a web-based block randomization system. Randomization was stratified by site and transcatheter heart valve type (balloon-expandable vs. self-expanding). To allow for a learning curve with this new device, up to three-proctored roll-in cases were performed at centres whose investigators did not have prior experience with the TG device. Transcatheter aortic valve replacement was performed with commercial transcatheter valve systems according to standard institutional procedures under local or general anaesthesia. Dual antiplatelet therapy with aspirin and clopidogrel was recommended for 6 months. The TG embolic deflection device (Keystone Heart Ltd, Caesarea, IL, USA) is a temporary, single-use filter made of a fine nickel-titanium alloy mesh, delivered through a contralateral 9 Fr femoral arterial sheath that accommodates the pigtail catheter and therefore does not require additional access. Under fluoroscopic guidance, the TG device is positioned in the aortic arch to cover the ostia of the three major cerebral arteries (innominate, left common carotid, and subclavian), and anchored in place by a stabilizer positioned in the proximal innominate artery (*Graphical abstract*). The filter maintains cerebral blood flow through 130 × 250 µm pores while deflecting larger emboli to the descending aorta. The TG is intended to be positioned in the aortic arch prior to TAVR delivery, maintained in position for the duration of the TAVR procedure, and withdrawn after completion of the procedure.

Enrolled patients underwent detailed clinical and neurologic assessments at baseline, before discharge or 2–5 days, and at 30 and 90 days after the procedure. Neurologic assessments were performed by a board-certified neurologist blinded to DW-MRI findings and treatment allocation and included the National Institutes of Health Stroke Scale (NIHSS) and the Modified Rankin Scale (mRS). Cognitive evaluation included the Montreal Cognitive Assessment (MoCA)[24] and Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)[25] at all time-points. Brain DW-MRI using a standardized image acquisition protocol (1.5 T) was performed 2–5 days post-procedure to define the ischaemic burden of the TAVR procedure by an independent MRI Core Laboratory [Buffalo Neuroimaging Center, Buffalo, NY (BNAC)] using validated methods. Supplementary material online, *Appendix* describes the methodology for brain DW-MRI acquisition and analysis. Independent site monitoring was performed for 100% of clinical fields and endpoint events. Procedural angiograms were acquired using a standard angiographic imaging protocol and reviewed by an independent Angiographic Core Laboratory (Yale Cardiovascular Research Group, New Haven, CT, USA) to assess device positioning.

Endpoints and outcome measures

The primary safety endpoint measured at 30 days was defined according to the Valve Academic Research Consortium 2 (VARC-2) as a composite of all-cause death, stroke, life-threatening or disabling bleeding, stage 2–3 acute kidney injury (AKI), coronary artery obstruction requiring intervention, major vascular complications, and valve-related dysfunction requiring repeat procedure.[26] The primary efficacy endpoint was a hierarchical composite of (i) all-cause mortality or any stroke at 30 days, (ii) NIHSS worsening from baseline to 2–5 days post-procedure or MoCA worsening (decrease of three points or more from baseline) at 30 days, and (iii) total volume of cerebral ischaemic lesions detected by DW-MRI performed 2–5 days post-procedure. Cumulative scores based on the Finkelstein–Schoenfeld methodology[27] were summed for each subject, and outcomes compared between treatment groups, with higher scores indicating a better outcome. Results are also presented using the method described by Pocock *et al.*[28] as a win ratio (number of wins divided by losses) and a win percentage (number of wins divided by the sum of the number of wins and losses) for ease of interpretation. Hypothesis-driven secondary endpoints included Neurologic Academic Research Consortium (NeuroARC)-defined central nervous system infarction,[29] NIHSS score worsening from baseline, and total volume of cerebral ischaemic lesions.

Secondary safety outcomes included in-hospital procedure safety, TAVR device success (VARC-2 defined), all-cause and cardiac death, and bleeding and vascular complications (all defined according to VARC-2).[26] Stroke and neurologic events were defined according to VARC-2 and the NeuroARC definitions.[29] Secondary efficacy endpoints included cognitive measures defined by the post-procedure MoCA scores and MoCA worsening from baseline (decrease by >2 points), neurologic measures of worsening NIHSS score, and DW-MRI measures of cerebral injury including the number, size, and total volume of ischaemic brain lesions (Supplementary material online, *Figure S2*). A *post hoc* DW-MRI multi-

Table 1 Baseline demographics, clinical presentation, and procedure details

Patient characteristics	Roll-in TriGuard HDH (*n* = 54)	TriGuard HDH (*n* = 141)	Control group (*n* = 63)	*P*-value*
Age (years), mean ± SD	80.4 ± 7.5	79.8 ± 7.3	81.5 ± 7.1	0.1254
Male sex, %	55.6	56.7	66.7%	0.2170
STS score, mean ± SD	4.7 ± 2.4	4.6 ± 2.8	4.8 ± 3.1	0.7207
EuroScore II, mean ± SD	4.7 ± 5.0	4.8 ± 4.1	5.5 ± 4.1	0.2679
History of congestive heart failure	27/51 (52.9)	48/135 (35.6)	23/62 (37.1)	0.8737
Diabetes mellitus (DM)	16/54 (29.6)	60/140 (42.9)	20/63 (31.7)	0.1628
Insulin dependent (IDDM)	3 (23.1)	8/140 (5.7)	10/63 (15.9)	0.0300
Diet-controlled	4 (36.4)	15/140 (10.7)	7/63 (11.1)	1.0000
Oral hypoglycaemic	13 (24.1)	40/140 (28.6)	7/63 (11.1)	0.0067
Prior atrial fibrillation/atrial flutter	13 (24.1)	45/136 (33.1)	16/62 (25.8)	0.3246
Prior CABG	18 (33.3)	29 (21.5)	10 (16.1)	0.4447
Prior PCI	14 (27.5)	34 (26.2)	18 (30.0)	0.6024
Prior stroke or TIA	6/54 (11.1)	18/137 (13.1)	7/62 (11.3)	0.8200
Prior cerebral vascular attack (CVA)	6 (11.1)	10 (7.5)	4 (6.7)	1.0000
Prior transient ischaemic attack (TIA)	0 (0.0)	10 (7.7)	4 (6.7)	1.0000
History of renal disease	5 (9.3)	27/136 (19.9)	11/62 (17.7)	0.8464
History of PVD	7 (13.0)	15/134 (11.2)	8/59 (13.6)	0.6359
History of aortic disease (aneurysm)	4 (7.4)	6/137 (4.4)	0/63 (0.0)	0.1796
Porcelain aorta/severely atherosclerotic aorta	0 (0.0)	0/137 (0.0)	3/63 (4.8)	0.0302
Carotid artery disease	19 (35.8)	22/129 (17.1)	6/59 (10.2)	0.2730
Chronic obstructive lung disease	14 (25.9)	25/136 (18.4)	10/60 (16.7)	0.8420
Home oxygen use	5 (9.3)	2/139 (1.4)	1/61 (1.6)	1.0000
Severe pulmonary HTN	1 (1.9)	8/136 (5.9)	1/61 (1.6)	0.2789
Left ventricular ejection fraction, mean ± SD	58.8 ± 12.1 (53)	57.8 ± 10.8 (131)	56.2 ± 11.8 (60)	0.3443
NYHA class III/IV at baseline	35/54 (64.8)	96/138 (69.6)	49/63 (77.8)	0.2414
Antiplatelet therapy at 1 month	53/54 (98.1)	127/137 (92.7)	59/63 (93.7)	1.0000
Dual antiplatelet therapy (ASA + clopidogrel)	34/49 (69.4)	78/136 (57.4)	31/62 (50.0)	0.3583
Monotherapy (ASA or clopidogrel)	13/49 (26.5)	49/136 (36.0)	28/62 (45.2)	0.2713
Anticoagulant therapy				
Warfarin	4/49 (8.2)	7/123 (5.7)	1/51 (2.0)	0.4397
Warfarin + antiplatelet	4/49 (8.2)	7/123 (5.7)	1/51 (2.0)	0.4397
NOAC	4/49 (8.2)	28/123 (22.8)	10/51 (19.6)	0.6924
NOAC + antiplatelet	4/49 (8.2)	20/123 (16.3)	7/51 (13.7)	0.8193

Values are expressed as *n* (%) unless otherwise indicated.
*Statistical comparison between randomized groups (excludes roll-in).
ASA, Aspirin; CABG, coronary artery bypass grafting; HTN, Hypertension; NOAC, New Oral Anticoagulant; NYHA, New York Heart Association class; PCI, percutaneous coronary intervention; PVD, peripheral vascular disease; STS, Society of Thoracic Surgeons; TIA, transient ischaemic attack.

threshold, lesion-wise analysis of supra-threshold cerebral ischaemic lesion (SCIL) volumes is described in the Supplementary material online, *Appendix*. Secondary performance measures included TG device success, defined as successful TG delivery and deployment with complete coverage of all cerebral vessels throughout TAVR advancement, deployment, implantation, and retrieval adjudicated by independent Angiographic Core laboratory.

Statistical analysis

The primary safety endpoint was a comparison of the 30-day safety event rate in the TG group to a performance goal of 34.4% derived from published TAVR literature (Supplementary material online, *Appendix*). The primary endpoint was met if the upper bound of the one-sided 95% confidence interval (CI) of the 30-day safety event rate was significantly less than the performance goal. A sample size of 179 evaluable patients in the intervention group and a one-sided alpha = 0.05 level was estimated to provide 87.5% power using a one-sample z-test for proportions; a 28.5% critical value would be required to reject the null hypothesis. All primary and secondary safety outcomes were tested in the as-treated population according to the protocol. As treated for TG was defined as patients having established arterial access for intended TG use. Patients without TG access were analysed as controls.

The primary efficacy hypothesis was that TAVR with TG protection was superior to unprotected TAVR based on the pre-specified hierarchy of adverse outcomes determined by pairwise comparisons among all subjects according to the Finkelstein–Schoenfeld method.[27] Briefly, each

Table 2 Procedure and device performance

Procedure details	Roll-in TriGuard HDH (*n* = 54)	TriGuard HDH (*n* = 141)	Control group (*n* = 63)	*P*-value
CoreValve	24/53 (45.3)	44/136 (32.4)	22/62 (35.5)	0.7455
Medtronic CoreValve	1/53 (1.9)	1/136 (0.7)	1/62 (1.6)	0.5293
Medtronic CoreValve Evolut R	15/53 (28.3)	33/136 (24.3)	17/62 (27.4)	0.7246
Medtronic CoreValve Evolut PRO	8/53 (15.1)	10/136 (7.4)	4/62 (6.5)	1.0000
Sapien	29/53 (54.7)	85/136 (62.5)	37/62 (59.7)	0.7536
Edwards Sapien XT	0/53 (0.0)	0/136 (0.0)	0/62 (0.0)	
Edwards Sapien 3	29/53 (54.7)	85/136 (62.5)	37/62 (59.7)	0.7536
Other	0/53 (0.0)	7/136 (5.1)	3/62 (4.8)	1.0000
Aortic Balloon Valvuloplasty performed	26/54 (48.1)	58/135 (43.0)	36/62 (58.1)	0.0650
TAVR device success (VARC-2 defined)	45/53 (84.9)	122/136 (89.7)	56/62 (90.3)	1.0000
Femoral Access	54 (100)	136 (100)	62 (100)	1.0000
Number of TAVR devices implanted				
1	50 (92.6)	132 (97.1)	61 (98.4)	1.0000
2	2 (3.7)	3 (2.2)	1 (1.6)	1.0000
TriGuard performance measures				
Successful device deployment	49/54 (90.7)	127/136 (93.4)	NA	
Device deployment time, median (IQR)	6 (3–19)	5 (2–15)	NA	
At least one TriGuard Used	54/54 (100.0)	135/141 (95.7)	NA	
Successful on 1st attempt	47/54 (87.0)	122/141 (86.5)	NA	
Device interference (any)	2/54 (3.7)	12/136 (8.8)	NA	

Values are expressed as *n* (%) unless otherwise indicated.

subject in the trial was compared with every other subject based on the hierarchy. For example, if Subject A dies or has stroke and Subject B survives free of stroke to 30 days, Subject B wins (score +1) and Subject A loses (score -1). If both subjects die or have a stroke, it is equilibrium (score 0). If both subjects survive free of stroke to 30 days, the comparison moves to the next tier of the hierarchy. After all between-subject comparisons have been performed, scores are summed to obtain a cumulative score for each subject, and outcomes between treatment groups are then compared. Based on estimated event rates for each tier of the primary efficacy outcomes from 1000 simulated samples (Supplementary material online, *Appendix*), a sample size of 285 subjects (190 in the TG group and 95 in the control group) including a 5% drop out rate, would provide >90% power to demonstrate superiority of TG, using the Mann–Whitney *U* test to compare outcomes between treatment groups. The null hypothesis was tested at a two-sided 0.049 level of significance allowing for an interim analysis of the first 90 patients, which was planned for sample size re-estimation to ensure sufficient power for efficacy.

Hypothesis-driven secondary endpoints were planned to be tested sequentially only if both primary endpoints were met to preserve the alpha level. The primary efficacy outcome was tested in the efficacy intention to treat (eITT) population, based on randomized allocation but excluding patients requiring conversion to surgery or prolonged cardiac arrest (>3 min) prior to DW-MRI. Continuous variables are presented as mean ± standard deviation when the data are approximately normally distributed. Skewed data, such as those obtained via 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. Additional *post hoc* analysis of imaging outcomes was performed as described in the Supplementary material online, *Appendix*.

Results

Patient and procedural characteristics

From June 2016 to July 2017, a total of 258 patients were enrolled in the REFLECT I trial at 20 US and 6 European centres (Supplementary material online, *Appendix*). There were 54 roll-in patients and 204 patients randomized 2:1 to TG (*n* = 141) or control (*n* = 63). Prior to completing enrolment, the study was suspended at the recommendation of the DSMC, and the sponsor elected not to resume the trial in order to initiate evaluation of the next generation TriGUARD 3 device in the REFLECT II trial. The REFLECT I trial remained blinded in order to preserve the possibility of pooling the control patients for the primary analysis of the REFLECT II trial evaluating the next generation TriGUARD 3 device. Patient enrolment and follow-up rates are detailed in Supplementary material online, *Figure S1*. Clinical follow-up at 30 days was available in 98% in both groups, and at 90 days in 96% of TG and 93% of control subjects. Patient characteristics were well-matched between groups (*Table 1*). The study population was generally representative of patients meeting contemporary indications for TAVR in both TG and control groups with overall intermediate surgical risk (mean STS scores: 4.6 ± 2.8 vs. 4.8 ± 3.1), severe functional limitations (NYHA class III/IV 69.6% vs. 77.8%), frequent comorbidities, and a 30% prior history of atrial fibrillation. Control patients had more porcelain aorta ($P = 0.03$) and insulin-dependent diabetes ($P = 0.03$) compared with TG patients (*Table 1*).

A total of 136/141 patients underwent TAVR in the TG arm (5 patients were withdrawn prior to valve implantation) and 62/63 control patients underwent TAVR (1 patient withdrew consent),

Table 3 Safety and efficacy outcomes

Primary outcomes	TriGuard HDH (*n* = 141)	Control group (*n* = 63)	RR Risk difference* (95% CI)	*P*-value
Primary safety at 30 days*	29/133 (21.8%)	35%		<0.0001
Primary efficacy score, mean ± SD	-5.3 ± 99.8	11.8 ± 96.4		0.3140
Win ratio	0.80	1.24		
Win percentage	44.6%	55.4%		
All-cause mortality or any stroke at 30 days	15/132 (11.4%)	4/59 (6.8%)		0.4364
NIHSS worsening at post-procedure or MoCA worsening at 30 days follow-up**	23/127 (18.1%)	8/60 (13.3%)		0.5286
Total cerebral lesion volume, mm^3, median (IQR)	231 (56–631)	243 (84–484)		0.9448
Powered secondary outcomes				
CNS infarction at 30 days	93/132 (70.5%)	49/61 (80.3%)	0.88 (0.74–1.04)	0.1639
NIHSS worsening at 30 days	7/98 (7.1%)	1/42 (2.4%)	3.00 (0.38–23.63)	0.4353
Total cerebral lesion volume, mm^3, median (IQR)	229 (46–631)	235 (81–484)		0.8854
Secondary safety				
Composite safety at 30 days	29/133 (21.8%)	5/59 (8.5%)	2.57 (1.05–6.32)	0.0254
Death	2/131 (1.5%)	0/59 (0.0%)	1.5% (-0.6% to 3.6%)*	1.0000
Stroke	14/131 (10.7%)	4/59 (6.8%)	1.58 (0.54–4.59)	0.5929
Life-threatening or disabling bleeding	4/130 (3.1%)	0/59 (0.0%)	3.1% (0.1–6.1%)[a]	0.3115
Acute kidney injury (stage 2/3)	0/129 (0.0%)	0/59 (0.0%)	—	NA
Coronary artery obstruction requiring intervention	0/129 (0.0%)	0/59 (0.0%)	—	NA
Major vascular complication	16/130 (12.3%)	1/59 (1.7%)	7.26 (0.99–53.48)	0.0248
Valve-related dysfunction	0/129 (0.0%)	0/59 (0.0%)	—	NA
Secondary efficacy				
MoCA worsening from baseline				
Post-procedure/discharge	12/108 (11.1%)	8/48 (16.7%)	0.67 (0.29–1.53)	0.4363
30 days post-procedure	13/94 (13.8%)	3/42 (7.1%)	1.94 (0.58–6.44)	0.3895
90 days post-procedure	8/95 (8.4%)	3/38 (7.9%)	1.07 (0.30–3.81)	1.0000
NIHSS worsening from baseline				
Post-procedure/discharge	14/117 (12.0%)	5/56 (8.9%)	1.34 (0.51–3.54)	0.6145
30 days post-procedure	7/98 (7.1%)	1/42 (2.4%)	3.00 (0.38–23.63)	0.4353
90 days post-procedure	3/100 (3.0%)	1/41 (2.4%)	1.23 (0.13–11.48)	1.0000
New neurologic impairment at post-procedure/discharge	11/117 (9.4%)	4/56 (7.1%)	1.32 (0.44–3.95)	0.7764
DW-MRI	*N* = 111	*N* = 58		
Presence of cerebral ischaemic lesions	97/111 (87.4%)	51/58 (87.9%)	0.99 (0.88–1.12)	1.0000
Number of cerebral ischaemic lesions, mean±SD	5.5 ± 6.4	5.0 ± 5.9	—	0.5791
Average volume cerebral ischaemic lesions, mm^3, Median (IQR)	62 (43–102)	66 (45–97)	—	0.8776
Maximum volume cerebral ischaemic lesions, mm^3, Median (IQR)	118 (54–270)	108 (61–270)	—	0.6575
Total volume of cerebral ischaemic lesions, mm^3, Median (IQR)	229 (46–631)	235 (81–484)	—	0.8640
Total non-DW T2-FLAIR ischaemic volume, mm^3, Median (IQR)	3174 (1450–8777)	4437 (1809–10 987)	—	0.4061

[a]Risk difference is reported when one group has a 0 event rate.
CI, confidence interval; CNS, central nervous system; DW-MRI, diffusion-weighted magnetic resonance imaging; IQR, interquartile range; MoCA, Montreal Cognitive Assessment; NIHSS, National Institutes of Health Stroke Scale; SD, standard deviation.

comprising the primary as-treated population. Balloon-expandable Edwards SAPIEN valves (Edwards Lifesciences, Irvine, CA, USA) were used in 62.5% of TG patients and 59.7% of controls, whereas self-expanding CoreValve transcatheter valves (Medtronic, Dublin, IE) were used in 32.4% of TG and 35.5% of control patients; the remaining 5% of subjects received other commercial valves (*Table 2*). All valves were implanted via the transfemoral approach. Transcatheter aortic valve replacement was successful in 90% of cases in both groups.

TriGuard performance

A total of 135/136 patients who underwent TAVR in the TG group received a TG device; one randomized patient withdrew consent prior to TG device introduction. The device was successfully delivered and positioned in the aortic arch to cover all three cerebral inflow vessels prior to TAVR in 93.4% (127/136) of cases. The operator-reported interference of TG with the TAVR system in 8.8% (12/136) of cases (*Table 2*; *Graphical abstract*). The TG device success

Table 4 Safety and efficacy outcomes to 90 days

	In-hospital			30 days			90 days		
	TriGuard HDH System (*n* = 1419)	Control group (*n* = 63)	RR (95% CI)	TriGuard HDH System (*n* = 141)	Control group (*n* = 63)	RR (95% CI)	TriGuard HDH System (*n* = 141)	Control group (*n* = 63)	RR (95% CI)
Safety composite: all death, stroke, AKI stage 3	13/136 (9.6)	4/62 (6.5)	1.48 (0.50–4.36)	15/132 (11.4)	4/59 (6.8)	1.68 (0.58–4.83)	17/129 (13.2)	6/54 (11.1)	1.19 (0.49–2.84)
MACCE	27/141 (19.1)	5/63 (7.9)	2.41 (0.97–5.98)	29/133 (21.8)	5/59 (8.5)	2.57 (1.05–6.32	30/130 (23.1)	7/55 (12.7)	1.81 (0.85–3.88)
All-cause mortality, *n* (%)	0/141 (0.0)	0/63 (0.0)	—	2/131 (1.5)	0/59 (0.0)	—	3/126 (2.4)	2/53 (3.8)	0.63 (0.11–3.67)
All stroke, *n* (%)	13/141 (9.2)	4/63 (6.3)	1.48 (0.50–4.36)	14/131 (10.7)	4/59 (6.8)	1.58 (0.54–4.59)	15/127 (11.8)	4/52 (7.7)	1.54 (0.53–4.41)
Life-threatening/disabling bleeding, *n* (%)	4/141 (2.8)	0/63 (0.0)	—	4/130 (3.1)	0/59 (0.0)	—	4/124 (3.2)	0/51 (0.0)	—
Acute kidney injury—Stage 2 or 3, *n* (%)	0/141 (0.0)	0/63 (0.0)	—	0/129 (0.0)	0/59 (0.0)	—	0/123 (0.0)	0/51 (0.0)	—
Major vascular complications, *n* (%)	16/141 (11.3)	1/63 (1.6)	7.29 (0.99–53.78)	16/130 (12.3)	1/59 (1.7)	7.26 (0.99–53.48)	16/125 (12.8)	1/52 (1.9)	6.66 (0.91–48.90)
TriGuard access site-related	7/141 (5.0)	0/63 (0.0)	—	7/130 (5.4)	0/59 (0.0)	—	7/124 (5.6)	0/51 (0.0)	—
TAVI access site-related	10/141 (7.1)	0/63 (0.0)	4.33 (1.04–18.02)	10/129 (7.8)	0/59 (0.0)	4.34 (1.05–18.05)	10/124 (8.1)	0/51 (0.0)	3.91 (0.94–16.17)
All-cause deaths									
Cardiovascular death, *n* (%)	0/141 (0.0)	0/63 (0.0)	—	2/131 (1.5)	0/59 (0.0)	—	3/126 (2.4)	0/51 (0.0)	—
Non-cardiovascular death, *n* (%)	0/141 (0.0)	0/63 (0.0)	—	0/129 (0.0)	0/59 (0.0)	—	0/123 (0.0)	2/53 (3.8)	—
Neurological events									
Stroke (VARC-2 defined)									
Ischaemic stroke, *n* (%)	13/141 (9.2)	4/63 (6.3)	1.48 (0.50–4.36)	13/130 (10.0)	4/59 (6.8)	1.47 (0.50–4.33)	13/126 (10.3)	4/52 (7.7)	1.34 (0.46–3.92)
Haemorrhagic stroke, *n* (%)	0/141 (0.0)	0/63 (0.0)	—	1/130 (0.8)	0/59 (0.0)	—	1/124 (0.8)	0/51 (0.0)	—
Undetermined, *n* (%)	0/141 (0.0)	0/63 (0.0)	—	0/129 (0.0)	0/59 (0.0)	—	1/123 (0.8)	0/51 (0.0)	—
Disabling stroke, *n* (%)	3/141 (2.1)	0/63 (0.0)	—	4/131 (3.1)	0/59 (0.0)	—	4/127 (3.1)	0/51 (0.0)	—
Non-disabling stroke, *n* (%)	10/141 (7.1)	3/63 (4.8)	1.52 (0.43–5.33)	10/129 (7.8)	3/59 (5.1)	1.52 (0.44–5.34)	11/123 (8.9)	3/51 (5.9)	1.52 (0.44–5.22)
Transient ischaemic attack (TIA), *n* (%)	1/141 (0.7)	1/63 (1.6)	0.46 (0.03–7.17)	1/129 (0.8)	1/59 (1.7)	0.46 (0.03–7.19)	1/123 (0.8)	1/51 (2.0)	0.41 (0.03–6.50
Stroke (NeuroARC defined)									
Overt CNS injury, *n* (%)	13/141 (9.2)	4/63 (6.3)	1.45 (0.49–4.28)	14/131 (10.7)	4/59 (6.8)	1.58 (0.54–4.59	15/127 (11.8)	4/52 (7.7)	1.54 (0.53–4.41)
Covert CNS injury, *n* (%)	65/141 (46.1)	38/63 (60.3)	0.76 (0.58–1.00)	93/132 (70.5)	49/61 (80.3)	0.88 (0.74–1.04)	93/128 (72.7)	49/60 (81.7)	0.89 (0.76–1.04)
CNS haemorrhage, *n* (%)	0/141 (0.0)	0/63 (0.0)	—	0/129 (0.0)	0/59 (0.0)	—	0/123 (0.0)	0/51 (0.0)	—
Neurological dysfunction w/o CNS injury, *n* (%)	2/141 (1.4)	1/63 (1.6)	0.91 (0.08–9.87)	2/129 (1.6)	2/60 (3.3)	0.47 (0.07–3.22)	2/123 (1.6)	2/52 (3.8)	0.42 (0.06–2.92)
Stroke disability									
Fatal	1/136 (0.7)	0/62 (0.0)	—	1/136 (0.7)	0/62 (0.0)	—	1/130 (0.8)	0/59 (0.0)	—
Disabling	2/136 (1.5)	0/62 (0.0)	—	3/136 (2.2)	0/62 (0.0)	—	3/130 (2.3)	0/59 (0.0)	—
Non-disabling	10/136 (7.4)	3/62 (4.8)	1.52 (0.43–5.33)	8/136 (5.9)	1/62 (1.6)	1.52 (0.43–5.33)	10/129 (7.8)	3/59 (5.1)	1.52 (0.43–5.33)
Stroke recovery									
Complete recovery	7/136 (5.1)	3/62 (4.8)	1.06 (0.28–3.98)	6/136 (4.4)	1/62 (1.6)	2.74 (0.34–22.24)	7/129 (5.4)	3/59 (5.1)	1.07 (0.29–3.98)
Incomplete recovery	5/136 (3.7)	0/62 (0.0)	—	6/136 (4.4)	0/62 (0.0)	—	6/131 (4.6)	0/59 (0.0)	—

AKI, acute kidney injury; CI, confidence interval; CNS, central nervous system; MACCE, major adverse cardiac and cerebrovascular events; RR, relative risk.

Table 5 ***Post hoc*** **multi-threshold lesion-wise analysis of total volume of cerebral lesions**

Lesion size threshold	FC				eITT			
	Reduction (%)	TriGuard HDH ($n = 64$) mm^3 (mean)	Controls ($n = 57$) mm^3 (mean)	*P*-value	Reduction (%)	TriGuard HDH ($n = 111$) mm^3 (mean)	Controls ($n = 57$) mm^3 (mean)	*P*-value
All lesions	35.5	427.40	662.63	0.260	7.3	614.01	662.63	0.831
Lesion >500 mm^3	71.0	87.46	301.64	0.200	29.4	213.04	301.64	0.641
Lesion >1000 mm^3	100.0	0.0	262.28	0.105	50.3	130.35	262.28	0.475

eITT, efficacy intention to treat; FC, full coverage.

was achieved in 57.3% (78/136), as defined by independent angiographic core laboratory confirmation that the TG device provided complete coverage of all three cerebral vessels throughout the TAVR procedure. The device was successfully retrieved intact in all cases.

Safety outcomes

The primary safety outcome at 30 days occurred in 21.8% (95% CI 15.1–29.8%) of subjects in the TG group, meeting the primary safety endpoint compared with the pre-specified performance goal of 34.4% ($P < 0.001$) (*Table 3*, *Graphical abstract*). The composite 30-day safety event rate was significantly higher in the TG group compared with controls [21.8% vs. 8.5%; relative risk (RR) 2.57, 95% CI 1.05–6.32; $P = 0.025$] driven by a significantly higher rate of major vascular complications (12.3% vs. 1.7%; RR 7.26, 95% CI 0.99–53.48; $P = 0.025$), mostly related to TAVR access site major vascular complications that were more common in the TG vs. the control group (7.1% vs. 0%; RR 4.33, 95% CI 1.04–18.02; $P = 0.033$) (*Table 4*). There were no significant between-group differences in death ($P = 1.0$), stroke ($P = 0.59$), life-threatening bleeding ($P = 0.31$), or stage 2/3 AKI at 30 days. These results were consistent at all time-points, including in-hospital and at 30- and 90-day follow-up. The composite safety endpoint of all-cause death, stroke, and AKI stage 3 was not significantly different between groups at any time-point (*Table 3*). In addition, safety outcomes were similar between controls and the 57.3% of TG patients with device success (all-cause death, stroke, and stage 3 AKI composite 11.5% vs. 6.5%, $P = 0.386$).

Efficacy outcomes

The primary hierarchical efficacy endpoint was not significantly different between groups, with a mean score (higher is better) of -5.3 ± 99.8 for TG and 11.8 ± 96.4 for controls ($P = 0.314$), corresponding to a win percentage of 44.6% for TG and 55.4% without protection in the pre-specified eITT and ITT populations (same populations as no exclusions were met for eITT) (*Table 3*). Therefore, the primary efficacy endpoint was not met, and testing of all secondary endpoints was exploratory. Similar results were seen in patients with complete cerebral coverage (mean score of -2.0 ± 71.4 for TG and 2.5 ± 70.1 for controls, $P = 0.766$, with a comparable win percentage of 48% vs. 52%). The secondary endpoints of CNS infarction ($P = 0.163$), NIHSS worsening from baseline to 30 days ($P = 0.435$), and total volume of cerebral ischaemic lesions ($P = 0.885$) were not significantly different between groups. There was numerically less covert CNS injury with TG both in-hospital (46.1% vs. 60.3%, $P = 0.0698$) and at 5 days (61.7% vs. 76.2%, $P = 0.054$) compared with controls. Similar overall results were found in the 57.3% of patients with device success compared with controls (ischaemic stroke: 6.4% vs. 6.5%, $P = 1.00$; covert strokes: 50% vs. 61.3%, $P = 0.231$). Neurocognitive screening with MoCA did not demonstrate any differences in mean scores between groups post-procedure (22.1 ± 4.4 vs. 21.9 ± 4.2, $P = 0.86$), at 30 days (22.3 ± 4.7 vs. 22.5 ± 4.3, $P = 0.96$), or at 90 days (22.6 ± 4.7 vs. 22.1 ± 4.7, $P = 0.54$). There was no difference in the change in MoCA scores compared with baseline at any time-point (*Table 3*). The RBANS assessment of overall cognitive functioning in five major domains (including immediate memory, visuospatial, language, attention, and delayed memory) revealed no differences in the overall scores or sub-scores between groups at any time-point.

Brain imaging with DW-MRI was performed in 113/136 patients (83.1%), and interpretable in 111/136 TG patients (81.6%) and 58/63 control patients (93.5%) (Supplementary material online, *Appendix*). There were no between-group differences in the incidence of ischaemic lesions or the total lesion volume by DW-MRI at 2–5 days [median (IQR): 229 mm^3 (46–631) TG vs. 235 mm^3 (81–484) control; $P = 0.885$] (*Table 3*). Among patients with full coverage of all three cerebral vessels (57.3%), TG was associated with a numerical 26% reduction in total lesion volume [median (IQR): 174 mm^3 (45–556) vs. 235 mm^3 (81–484); $P = 0.278$] and a smaller maximum lesion volume (2902 mm^3 vs. 8134 mm^3) compared with controls. National Institutes of Health Stroke Scale worsened as lesion size increased ($r = 0.349$, $P < 0.001$) (Supplementary material online, *Figure S3*).

Post hoc multi-threshold lesion- and voxel-wise analyses

A multi-threshold, lesion-wise analysis of SCIL volume above incremental thresholds from >100 to >1000 mm^3 showed reductions in larger ischaemic brain lesions with TG for SCIL volumes >500 mm^3 (-29.4%) and >1000 mm^3 (-50.3%) (*Graphical abstract*; *Table 5* and Supplementary material online, *Figure S4* and *Table S1-1*). In the full coverage group with complete coverage throughout the procedure, more pronounced (but still non-significant) reductions were observed: >500 mm^3 (-71.0%) and >1000 mm^3 (-100%) (*Table 5* and Supplementary material online, *Figure S5* and *Table S1-2*). Exploratory

visualizations of lesion size and spatial distribution are also provided (Supplementary material online, *Figures* S4 *and S5*).

Discussion

The REFLECT I clinical trial demonstrated that cerebral embolic protection with the TG device during TAVR was safe in comparison with a pre-specified performance goal based on historical data, meeting its primary safety endpoint. However, TG did not reach its predefined efficacy endpoint compared with controls in the primary hierarchical composite of all death and stroke, NIHSS or MoCA worsening, and total cerebral lesion volume.

The clinical need for CEP is well established; however, adoption is estimated to be below 10% in clinical practice. Currently, the Sentinel CEP (Boston Scientific, Natick, MA, USA) is the only US approved device for use with TAVR. While this device protects only two of the three cerebral vessels, it demonstrated debris capture without reduction in brain MRI lesion volume, and conclusive evidence of clinical benefit is still lacking.[30] The ideal CEP device should be safe, easy to position, and require minimal operator attention once in position. To be effective, the device should have minimal interaction with the TAVR delivery system or other interventional equipment and provide a complete and stable seal of all cerebral arteries for the entire TAVR procedure. Meeting these requirements is challenging from the perspectives of both CEP design and clinical evaluation. Determining the safety and effectiveness of CEP is a complex interplay of (i) identifying a narrow clinical benefit signal in a complex patient population with highly confounded neurologic outcomes, (ii) making a clear distinction between events that are attributable to CEP and TAVR or other adjunctive procedures, and (iii) accounting for CEP–TAVR interactions that are at best difficult to measure.

While the TG met its primary safety endpoint, the composite safety event rate at 30 days was significantly higher with TG compared with controls (RR 2.57, 95% CI 1.05–6.32). While this result appears to be primarily driven by a significantly higher rate of TAVR-related vascular complications in the TG group (RR 4.33, 95% CI 1.04–18.02), other component endpoints of the safety composite, including death and stroke, were numerically higher with TG compared with controls, and contributions of the device to these multifactorial events cannot be conclusively ruled out. It is important to note, however, that the study was severely underpowered for a comparison of these infrequent events, and the play of chance cannot be excluded. In the more narrowly defined safety composite of all-cause death, stroke, and stage 3 AKI, outcomes were similar between groups (9.2% vs. 6.3%, $P = 0.592$). It should also be highlighted that the control group in REFLECT I had a lower-than-expected event rate despite having a higher frequency of porcelain aorta, and control patients experienced no deaths or bleeding complications, which is not representative of reported outcomes in similar populations. This may in part be attributed to the small control sample size resulting from the 2:1 randomization ratio compounded by early termination of the study.

Regarding efficacy, in this trial, strokes were numerically more common in the TG group compared with controls overall (10.7% vs. 6.8%, $P = 0.59$); however, this difference was not statistically significant. Because stroke can be caused by factors other than cerebral embolization, CEP devices cannot be expected to eliminate stroke altogether. Factors that confound peri-procedural stroke comparisons include patient-related factors (e.g. prior stroke, atrial fibrillation, carotid disease), and procedure-related complications (e.g. conversion to surgery, other left-sided procedures, cardiopulmonary resuscitation) that can dilute a signal of benefit derived from the CEP device. Therefore, surrogate measures of efficacy have been employed to increase the sensitivity to potential benefits. In REFLECT I, CNS infarction in-hospital (46.1% vs. 60.3%, $P = 0.06$) and at 5 days (61.7 vs. 76.2%, $P = 0.054$), as well as DW-MRI total lesion volume, numerically favoured the use of TG protection. In addition, among patients with TG device success and compete cerebral coverage throughout the TAVR procedure, there was a 26% reduction in total lesion volume and a more pronounced reduction in larger ischaemic brain lesions in the *post hoc* multi-threshold lesion-wise analysis. While not statistically significant, in aggregate, these results provide supportive evidence that TG may provide protection from larger cerebral emboli when complete three-vessel coverage is achieved. While many studies have shown that DW-MRI lesion size post-procedure is associated with stroke and postoperative cognitive decline,[30–33] the modest effects in REFLECT I did not translate into measurable clinical, neurologic, or neurocognitive benefits, and the degree to which such effects justify the inherent risks related to vascular access cannot be determined. It should also be noted that while NIHSS worsening was higher in the TG arm, this tool is validated to evaluate patients with suspected stroke rather than serial evaluation in a trial population for stroke surveillance. Furthermore, the threshold defining a clinically meaningful increment in NIHSS worsening has not been defined.

Fundamentally, the REFLECT I trial established that the TG device was not sufficiently stable, with only 57.3% of patients having complete cerebral coverage throughout the TAVR procedure, which may explain the lack of efficacy in the overall trial. Observed reasons for lack of coverage included device movement, passage of the TAVR delivery system behind the filter, tangling of the TAVR and TG delivery systems, or withdrawal of the filter before the TAVR delivery system. In the DEFLECT III randomized trial ($n = 85$), the device achieved complete coverage in 87% of cases, highlighting the challenges of deploying an early-stage device to a larger number of sites and operators. This observation led to the development of the next generation TriGUARD 3 device, featuring a larger self-stabilizing frame in the aortic arch. With greater ease of use and stability, this newer generation device is expected to provide greater efficacy.

Limitations

The REFLECT I trial was suspended early limiting the sample size of the trial. Apparent differences in secondary endpoint rates should be interpreted with caution due to the small overall sample size, imbalanced randomization, and unrepresentatively low control group event rates. In addition, patient withdrawal from the study and loss to clinical and DW-MRI follow-up limit secondary efficacy comparisons,

which are underpowered and should be considered hypothesis-generating.

Conclusions

The REFLECT I trial demonstrated that TG cerebral protection during TAVR was safe compared with a historical performance goal but did not meet the primary effectiveness endpoint compared with unprotected TAVR. The observed numeric reduction in early covert central nervous system injury and in larger ischaemic brain lesions among patients with full three-vessel coverage throughout the procedure suggest potential benefits of embolic deflection when stability is achieved.

Supplementary material

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

Funding

This work was supported by an unrestricted research grant from Keystone Heart, Ltd Tampa, FL, USA and Venus Medtech Inc. Hangzhou, China.

Conflict of interest: A.J.L. has equity in Venus Medtech and received consulting fees or honoraria from Keystone Heart, Emblok, Emboline, VeoSource, Medtronic, Boston Scientific, and Astra Zeneca. T.N. has equity in Venus Medtech and received consulting fees or honoraria from Keystone Heart, Edwards LifeSciences, Medtronic, and Boston Scientific. R.Z. received personal compensation from Bristol Myers Squibb, EMD Serono, Sanofi, Keystone Heart, Protembis, and Novartis for speaking and consultant fees. He received financial support for research activities from Sanofi, Novartis, Bristol Myers Squibb, Mapi Pharma, Keystone Heart, Protembis, Boston Scientific, and V-WAVE Medical. M.G.D. received personal compensation from Novartis, EMD Serono, and Keystone Heart, and financial support for research activities from Bristol Myers Squibb, Novartis, Mapi Pharma, Keystone Heart, Protembis, and V-WAVE Medical.

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