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Rate of peri-procedural stroke observed with cerebral embolic protection during transcatheter aortic valve replacement: a patient-level propensity-matched analysis

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Aims The role of cerebral embolic protection (CEP) in transcatheter aortic valve replacement (TAVR) remains controversial. Randomized trials have not been powered to demonstrate a reduction in stroke rates. The aim of this patient level pooled analysis was to validate the impact of the dual-filter CEP device (Claret Medical Inc., CA, USA) on peri-procedural stroke in a large number of TAVR patients.

Methods and results Patients from the SENTINEL US IDE trial were combined with the CLEAN-TAVI and SENTINEL-Ulm study in a patient level pooled analysis ($N = 1306$). Propensity score matching was performed to adjust for possible confounders. The primary endpoint was procedural stroke within 72 h post-TAVR according to Valve Academic Research Consortium-2 criteria. The secondary endpoint was the combination of all-cause mortality or all-stroke within 72 h after TAVR. In the propensity-matched population, 533 patients underwent TAVR without CEP and 533 patients underwent TAVR with CEP. TAVR patients without vs. with CEP were similar with respect to baseline characteristics, procedural approach, or valve type. In patients undergoing TAVR with dual-filter CEP, procedural all-stroke was significantly lower compared with unprotected procedures [1.88% vs. 5.44%, odds ratio 0.35, 95% confidence interval (CI) 0.17–0.72, relative risk reduction 65%, $P = 0.0028$]. In addition, all-cause mortality and all-stroke were significantly lower (2.06% vs. 6.00%, odds ratio 0.34, 95% CI 0.17–0.68, relative risk reduction 66%, $P = 0.0013$).

Conclusion Our findings suggest that TAVR with the dual-filter CEP device is associated with a significant lower rate of peri-procedural stroke compared with unprotected procedures. However, randomized trials are still needed to clarify this issue.

Keywords TAVR • Cerebral embolic protection • Stroke • Outcome

Introduction

Stroke following transfemoral aortic valve replacement is a serious complication substantially increasing acute and long-term morbidity and mortality.[1–4] Stroke is often under recognized and under reported as few studies have included formal neurologist clinical assessment.[5]. With careful neurological examination, stroke rates have been reported of up to 10.0% following TAVR.[6,7] Recently, the

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U.S. Food and Drug Administration (FDA) approved the Sentinel Cerebral Protection System (Claret Medical, Santa Rosa, CA, USA).[8] In the randomized SENTINEL trial, there was a 44% decrease in lesion volume on cerebral magnetic resonance imaging (MRI) with use of the dual-filter cerebral embolic protection (CEP) device, which however, did not reach statistical significance. In addition, the primary safety endpoint at 30 days (major adverse cardiac and cerebrovascular events including stroke) was statistically not significant different between groups. However, in a *post hoc* analysis clinically overt peri-procedural strokes were reduced from 8.2% in unprotected TAVR patients to 3.0% ($P = 0.05$) in TAVR patients with CEP[9] in the first 72 h.

However to date, randomized trials for CEP have not been designed or powered for hard clinical endpoints to unequivocally demonstrate the impact of CEP on clinical stroke rates.[6,7,10]

The aim of this patient level pooled analysis was to validate the efficacy of the Claret Sentinel CEP device on peri-procedural stroke in a large number of patients undergoing TAVR.

Methods

Patient selection

This patient level pooled analysis includes 1306 patients with symptomatic severe aortic stenosis undergoing TAVR. In total, 363 patients were enrolled in the randomized SENTINEL US IDE study[7] with 244 patients undergoing TAVR with CEP and 119 patients undergoing TAVR without CEP. In the CLEAN-TAVI study, 100 patients were enrolled with a 1:1 randomization.[6] In the SENTINEL-Ulm registry (University Hospital of Ulm, Ulm, Germany), 843 patients underwent TAVR including 423 sequential patients with CEP and 420 patients undergoing TAVR without CEP. Baseline data included age, sex, Society of Thoracic Surgeons (STS)-Score, diabetes mellitus, body mass index, history of atrial fibrillation, coronary artery disease, history of percutaneous coronary intervention or cardiac surgery, history of stroke or transient ischaemic attack (TIA), porcelain aorta, peripheral vascular disease (PVD), New York Heart Association (NYHA) classification, aortic valve area index, and mean aortic valve gradient assessed by echocardiography. All cases were reviewed in centre by the inter-disciplinary heart team and agreed eligible for the transcatheter approach. There were no valve-in-valve procedures.

Cerebral embolic protection device

The Sentinel device (Claret Medical, Inc., Santa Rosa, CA, USA) is a dual-filter-based intra-luminal embolic protection device inserted through a 6-Fr sheath introduced via the right radial, ulnar, or brachial artery prior to passage across the aortic arch of any other device. The proximal filter consists of a radiopaque nitinol frame with a 140 µm pore polyurethane filter and is positioned in the brachiocephalic trunk. The second filter is similarly constructed and is inserted in the left common carotid artery. The two filters cover all brain areas supplied by the right vertebral and right and left carotid arteries comprising more than 90% of the cerebral blood flow. Only the territory supplied by the left vertebral artery remains unprotected. In the randomized SENTINEL US IDE[7] and CLEAN-TAVI[6] trials, the CEP system was used according to instruction of use if diameters of the arteries at the site of filter placement were 9–15 mm for the brachio-cephalic trunk and 6.5–10 mm for the left common carotid artery. In the TAVR patients treated with CEP in SENTINEL-Ulm no measurements of vessel diameters for CEP were performed, representing a consecutive all-comers population. The protection device was not used in certain anatomic variants: left common carotid artery stenosis, atypical insertion of the right subclavian artery, or other atypical anatomy, which would not allow accurate positioning of both filters. Peri-procedural complications and in hospital clinical outcomes were assessed according to the Valve Academic Research Consortium-2 (VARC-2) criteria.[11] TAVR procedures were performed according to institutional standards including local or general anaesthesia. The protocol complies with the Declaration of Helsinki and was approved by the ethics committee. Written informed consent was obtained from all patients.

Study endpoints

The primary endpoint was peri-procedural stroke within 72 h post-TAVR according to VARC-2 criteria. The secondary endpoint was the combination of all-cause mortality or all-stroke within 72 h after TAVR.

Statistical analysis

Categorical parameters are presented as counts and percentages and were compared by Pearson's χ^2 test and the Fisher's exact test as appropriate. Continuous variables are presented as mean ± standard deviation. The outcome of patients with CEP was compared with patients without CEP. Groups were compared with the two-sample *t*-test or Mann–Whitney *U* test. To account for differences between patients with and without CEP from the randomized SENTINEL US IDE study, the CLEAN-TAVI trial, and the SENTINEL-Ulm all-comers study, we performed a propensity score analysis based on an optimal matching attempt (SAS 9.4, SAS Institute GmbH, Heidelberg, Germany). Matching was done for valve type, STS score, atrial fibrillation (AF), diabetes mellitus, gender, coronary artery disease (CAD), and PVD. We used the Mantel–Haenszel test for calculation of odds ratios and confidence intervals (CIs) of the endpoints. In addition, we performed the Breslow-Day test to evaluate the homogeneity of the odds ratios. A *P*-value <0.05 was considered to be statistically significant and tests were two-sided. Statistical analysis was performed using Statistica version 10 (StatSoft, Tulsa, OK, USA).

Results

In total, 717 patients underwent protected TAVR with CEP and 589 patients were treated with TAVR without CEP. After propensity score matching, 533 patients with CEP were compared with 533 patients undergoing TAVR without CEP. In the propensity-matched population, TAVR patients without vs. with CEP were similar with respect to age, sex, STS score for mortality, diabetes mellitus, body mass index, history of AF, CAD, porcelain aorta, PVD, NYHA class, or aortic valve area index as detailed in *Table 1*. Mean aortic valve gradient was significantly higher in patients with use of CEP (*Table 1*). In SENTINEL-Ulm, TAVR was performed under conscious sedation in all patients. For the total study group of 1066 matched patients, non-general anaesthesia was used significantly more in patients without CEP compared to patients with CEP (*Table 2*). About 98.5% of patients underwent TAVR by the transfemoral approach. There was no difference regarding pre-dilation and need for post-dilatation, fluoroscopy, or total procedure time in patients without vs. with CEP (*Table 2*).

In patients undergoing TAVR with CEP, all-stroke within 72 h was significantly reduced compared with unprotected procedures (1.88% vs. 5.44%, odds ratio 0.35, 95% CI 0.17–0.72, relative risk reduction 65%, absolute risk reduction 3.54%; $P = 0.0028$; *Take home figure* and *Table 3*). There was no stroke-related death within 72 h after the

Table 1 Patient baseline characteristics

	No cerebral embolic protection	Cerebral embolic protection	*P*-value
Age (years)	81.0 ± 6.6	81.2 ± 7.1	0.75
Female	52.9 (282/533)	52.9 (282/533)	1.0
STS score for mortality	6.6 ± 4.9	6.4 ± 4.2	0.32
Diabetes mellitus	32.7 (174/533)	30.1 (170/533)	0.79
BMI (kg/m^2)	27.2 ± 4.8	27.3 ± 5.3	0.80
History of atrial fibrillation	36.8 (196/533)	35.3 (188/533)	0.61
Coronary artery disease	59.3 (316/533)	61.2 (326/533)	0.53
History of PCI	25.3 (135/533)	23.3 (124/533)	0.43
History of cardiac surgery	13.1 (70/533)	12.6 (67/533)	0.78
History of stroke/TIA	11.3 (60/533)	10.9 (58/533)	0.34
Porcelain aorta	3.7 (18/482)	3.0 (15/500)	0.52
Peripheral vascular disease	9.4 (50/533)	10.3 (55/533)	0.61
NYHA III/IV	78.3 (415/530)	76.3 (405/531)	0.43
Aortic valve area index (cm^2)	0.31 ± 0.10	0.32 ± 0.10	0.13
Aortic valve gradient (mmHg)	38.5 ± 14.9	40.8 ± 15.4	0.02

Values are expressed as mean ± standard deviation or % (*n*/*N*).
BMI, body mass index; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; TIA, transient ischaemic attack.

Table 2 Procedural data

	No cerebral embolic protection	Cerebral embolic protection	*P*-value
Non-general anaesthesia	84.9 (448/528)	77.4 (412/532)	0.002
Transfemoral TAVR	99.1 (528/533)	97.9 (522/533)	0.13
Balloon-expandable device	63.0 (336/533)	63.0 (336/533)	1.0
Mechanically implanted device	16.0 (85/533)	16.0 (85/533)	1.0
Self-expandable device	21.0 (112/533)	21.0 (112/533)	1.0
Pre-dilation	81.9 (425/519)	80.6 (415/515)	0.59
Post-dilation	5.3 (28/525)	4.9 (25/512)	0.74
Fluoroscopy time (s)	1416 ± 1343	1552 ± 1390	0.11

procedure in both groups. In addition, all-cause mortality and all-stroke was significantly reduced (2.06% vs. 6.00%, odds ratio 0.34, 95% CI 0.17–0.68, relative risk reduction 66%, absolute risk reduction 3.94%, $P = 0.0013$; *Figure 1* and *Table 3*). *P*-values of the Breslow-Day test for all-stroke was 0.51, disabling stroke 0.18, non-disabling stroke 0.11, and stroke or mortality 0.56, demonstrating that odds ratios were not different from the three studies.

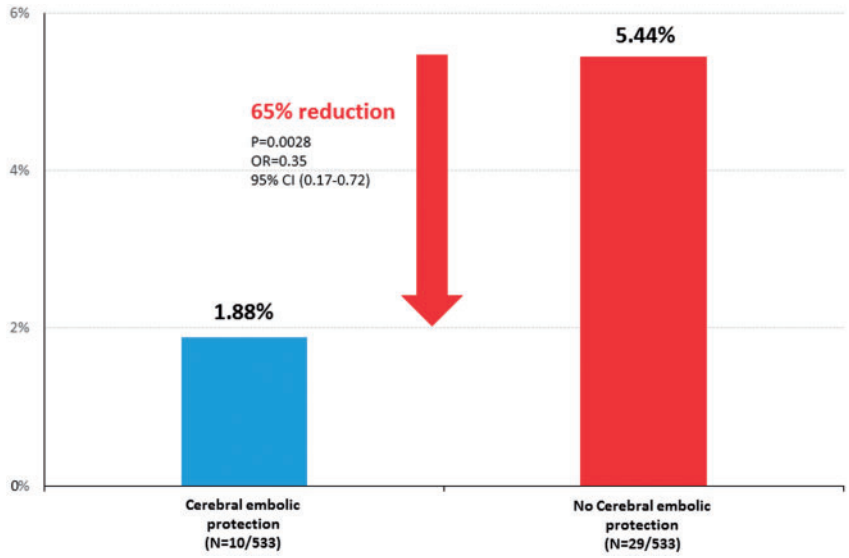
We performed a subgroup analysis regarding the use of general ($N = 200$) or local anaesthesia ($N = 860$). In patients with general anaesthesia rate of all-stroke was statistically not different between both groups (2.50% vs. 5.00%, $P = 0.36$). In patients undergoing TAVR with non-general anaesthesia, the primary endpoint of all-stroke was also lower with CEP vs. without CEP (1.70% vs. 5.58%, $P = 0.0045$) as detailed in *Figure 2*.

We also performed a subgroup analysis regarding usage of different valve types. The primary endpoint was lower with use of CEP in the subgroup of patients treated with a balloon-expandable valve ($N = 672$), mechanically implantable valve ($N = 170$), as well as self-expandable valve ($N = 224$). Rates for all-stroke were for patients with vs. without protection 0.89% vs. 3.57%, 2.35% vs. 7.06%, and 4.46% vs. 9.82%, respectively. *P*-value for interaction was 0.80.

Discussion

This patient level pooled analysis shows that TAVR with a dual-filter CEP device is associated with a significant lower rate of peri-procedural stroke compared with unprotected TAVR procedures.

Published randomized trials to date have not been powered to demonstrate a significant reduction in stroke rates. The randomized SENTINEL trial included 363 patients with a 2:1 randomization for CEP vs. no CEP.[7] Within 72 h there was a strong trend regarding stroke reduction with CEP compared with unprotected TAVR procedures 3.0% vs. 8.2% ($P = 0.053$). In the European randomized



Take home figure Significant lower rate of all procedural strokes in patients undergoing transcatheter aortic valve replacement (TAVR) with use of the dual-filter embolic protection device compared to patients with unprotected TAVR.

Table 3 Outcome within 72 h

	No cerebral embolic protection	Cerebral embolic protection	OR (95% CI)	*P*-value
Mortality or stroke	6.00 (32/533)	2.06 (11/533)	0.34 (0.17–0.68)	0.0013
All-stroke	5.44 (29/533)	1.88 (10/533)	0.35 (0.17–0.72)	0.0028
Disabling stroke	2.44 (13/533)	0.38 (2/533)	0.14 (0.03–0.66)	0.0045
Non-disabling stroke	3.00 (16/533)	1.50 (8/533)	0.53 (0.23–1.24)	0.13

Values are expressed as % (*n*/*N*).
CI, confidence interval; OR, odds ratio.

CLEAN-TAVI study with the dual-filter CEP device of 100 patients with a 1:1 randomization, 98% of patients in both groups had new cerebral lesions on MRI. Median new lesion volume was significantly lower in the device group than in the control group. Median total number of new lesions at 2 days was also significantly lower in the CEP group than in the control group. However, these neuro-imaging differences did not translate into a significant reduction in clinical stroke, which occurred in 10% of patients in the device group and 10% in the control group.[6] The first randomized controlled trial (MISTRAL-C) of the Claret dual-filter device was led by Van Mieghem *et al.*,[10] and enrolled 65 TAVR patients. Neuro-cognitive deterioration was present in 4% of patients with protection vs. 27% of control patients ($P = 0.017$).[10] In addition, patients with CEP had numerically fewer new lesions on cerebral MRI and a smaller total lesion volume. About 27% of protected patients and only 13% of control patients had no new lesion.

Our patient level pooled analysis includes a large patient population undergoing TAVR with dual-filter CEP. In a propensity-matched patient population ($N = 1066$) including 533 patients undergoing protected TAVR, we report a significant 65% relative risk reduction and 3.54% absolute risk reduction in procedural strokes. The rate of disabling stroke was substantially lower with use of CEP compared with unprotected procedures (0.38% vs. 2.44%, $P = 0.0045$). In the protected arm, the rate of non-disabling stroke was higher than the rate of disabling strokes. This finding suggests that with use of CEP large debris particles are captured, whereas smaller particles (<140 μm) may pass the filter. Hence, although rate of stroke is significantly lower with CEP, usage of the filter system does not result in complete protection from peri-procedural stroke during TAVR. In addition, the combined endpoint of death and stroke was also significantly lower with a 3.94% absolute and 66% relative risk reduction with use of CEP. The relative risk reduction observed in the endpoint of all-stroke and the endpoint of mortality plus stroke was similar since there was no stroke-related death within the first 72 h.

The primary endpoint of the SENTINEL trial was MRI-measured new brain lesion volume, which was lower in protected patients

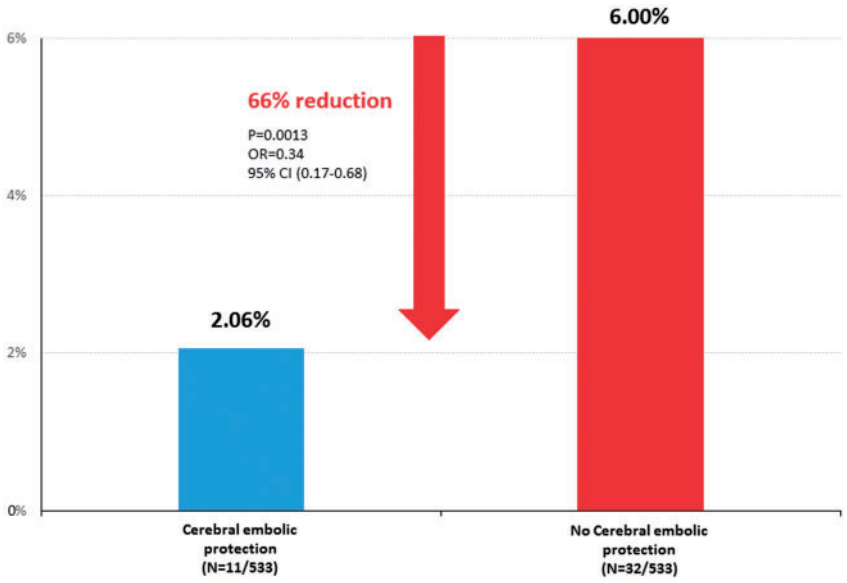


Figure 1 Significant lower rate of the combined endpoint death and all procedural strokes in transcatheter aortic valve replacement patients with use of the dual-filter embolic protection device.

Subgroup	No. of patients	protection	no protection	Odds-ratio (95% CI)	p-value
Total population	1066	10/533 (1.88%)	29/533 (5.44%)	0.34 (0.17-0.68)	0.0013
Anesthesia					
general	200/1066 (18.8%)	3/120 (2.50%)	4/80 (5.00%)	0.49 (0.11-2.26)	0.36
non-general	860/1066 (80.8%)	7/412(1.70%)	25/448 (5.58%)	0.29 (0.13-0.68)	0.0045
Valve type					
balloon expandable	672/1066 (63.0%)	3/336 (0.89%)	12/336 (3.57%)	0.24 (0.07-0.82)	0.029
mechanically expandable	170/1066 (15.9%)	2/85 (2.35%)	6/85 (7.06%)	0.32 (0.06-1.64)	0.17
self expandable	224/1066 (21.0%)	5/112 (4.46%)	11/112 (9.82%)	0.43 (0.14-1.29)	0.13

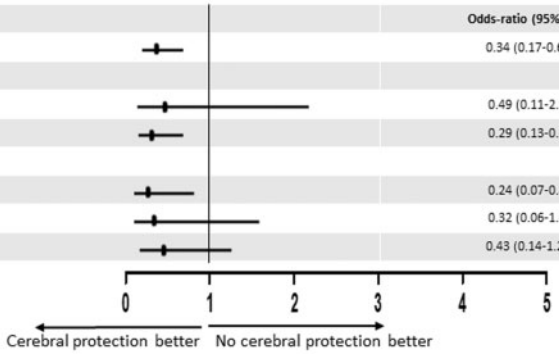


Figure 2 Subgroup analysis demonstrates a lower rate for the primary endpoint all-stroke in general and non-general anaesthesia as well as in all subgroups of implanted transcatheter aortic valve replacement devices with use of the dual-filter embolic protection device.

compared with control patients, but did not reach statistical significance.[7] The trial did not meet the primary endpoint and was underpowered for study clinical events at 30 days. However, in a meta-analysis including a larger number of patients there was a significant reduction of MRI lesion volume with CEP compared with no CEP[12,13] and a significant reduction in death and stroke with use of CEP compared with patients undergoing unprotected TAVR.[14]

It is not possible to predict the risk of stroke in a single patient undergoing TAVR since there are several potential contributing factors such as age, valve calcification, LVOT calcification, AF, aortal plaques, or calcification which may be associated with the occurrence of stroke. We focused our analysis on disabling and non-disabling stroke, hard clinical endpoints which can be objectively assessed. Inclusion of other neurological diagnoses such as dementia, ataxia, or TIA might result in an even higher rate of reduced events with the protection device. [15–21]Currently, there is no algorithm to predict occurrence of stroke in patients undergoing TAVR.[22–24]

The currently available double filter CEP device is designed to filter blood flow within the brachiocephalic artery and the left common carotid artery, prior to reaching the cerebral circulation. Debris is captured within the filter rather than deflected to the peripheral circulation. Most imaging studies agreed that ischaemic findings were mainly multiple and disseminated in both cerebral hemispheres and vascular territories after TAVR.[25–30] Additional selective filter placement in the left vertebral artery demonstrated an equal amount of debris and particle size as in the dual-filter system[31] supporting the idea of complete filter-based cerebral protection in patients undergoing TAVR.

Limitations

Patients treated in Ulm are from a single centre. In addition, the number of non-randomized patients is numerically much higher than randomized patients, which may impact results. Furthermore, residual differences for general anaesthesia and aortic valve gradient persist in spite of propensity score matching although there was homogeneity in odds ratios. All-stroke at 72 h was not the primary endpoint of the SENTINEL and CLEAN-TAVI studies. Therefore, our results should be highlighted as hypothesis generating with further studies necessary for definitive conclusions to be reached. The randomized SENTINEL and CLEAN-TAVI trials and patients from Ulm had different event committees and different adjudication processes, all of which may introduce significant variability and possible bias in the selected endpoint. Patients included in the SENTINEL trial randomized to the unprotected group and about half of patients randomized to the protected group, received cerebral MRI for assessment of both new lesions and lesion volume. In CLEAN-TAVI, all patients underwent cerebral MRI. In contrast, patients included from the SENTINEL-Ulm group received cerebral MRI only if there was a clinical suspicion of stroke following assessment by a neurologist. These different approaches could have an impact on stroke adjudication. In addition, since stroke due to embolic particles often affects multiple vascular territories, it is difficult to assess whether the stroke is solely related to protected or unprotected territories. Subgroup analyses represent a *post hoc* analysis with limited power due to small patient numbers. Given the differences in methodology between the randomized and non-randomized data and the non-prespecified primary endpoint within 72 h, results should be considered hypothesis generating. To prove this hypothesis, a large randomized trial on CEP is required. In addition, the results of this study are based on a single specific CEP device and are not generalizable to other CEP devices. Furthermore, a substantial number of strokes are not directly related to the procedure itself and cannot be prohibited by any kind of CEP device.

Conclusion

Our findings suggest that TAVR with the dual-filter CEP device is associated with a significant lower rate of peri-procedural stroke compared with unprotected procedures. However, randomized trials are still needed to clarify this issue.

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Conflict of interest: J.S. and S.R.K. have no conflict of interest. S.K. is consultant for Claret Medical, Abbott, and Merrill Lifesciences; member of the advisory board for Thubrikar Aortic Valve, Dura Biotech, and BioTrace Medical. A.L. is a consultant to Medtronic, Edwards, Biotronic, Zoll, HLT, and Boston Scientific; received speaker honoraria from Edwards, Medtronic, Boston Scientific, Bayer, Astra Zeneca, Abbott, and Novartis. He is a stock option owner of Claret Medical, Transverse Medical, and Emboline. He received grant support from Claret Medical, Medtronic, Abbott, and Edwards. J.W. is consultant for Boston Scientific and Abbott; received research grants from Abbott, Boston Scientific, Edwards, and Medtronic; and speaker honoraria from Medtronic, Boston Scientific, and Claret Medical. S.H. has no conflict of interest. R.M. received research grants from Edwards, Boston scientific, Claret Medical, Medtronic, and Abbott. R.M. and W.R. have no conflict of interest. M.L. received research grants for fellows from Claret, and is member of the scientific advisory board for Boston Scientific. All authors have participated in the work and have reviewed and agree with the content of the article.

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