National Institute for Health and Care Excellence

IP1237 Percutaneous insertion of a cerebral protection device to prevent cerebral embolism during TAVI

IPAC date: 14 March 2019

Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Company Keystone Heart	**Overview**	TriGUARD 3 complementary information. TriGUARD 3 complementary info	Thank you for your comment and for sending us information about ongoing and upcoming clinical studies. The IP programme issues guidance on procedures rather than individual devices. The ongoing REFLECT trial is already included in the overview under the "Ongoing trials" section. The TRiGUARD 3 – First in man study (n=10 patients) has been included in the "Ongoing trials" section of the overview. The TriGUARD 3 EU post-Market study (multicenter registry; n=500 patients) has also been included in the "Ongoing trials" section of the overview.

2	Consultee 2 Company Boston Scientific	**2.2**	The aim of using a cerebral protection device is to prevent stroke and to avoid cerebral ischemic lesions which have been shown to be associated with a decline in neurological and neurocognitive function. Subclinical ischaemic lesions may lead to neurocognitive decline on the mid or long term.	Thank you for your comment. Section 2.2 of the draft guidance has been changed as follows: *''Percutaneous insertion of a cerebral protection device aims to prevent debris dislodged during TAVI from passing into the cerebral circulation. The aim is to reduce the risk of cerebral ischaemic events including a stroke.''*
3	Consultee 2 Company Boston Scientific	**1.5**	We would like the committee to consider the following evidence that details: Two risk models were developed from the STS/ACC TVT Registry to assess in-hospital stroke and predictors of stroke following TAVI. In-hospital stroke occurred in 2.6% of ~ 41,000 patients undergoing TAVI. Co-morbidities adjusted difference by year was not statistically different, other than advanced age, no other comorbidities predicted stroke occurrence (adj OR=1:17, p<0.05). Garg et al, Stroke 2018; 49:AWP In a propensity score matched study, procedure without use of a cerebral protection device was the only independent protector (p=0.04) for the occurrence of stroke within 7 days, but not STS score for mortality, sex, diabetes, valve calcification, or atrial fibrillation. Seeger J et al. JAAC Cardiovasc Interv 2017; 10(22): 2297-303.	Thank you for your comment. The Garg (2018) study aims to estimate the incidence, predictors and outcomes of in-hospital stroke in patients undergoing TAVR. It does not assess the efficacy or safety of cerebral protection to prevent cerebral embolism during TAVI. Therefore, it won't be included in the overview. The Seeger (2017) study is already included in the main extraction table in the overview (Table 2).
4	Consultee 2 Company	**2.1**	We would suggest the committee to consider the following addition :	Thank you for your comment.

	Boston Scientific		However, during the TAVI procedure as during the surgical procedure, debris may be dislodged which can embolise to the cerebral circulation and cause a transient ischaemic attack or stroke.	Section 2.1 of the guidance has been changed as follows: *"2.1 Transcatheter aortic valve implantation (TAVI) aims to provide a less invasive alternative to open cardiac surgery for treating aortic stenosis, avoiding the need for sternotomy and cardiopulmonary bypass. However debris may be dislodged during the TAVI procedure. This can enter the cerebral circulation and embolise, causing cerebral ischaemic events including a stroke."*
5	Consultee 2 Company Boston Scientific	**2.2**	Same as above, the aim of using a cerebral protection device is to prevent stroke and to avoid cerebral ischemic lesions which have been shown to be associated with a decline in neurological and neurocognitive function. Subclinical ischaemic lesions may lead to neurocognitive decline on the mid or long term.	Thank you for your comment. Please refer to comment 2.
6	Consultee 2 Company Boston Scientific	**2.3**	The Sentinel device is not placed in the aortic arch, as described by the draft. One filter is delivered to the brachiocephalic artery (proximal filter), and the other to the left common carotid artery (distal filter).	Thank you for your comment. This section of the guidance is intended to be a brief summary of the way the procedure is typically done. Section 2.3 of the guidance has been changed to:

				"2.3 During the TAVI procedure, before the valve is inserted, a cerebral protection device is inserted percutaneously through the radial or femoral artery. Depending on the type of device used, it is placed into the aortic arch or into the brachiocephalic (innominate) and left common carotid arteries. It is deployed to protect the ostia of the brachiocephalic (innominate) artery and the left common carotid artery. It may also protect the left subclavian artery, depending on the type of device used. It works either by filtering dislodged debris from the blood, or by deflecting dislodged debris away from the cerebral circulation to the systemic circulation. The device is removed at the end of the TAVI procedure."
7	Consultee 2 Company Boston Scientific	**3.1**	The evidence accessed We would like to ask the committee to consider and include this new evidence in the evaluation : Seeger J et al, European Heart Journal 2018 0, 1-7. A patient pooled analysis combining patients from the SENTINEL US IDE trial with the CLEAN -TAVI and SENTINEL- Ulm study was published December 2018 in European Heart Journal (n=1306). In the propensity matched population, 533 patients underwent TAVR without CEP and 533 with CEP. In patients undergoing TAVR with dual filter CEP, procedural all-stroke was significantly lower compared with unprotected procedures	Thank you for your comment and for providing information about new publications. The Seeger (2018) study was retrieved by the update literature search and has been included in Table 2.

			[1.88% vs 5.44%, OR 0.35, 95% CI 0.17-0.72, RR 65% p= 0.0028]. the combined patients from the SENTINEL US IDE, CLEAN-TAVI and SENTINEL-Elm studies reported: all cause mortality and all-cause mortality and all-stroke were significantly lower (2.06% vs 6%, OR 0.34, 95% CI 0.17-0.68, RRR 66%, p= 0.0013). There was no stroke-related deaths within 72-hr after the procedure in both groups. All-cause mortality and all-stroke were significantly lower (2.06% vs. 6.00%, odds ratio 0.34, 95% CI 0.17â€"0.68, relative risk reduction 66%, P = 0.0013).	
8	Consultee 2 Company Boston Scientific	**3.1**	We would also like to highlight some evidence that the committee missed in presenting results from reference 7 (Seeger et al 2017) for peri-procedural stroke : stroke was significantly lower with use of the protection device compared with unprotected procedures within 48 hr (3.6% vs 1.1%; p Â¼ 0.03; OR: 0.29; 95% CI: 0.10 to 0.93; nnt 31). For the same reference 7, but looking at stroke or all-cause mortality, we would suggest to add the number needed to treat [NNT] 21.	Thank you for your comment. The Seeger (2017) study is included in Table 2 but the following information was missed: '' Stroke was significantly lower with use of the protection device compared with unprotected procedures within 48 h (3.6% vs. 1.1%; p= 0.03; OR: 0.29; 95% CI: 0.10 to 0.93; NNT 31).'' This has been included in the table and in the Efficacy summary section.
9	Consultee 2 Company Boston Scientific	**3.1**	Looking specifically at TIA we would like to highlight some evidence that the committee missed in presenting reference 8 (prospective case series of 40 patients having cerebral protection with a dual filter device during	Thank you for your comment. For study 8 (Naber 2012) which is included in Table 2, it is already mentioned in the efficacy column that ''

			TAVI): this study reported no procedural transient ischaemic attacks.	No procedural transient ischaemic attacks, minor strokes or major strokes occurred." Therefore, no change has been be made.
10	Consultee 2 Company Boston Scientific	**3.1**	In the subsection on neurocognitive function, Page 6 of overview document, missed evidence by the committee for Reference 6: neurocognitive deteriotiation difference was statistically significant (p-0.017).	Thank you for your comment. For study 6 (Van Mieghem 2016), it is already written in Table 2 that the neurocognitive deterioration difference was statistically significant (p=0.017). This has been added into the efficacy summary section.
11	Consultee 2 Company Boston Scientific	**3.1**	In the subsection on development of new cerebral lesions, we would like to suggest considering missing data for reference 3: the median total new lesion volume in protected territories was 42% lower, thereby meeting the 30% pre-specified success criteria.	Thank you for your comment. This comment refers to Study 3 (Kapadia 2017). *"The median total new lesion volume in protected territories was 42% lower, thereby meeting the 30% pre-specified success criteria, but it was not significantly different in device versus control arms (102.8 mm^3 vs. 178.0 mm^3; p= 0.33)."* has been added to Table 2.
12	Consultee 2 Company Boston Scientific	**3.1**	We would like to suggest considering missing data for reference 6: in the study : follow up MRI was completed in 57% of the patients, a mean of 5.0Â±1.1 days post TAVI.	Thank you for your comment This comment refers to Study 6 (Van Mieghem 2016).

			Twenty-eight patients did not undergo a follow-up MRI. Overall, 78% of patients with follow-up MRI had new brain lesions	It is already written in Table 2 under the section "Follow-up issues" that: *"Patients had DW-MRI and extensive neurological examination, including neurocognitive testing 1 day before and 5 to 7 days after TAVI. Follow-up DW-MRI was completed in 57% (37/65) of patients. Patients did not have a follow-up MRI for the following reasons: implantation of a non-MRI-compatible pacemaker (n=10), patient refusal (n=6), unstable clinical condition or deceased (n=5), logistical challenges (n=4) and delirium (n=3). The MRI exam was done with a 3.0 Tesla scanner."* The sentence *"Overall, 78% of patients with follow-up MRI had new brain lesions."* has been added to Table 2.
13	Consultee 2 Company Boston Scientific	**3.1**	We would also suggest a discussion about the challenges of looking at lesion number and volume for efficacy due to different study methodologies.	Thank you for your comment. The committee decided to add a committee comment in section 3.8 which says: *"3.8 Detecting cerebral lesions resulting from incomplete protection is challenging and the methods for doing it may have differed between the studies ."*

14	Consultee 2 Company Boston Scientific	**3.1**	The evidence accessed Page 5 of the overview document, the heading â€œStroke or all-cause mortality at 30-day follow-up (composite outcome)â€ should be revised, as results with shorter follow-up are also being described in this subsection. Also, composite scores should be described as standard deviation as in the publication.	Thank you for your comment. This section of the overview has been changed to clarify which follow-up time period is being reported on in this part of the efficacy section.
15	Consultee 2 Company Boston Scientific	**3.1**	New Evidence We recognised that studies addressing histopathology have not been considered. We would nevertheless like the committee to consider the following additional evidence coming from histopathology studies. Van Mieghem et al, Circulation 2013; 127:2194-2201. In this RCT of 363 patients cerebral embolic debris was generated in at least 99% of TAVI patients. One in four patients had an average of 25 pieces of debris >0.5 mm headed to the brain. Embolic debris included piece of calcium, valve and aortic tissue, myocardium or other organic or foreign matter. In a study on 40 patients who underwent transcatheter aortic valve replacement with the use of a dual filter-based embolic protection device (reference 8), embolic	Thank you for your comment. Histopathology studies are not usually considered by the IP committee.

			debris traveling to the brain was captured in 75% of the transcatheter aortic valve replacement procedures. The debris consisted of foreign of fibrin, or amorphous calcium and connective tissue derived most likely from either the native aortic valve leaflets or aortic wall.	
16	Consultee 2 Company Boston Scientific	**Overview**	Page 31 of the overview document discussed Validity and generalisability of the studies, it mentioned â€œthe valves used for the TAVI procedure also differ and might have an impact on the efficacy outcomes of the cerebral protection.â€ Nevertheless, CEP benefit has been demonstrated across all valve types.	Thank you for your comment. The committee decided to add a committee comment in section 3.9 of the guidance which says: *'' 3.9 The valves used for the TAVI procedure differ, but cerebral protection benefit during TAVI has been demonstrated across all valve types ."*
17	Consultee 2 Company Boston Scientific	**Overview**	Company engagement on Page 33 of the overview document should be updated to reflect, that Boston Scientific has also provided data to support the SIR.	Thank you for your comment. This section of the overview has been updated.
18	Consultee 2 Company Boston Scientific	**3.6**	Addressing committee comments, it is useful to note that most strokes occur within 72-hrs following TAVI, and to put this in relation with the fact that CEP devices are temporary and used only during the procedure	Thank you for your comment. The committee considered your comment but decided not to change the guidance.