OREGON HEALTH AND SCIENCE UNIVERSITY
OFFICE OF CLINICAL INTEGRATION AND EVIDENCE-BASED PRACTICE

Evidence-Based Practice Summary

Safety and efficacy of the Claret Medical Sentinel® Cerebral Protection System

BACKGROUND AND RATIONALE

In the past decade, transcatheter aortic valve replacement (TAVR) triggered a paradigm shift in the treatment of patients with severe symptomatic aortic stenosis who are at surgical risk, and has proven to have similar or even superior outcomes in comparison with surgical aortic valve replacement (SAVR).[1-8] However, periprocedural stroke during TAVR is a serious complication substantially increasing acute and long-term morbidity and mortality.[6,9-13] Similar to SAVR, the 30-day risk of stroke following TAVR ranges from 2 to 5%, and its occurrences is associated with a 3.5 fold increase in the risk of death in the first month following TAVR.[8,12-14] In patients with prohibitive risk or at high risk, the one year rate of any stroke is from 7% to 11% and major stroke occurs in close to 5% of patients after TAVR.[15] Despite improvements in TAVR technology and operator experience, the rate of post-TAVR 30-day stroke has been stable over time.[16] The majority of early post-TAVR strokes occurred within the first 3 days following TAVR and early stroke is independently associated with a significant increase in 30-day mortality.[16] Additionally, clinically "silent" brain infarctions seen on magnetic resonance imaging (MRI) are associated with neurocognitive function changes and these infarctions occur in as many of 80% of patients after TAVR.[9] The etiology of strokes and MRI perfusion abnormalities is multifactortial, most are the results of embolization of debris during the procedure.[9] Recent RCTs suggest that TAVR may be either non-inferior or superior to TAVR in low risk patients.[5,7,13] The expansion of TAVR to younger and lower risk patients reinforces the importance of minimizing periprocedural embolization to the brain.[8]

Cerebral Protection System (CPS)

Risks from TAVR led to the development of four unique Cerebral Protection Systems (CPS) in order to develop embolization of thrombotic or calcific debris during TAVR.[18] Recent meta-analyses found that all four CPS systems were associated with a nonsignificant trend towards lower risk for death and stroke, no differences were detected when restricting the analysis to randomized controlled trials.[1,18] Also, the use of CPS during TAVR is not associated with a reduced rate of new lesions as assessed by MRI.[1,18] The lack of significant benefit of CPS with regards to hard clinical endpoints including strokes and death has made it difficult to make any strong guidelines or recommendations regarding its use. Additionally, limited sample sizes and inadequate statistical power have limited interpretation of clinical endpoints to date.

Claret Medical Sentinel® Cerebral Protection System

The Claret Medical Sentinel® Cerebral Protection System (Sentinel CPS), approved by the Food and Drug Administration (FDA) for use in 2017, is a percutaneously delivered dual-filter embolic protection device, designed to capture and remove debris dislodged during endovascular procedures. Sentinel CPS utilizes an embolic filter delivered to the brachiocephalic artery (Proximal Filter), and a second embolic filter delivered to the left common carotid artery (Distal Filter). At the completion of the procedure, the filters and debris are recaptured into the catheter and removed from the patient. The Sentinel CPS consists of a 6 French catheter with deployable Proximal and Distal Filters, an Articulating Sheath, and an integral handle assembly. Table 1 and Table 2 provide information regarding the filter sizes and Sentinel CPS specifications.[19]

Table 1: Filter-Vessel Sizing Guide

REF (Model) Number for Ordering	Proximal Filter Size (mm)	Target Proximal Vessel Size (mm)	Distal Filter Size (mm)	Target Distal Vessel Size (mm)
CMS15-10C	15	9.0 – 15.0	10	6.5 – 10.0

Table 2: Sentinel System Specifications

Delivery Profile	6F
Working Length	95 cm
Articulating Sheath Length	4 cm
Guidewire Compatibility	0.014" (0.36 mm) diameter floppy tip coronary guidewire, 175 cm minimum length

Adverse events associated with transcatheter aortic valve replacement (TAVR) using the Sentinel System with commercially available TAVR devices and TAVR devices alone is presented in Table 3, all events adjudicated.[19]

Table 3: Adverse Events, ≤ 30 Days

	Sentinel System Arms N=244		Control Arm N=119	
Event Type	Total Events	Subjects w/Event(s)	Total Events	Subjects w/Event(s)
Acute kidney injury	7	2.9% (7)	5	2.5% (3)
Vascular complication	21	8.6% (21)	9	7.6% (9)
TAVR Access Site	20	8.2% (20)	9	7.6% (9)
Radial Artery	0	0% (0)	N/A	N/A
Brachial Artery	1	0.4% (1)	N/A	N/A
Stroke	13	5.3% (13)	12	9.2% (11)
Disabling	2	0.8% (2)	1	0.8 (1)
Non-disabling	11	4.5% (11)	9	7.6% (9)
TIA	1	0.4% (1)	1	0.8% (1)
Death	11	4.5% (11)	4	3.4% (4)

Note: AKI includes Class I, II, and III

ASK THE QUESTION

In patients undergoing transcatheter aortic valve replacement, what is the safety and efficacy of the Sentinel Cerebral Protection System?

SEARCH FOR EVIDENCE

Appendix C

CRITICALLY ANALYZE THE EVIDENCE

Over 60 research articles were found mentioning Sentinel Cerebral Protection System. Two systemic reviews, three RCTs and two prospective cohort studies were found comparing the clinical outcomes following TAVR with and without use of Sentinel Cerebral Protection System (Sentinel CPS). The systematic reviews combined outcomes from the Sentinel Trial (Kapadia 2017), CLEAN-TAVI (Haussig 2016) and SENTINEL-Ulm (Seeger 2017) studies. Ndunda's systematic review also included results from MISTRIAL-C (Van Mieghem 2016), which was the first Sentinel CPS randomized trial in 2016 that evaluated Sentinel CPS's safety and efficacy in the Netherlands. The brief mostly summarizes evidence from the systematic review's meta-analyses divided by outcomes, but breaks down

individual studies results when outcomes were not included in analysis. Individual studies were also appraised to identify study limitations that would affect overall level of evidence.

Stroke

Two systematic reviews and one prospective cohort study were found analyzing the efficacy of the Sentinel Cerebral Protection System on stroke rates. Ndunda 2019 compared the clinical outcomes following transcatheter aortic valve replacement (TAVR) with and without the use of the Sentinel Cerebral Protection System (Sentinel CPS). Meta-analysis included three randomized controlled trials (RCTs) and one observational study, all of which included symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic valve replacement as determined by the heart team. The study found there was a statistically significant lower rate of stroke at 30-days in the Sentinel CPS arm compared with control [3.5% vs 6.1%; RR 0.51 (95% CI: 0.29-0.90) I^2 = 0%]. Sensitivity analyses were done for 30-day stroke and mortality by removing one study at a time. When only RCTs were included, there was only a trend to lower 30-day stroke [5.4% vs 8.3% RR 0.64 (95% CI: 0.33-1.24) I^2 = 0%]. Another systematic review (Seeger 2019) was conducted to validate the impact of the dual-filter CEP device Sentinel CPS on peri-procedural stroke in a large number of TAVR patients. This meta-analysis included only patients from SENTINEL trial, combined with the CLEAN-TAVI and SENTINEL-Ulm study, and used propensity score matching to identify and exclude confounding variables in the analysis. The study found that in patients undergoing TAVR with dual-filter CEP, procedural all-stroke was significantly lower within 72 hours compared with unprotected procedures [1.88% vs. 5.44%, odds ratio 0.35, 95% CI 0.17-0.72, relative risk reduction 65%, P = 0.0028]. Lastly, one prospective cohort study (Kroon 2019) was included that compared the rate of neurological events in patients with or without cerebral embolic protection (CEP) during transcatheter aortic valve replacement (TAVR). The Sentinel CPS group experienced less neurological events at 24 hours (1% versus 4%; P = 0.035) and at 30 days (3% versus 7%; P = 0.029). There were significantly more disabling strokes in unprotected patients at 30 days (1% versus 4%; P = 0.039). CEP was associated with significantly fewer neurological events at 24 hours after TAVR (odds ratio, 0.20; 95% CI, 0.06-0.73; P = 0.015) by multiple regression analysis, while age and valve type did not contribute significantly. Overall, 67% (2 of 3) in the CEP versus 83% (10 of 12) in the non-CEP cohort experienced neurological events in protected areas (ie, not dependent on the left vertebral artery).

Overall there is **low quality evidence demonstrating that Sentinel CPS reduces the risk of stroke at 30 days**. The level of evidence was downgraded due to inconsistency among studies, mostly based on how outcomes are measured. Evidence is also imprecise due to lack of events across the body of evidence.

**Individual studies from systematic review were appraised to determine overall level of evidence, but were not included in summary*

New Lesion Volume

Three RCTs were found determining the effect of the Sentinel Cerebral Protection System on new lesion volume. Sentinel Trial (Kapadia 2017) found 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* = 0.25). Total new lesion volume in all territories was also not statistically different in device versus control arms (294 mm^3 vs. 309.8 mm^3; *P* 0.81). New lesion number in device versus control arms in both protected and all territories was unchanged. When analyzed by valve type, new lesion volume and number of both protected and all territories had significant differences. The median total new lesion volume at 30 days was 0 for both protected and all territories in the device and control arm. CLEAN-TAVI (Haussig 2016) found the number of new lesions was lower in the filter group, 4.00 (interquartile range {IQR], 3.00-7.25) vs 10.00 (IQR, 6.75-17.00) in the control group (different, 5.00 [IQR 2.00-8.00] P < .001). The last RCT (Van Mieghem 2016) included in the appraisal found new brain lesions in 78% of patients with follow-up MRI. Patients with the Sentinel CPS had numerically fewer new lesions and a smaller total lesion volume (95 mm3 [IQR 10-257] vs. 197 mm3 [95-525]). Overall, 27% of Sentinel CPS patients and 13% of control patients had no new lesions. Ten or more new brain lesions were found only in the control cohort (in 20% vs. 0% in the Sentinel CPS cohort, p=0.03).

Overall, there is **low quality evidence that the use of Sentinel CPS is associated with a reduction in new lesion volume in protected territories**, downgraded for imprecision because of number of participants in combined studies. Two of the RCTs did not include allocation concealment information in study design, also prognostic differences between arms at baseline was noted in two studies.

Mortality

One systematic review (Ndunda 2019) combined data from RCTs and found the risk of death at 30 days was lower in the Sentinel CPS arm [0.8% vs 2.7%; RR 0.34 (95% CI: 0.12-0.92) I^2 = 0%]. Sensitivity analyses were done for 30-day stroke and mortality by removing one study at a time. When only RCTs were included, there was only a trend to lower 30-day mortality [0.9% vs 2.6% RR 0.44 (95% CI: 0.12-1.68) I^2 0%]. When the study by Van Miegham was excluded, there was only a trend to lower 30-day mortality in the Sentinel CPS patients [0.9% vs 2.5% RR 0.36 (95% CI: 0.12-1.06) I^2 = 0%].

There is **low quality evidence that the risk of death is lower when using Sentinel CPS compared to no CPS**. There was inconsistency in the length of time that mortality was measured. Also, the body of evidence is imprecise because individual studies have not reported many events.

**Individual studies from systematic review were appraised to determine overall level of evidence, but were not included in summary*

Acute Kidney Injury

One systematic review (Ndunda 2019) evaluated impact on acute kidney injury. There was no significant difference in the risk of acute kidney injury [0.8% vs 1%; RR 0.85 (95% CI 0.22, 3.24) $I^2 = 0\%$].

There is **very low quality evidence that the risk of acute kidney injury is similar when using Sentinel CPS and no CPS**. Very few events were reported, therefore the evidence is imprecise and consistency cannot be determined.

**Individual studies from systematic review were appraised to determine overall level of evidence, but were not included in summary*

Major or life-threatening bleeding

One systematic review (Ndunda 2019) evaluated impact on major or life-threatening bleeding. The risk of major of life-threatening bleeding was lower in the Sentinel CPS group [3.3% vs 6.6%; RR 0.50 (0.26, 0.98) $I^2 = 16\%$].

There is **very low quality evidence that the risk of major or life-threatening bleeding is lower when using Sentinel CPS compared to no CPS**. Very few events were reported, therefore the evidence is imprecise and consistency cannot be determined.

**Individual studies from systematic review were appraised to determine overall level of evidence, but were not included in summary*

Major Vascular Complications

One systematic review (Ndunda 2019) evaluated impact on major vascular complications. No significant difference was found between both groups in major vascular complications [5.1% vs 6%; RR 0.74 (0.33, 1.67) $I^2 = 45\%$].

There is **very low quality evidence that there is no significant difference on major vascular complications when using Sentinel CPS compared to no CPS.** Very few events were reported, therefore the evidence is imprecise and consistency cannot be determined.

Neurocognitive function

Two RCTs reported the Sentinel CPS's impact on neurocognitive function. Sentinel Trial (Kapadia 2017) found neurocognitive function was similar in control subjects and patients with devices, but there was a correlation between lesion volume and neurocognitive decline ($p = 0.0022$). MISTRAL-C (Van Mieghem 2016) reported that neurocognitive deterioration was present in 4% of patients with Sentinel CPS vs. 27% of patients without ($p=0.017$).

There is **very low quality evidence that Sentinel CPS has an effect on neurocognitive function.** Effect was inconsistent between studies. Evidence was also imprecise.

Debris

One prospective study and two RCTs were identified that evaluated the effect on debris when using Sentinel CPS. One recent prospective study (Seeger 2018) evaluated the debris captured by the Sentinel CPS during transfemoral TAVR with different valve types. The filers of consecutive patients were collected and captured debris was analyzed by histopathology and histomorphometry. Three valve types were implanted: the balloon-expanded Edwards SAPIEN 3, the self-expanded Medtronic Evolut R, and the mechanically implantable Boston Scientific Lotus. With the balloon-expandable valve, there were significantly more patients with large debris measuring >/= 1,000 um. The number of particles in the proximal filter was significantly power with the Lotus (89.8 +/- 106.3) compared with the Evolut R (187.3 +/- 176.9) and Edwards SAPIEN 3 (172.3 +/- 133.5) valves (*P* = 0.035). Total tissue area in the proximal filter was significantly smaller for the Lotus compared with the other 2 valve types (7.1 +/- 6.3, 20.1 +/- 19.0, and 21.3 +/- 15.1 mm^2; *P* = 0.0014). In contrast, for the distal filter, there was no differences with respect to valve type for total tissue area, particle size, and number of particles. Sentinel Trial found debris within filters in 99% of patients included thrombus, calcification, valve tissue, artery wall, and foreign material. Conclusions TCEP was safe, captured embolic debris in 99% of patients, and did not change neurocognitive function. And finally, MISTRAL-C filters captured debris in all patients with Sentinel CPS protection.

There is **low quality evidence that Sentinel CPS has an effect debris captured compared.** Study designs were inconsistent, therefore consistency could not be determined. Evidence was also imprecise.

<u>Summary of Sentinel CPS studies</u>

Recent meta-analysis demonstrated a nonsignificant trend towards lower risk of stroke and mortality. Additionally, there was no evidence of difference between patients with or without Sentinel CPS for stroke, mortality, major bleeding, life-threatening bleeding, acute kidney injury or major vascular events. This brief provides low to very low quality evidence to the safety and efficacy of Sentinel CPS as adjunctive therapy to TAVR. The present findings are subject to the inherent limitations of the included studies: study design, sample size, treatment crossover, and lost to follow-up. Meta-analyses complement but do not replace adequately powered RCTs. Therefore, additional evidence on the effectiveness of Sentinel CPS is needed to improve our confidence in the results.

Meta-analysis was based on four studies. Findings from each study are outlined below:

Sentinel Study (Kapadia 2017) *FDA approved device based on study*	The randomized trial demonstrated an absolute 3.6% reduction of stroke within 30 days correlating to a 42% reduction of new lesion volumes on MRI in protected territories.

CLEAN-TAVI (Haussig 2016)	Randomized control trial with 100 patients that demonstrated a reduction in number (5 vs 10; P = 0.009) and volume of new cerebral lesions (205 MM3 vs. 472 mm3; P = 0.009) on diffusion-weighted MRI following TAVR with use of Sentinel CPS.
SENTINEL-ULM (Seeger 2017)	A prospective cohort study that found stroke-free survival occurred significantly less frequently with 2.1% (n = 6 of 280) in the protected group compared with 6.8% (n = 19 of 280) in the unprotected group.
MISTRAL-C (Van Mieghem 2016)	Used the Sentinel CPS in 65 patients, revealed a significant reduction in multiple new brain lesions from 20% to 0% (*P* = 0.03)

Study published since meta-analysis

Dutch Registry Study (Kroon 2019)	The Sentinel CPS group experiences les neurological events at 24 hours (1% vs. 4%; *P* = 0.039) and was associated with significantly few neurological events at 24 hours after TAVR (OR: 0.20; 95% CI 0.06-0.73; *P* = 0.015).

Upcoming studies:

PROECTED TAVR: In January 2020, a two-year study known as PROTECTED TAVR will begin recruiting 3000 participants with the aim of reevaulating the cerebral protection on MRI findings in a four-armed study (ballon vs self-expendable valves). PROTECTED TAVR will look at outcomes of all stroke (hemorrhagic, ischemic, or undetermined status; disabling or nondisabling) through 72 hours post TAVR procedure or discharge.

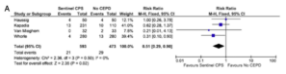
Dual-use: Preliminary evaluation has started for the use of combined CPS to cover both the carotid (anterior) and vertebral (posterior) circulation. A small pilot study evaluated the effect of additional selective filter protection to the left vertebral artery in 9 patients undergoing TAVR with Sentinel CPS. Debris was captured in all eft vertebral filters, and debris size and origin seemed similar to what was captured in the Sentinel.[20] This approach may be more clinically beneficial but requires further research to confirm pilot study results.

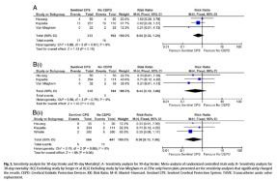
GRADE Table Templates

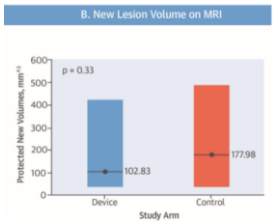
BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic
Modality: Sentinel Cerebral Protection System (Sentinel CPS)
Outcome: Stroke

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☒ Low
☐ Very Low

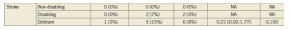
Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☐ High ☒ Medium ☐ Low	☒ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) – ***Methods for tracking outcomes varied*** ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Ndunda, P.M., et al. Year Published: 2019 Location: University of Kansas School of Medicine Journal: *Cardiovasc Revasc Med.*	To compare the clinical outcomes following transcatheter aortic valve replacement (TAVR) with and without the use of the Sentinel Cerebral Protection System (Sentinel CPS)	**Size:** 4 studies (3 RCTs and 1 cohort study). These studies had a total of 1330 patients with 606 assigned to the Sentinel CPS arms and 724 to the arms without cerebral embolic protection devices (CEPD) **Inclusion Criteria**: Studies were included if they were randomized controlled trials (RCTs) or controlled observational studies and compared TAVR using the Sentinel CPS versus TAVR without any embolic protection device. All studies included	**Type:** Systematic review with meta-analysis	**Results: There was a statistically significant lower rate of stroke at 30-days in the Sentinel CPS arm compared with control [3.5% vs 6.1%; RR 0.51 (95% CI: 0.29-0.90) I^2 = 0%]**  Sensitivity analyses were done for 30-day stroke and mortality by removing one study at a time. When only RCTs were included, there	**Study Limitations:** ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised ☒ Inappropriate pooled analysis **Haussig reported stroke at 7 days, the other three studies reported up to 30 days*

		symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic valve replacement as determined by the heart team. **Exclusion Criteria:** Individual studies specifically stated that they excluded patients with the listed characteristics as follows: an unsuitable anatomy for TAVR (Haussing, Van Mieghem, Seeger, Kapadia), permanent pacemaker or automated internal cardiac defibrillator (Haussig, Van Miegham), history of prior stroke (Haussig, Van Mieghem), carotid artery stenosis >70%, Stage IV – V chronic kidney disease, pregnancy (Haussig), inability to undergo MRI (Kapadia), patients undergoing valve-in-valve procedures (Seeger) and dementia (Van Mieghem).		was only a trend to lower 30-day stroke [5.4% vs 8.3% RR 0.64 (95% CI: 0.33-1.24) I^2 = 0%]. 	
Author: Seeger, J., et al. Year Published: 2019 Location: University of Ulm, Germany Journal: *Eur Heart J*	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	**Size:** 3 studies including 1306 patients; 533 patients underwent TAVR without CEP and 533 patients underwent TAVR with CEP **Inclusion Criteria**: Patients from SENTINEL US IDE trial, combined with the CLEAN-TAVI and SENTINEL-Ulm study	**Type:** Systematic Review with meta-analysis **Used propensity score matching*	**Results: In patients undergoing TAVR with dual-filter CEP, procedural all-stroke was significantly lower within 72 hours compared with unprotected procedures [1.88% vs. 5.44%, odds ratio 0.35, 95% CI 0.17-0.72, relative risk reduction 65%, *P* = 0.0028].**	**Study Limitations:** ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised ☐ Inappropriate pooled analysis
Author: Kroon, H.G., et al. Year Published: 2019 Location: the Netherlands Journal: *Circulation: Cardiovascular Interventions*	To compare the rate of neurological events in patients with or without cerebral embolic protection (CEP) during transcatheter aortic valve replacement (TAVR)	**Size:** 1000 TAVR patients, 433 with CEP **Inclusion Criteria**: All patients with severe degenerative aortic valve stenosis or regurgitation	**Type:** Prospective Cohort Study **Methods:** Data on clinical end points including neurological events </= 30 days post-TAVR were collected for all patients who underwent transfemoral	**Results:** The CEP group experienced less neurological events at 24 hours (1% versus 4%; *P* = 0.035) and at 30 days (3% versus 7%; *P* = 0.029). There were significantly more disabling strokes in unprotected patients at 30 days (1% versus 4%; *P* =	**Study Limitations:** ☐ None **Non-randomized Studies** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome

			TAVR in 2 academic tertiary care institutions.	0.039). CEP was associated with significantly fewer neurological events at 24 hours after TAVR (odds ratio, 0.20; 95% CI, 0.06-0.73; *P* = 0.015) by multiple regression analysis, while age and valve type did not contribute significantly. Overall, 67% (2 of 3) in the CEP versus 83% (10 of 12) in the non-CEP cohort experienced neurological events in protected areas (ie, not dependent on the left vertebral artery)	☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up
Appraisal of studies included in meta-analysis					
Author: Kapadia, S.R., et al. Year Published: 2017 Location: Cleveland Clinic Journal: *Journal of the American College of Cardiology* *Note: The study population was older (median age 83.4 years), the majority (52.1%) consisted of female patients, the median Society of Thoracic Surgeons score was 6.0%, and frequent comorbidities included atrial fibrillation (31.7%) and previous strokes (5.8%).* *Delivery and Retrieval of both filters were successful in 94.4% of patients. In the device arm vs the control arm, there was an increase in total procedure time (P = 0.01) and fluoroscopy time (P = 0.007).*	To evaluate the safety and efficacy of TCEP during TAVR. Methods Nineteen centers randomized patients undergoing TAVR to a safety arm, device imaging, and control imaging.	**Size:** 363 patients undergoing TAVR to a safety arm (n = 123), device imaging (n = 121), and control imaging (n = 119). **Inclusion Criteria**: Patients with severe symptomatic aortic stenosis and planned TAVR who were at high surgical risk. **Exclusion Criteria:** Known contraindications for right radial or brachial artery access and inability to undergo MRI brain evaluation for any reason.	**Type:** RCT **Methods:** Patients undergoing TAVR at 17 centers in US and Germany were prospectively randomized 1:1:1 into a safety arm (TCEP only) and 2 imaging cohorts, in which patients were randomly treated with TCEP (device arm) or without TCEP (control arm). 4 different TAVR devices were used in the trial. Blinded diffusion-weighted MRI and neurocognitive function assessments were performed in the device and control arms. Particulate debris from the extracted filters was studied in the device arms. All patients underwent rigorous neurological evaluations post-TAVR at 30 and 90 days. The primary safety endpoint consisted of major adverse cardiac and cerebrovascular events (MACCE) at 30 days, and the primary efficacy	**Results:** **Stroke rates were not significantly different in the device and safety arms versus the control arms (5.6% vs. 9.1%; *P* 0.25).** 	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☒ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☒ Difference in important prognostic factors at baseline

			endpoint was reduction in new lesion volume in protected brain territories on magnetic resonance imaging scans at 2 to 7 days.		
Author: Seeger, J., et al. Year Published: 2017 Location: University of Ulm, Germany Journal: *JACC: Cardiovascular Interventions*	To evaluate the impact of cerebral embolic protection on stroke-free survival in patients undergoing transcatheter aortic valve replacement (TAVR)	**Size:** 802 consecutive patients. 280 with Sentinel cerebral embolic protection device, 522 in patients without cerebral embolic protection **Inclusion Criteria**: Patients undergoing TAVR	**Type:** Prospective cohort study **Intervention**: Enrolled patients underwent diagnostic evaluation with routine laboratory testing, medical history with current medication, Society of Thoracic Surgeons (STS) score, New York Heart Association functional class, electrocardiography, echocardiography, heart catheterization, and multislice computed tomography. Neurological follow-up was done within 7 days post-procedure. The primary endpoint was a composite of all-cause mortality or all-stroke according to Valve Academic Research Consortium-2 criteria within 7 days.	**Results:** Stroke-free survival occurred significantly less frequently with 2.1% (n = 6 of 280) in the protected group compared with 6.8% (n = 19 of 280) in the unprotected group (p = 0.01; odds ratio 0.30; 95% CI 0.12 to 0.77; ARR 4.7%; NNT 21. With use of the Sentinel cerebral device rate of disabling and non-disabling stroke was significantly reduced from 4.6% to 1.4% (p = 0.03; OR 0.29; 95% CI 0.10 to 0.93; ARR 3.2%; NNT 31) compared with patients undergoing TAVR without cerebral protection.	**Study Limitations:** ☐ None **\Non-randomized Studies** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up
Author: Haussig, S., et al. Year Published: 2016 Location: University of Leipzig, Germany Journal: *JAMA*	To determine the effect of a cerebral protection device on the number and volume of cerebral lesions in patients undergoing TAVI	**Size:** 100 (50 control and 50 intervention) **Inclusion Criteria**: Symptomatic patients with severe aortic stenosis considered at increased risk for SAVR as determined by the heart team. **Exclusion Criteria:** Anatomy unsuitable for a safe TAVI, preexisting permanent pacemaker, stroke within the last 12 months, carotid artery stenosis of more than 70%, significant stenosis of the right	**Type:** RCT **Methods:** Patients were randomly assigned (1:1) to the control or filter group using the Claret Montage Dual Filter System. Follow-up assessments were performed at 2 days and 7 days after TAVI and were identical to the preprocedural tests. In addition to MRI, follow-up included serial neurological and neurocognitive assessments, New York Heart Association	**Results:** At 2 and 7 days in the intention-to-treat analysis, the number of patients with neurological symptoms indicative of stroke was 5 in the filter group and 5 in the control group; all were minor and non-disabling in nature. None of the patients had a transient ischemic attack since all patients with symptoms had positive brain imaging and were classified as stroke positive according to VARC2. At 2, 7, and 30 days, stroke	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☒ Difference in important prognostic factors at baseline

		subclavian artery or the brachiocephalic trunk, expected nonadherence to follow-up visits, participation in another clinical study, severe renal failure or pregnancy	classification, echocardiography, and documentation of adverse events and study end points. The primary end point was the numerical reduction in positive postprocedure DWMRI brain lesions relative to baseline and 2 days following TAVI in potentially protected territories. Only new lesions that were visible at 2 days, 7 days, or both but not present in the baseline scans were analyzed. Secondary end points included serial volumetric and numerical reductions in positive postprocedure DWMRI-perfused brain lesions at 2 and 7 days, as well as the results of serial neurological and neurocognitive assessments.	frequencies were similar between both groups. **eTable 8.** Neurological Outcome 	
Author: Van Mieghem, N.M., et al. Year Published: 2016 Location: Erasmus Medical Center, the Netherlands Journal: *Euro Intervention*	To determine whether use of the filter-based Sentinel™ Cerebral Protection System (CPS) during transcatheter aortic valve implantation (TAVI) can affect the early incidence of new brain lesions, as assessed by diffusion-weighted magnetic resonance imaging (DW-MRI), and neurocognitive performance	**Size:** 65 patients **Inclusion Criteria**: Patients deemed at high risk for SAVR by the Heart Team **Exclusion Criteria**: Presence of a permanent pacemaker or automated internal cardiac defibrillator (AICD) at baseline, a history of prior stroke with sequelae and dementia.	**Type:** RCT **Methods:** Patients were randomized 1:1 to transfemoral TAVI with or without the Sentinel CPS. Patients underwent DW-MRI and extensive neurological examination, including neurocognitive testing was completed in 57% and 80%, respectively.	**Results:** **No patients has a non-disabling stroke. 0 (0%) of patients had a Disabling stroke in the Sentinel arm and 2 (7%) in the No Sentinel arm. 1 (3%) patient had a Delirium stroke in the Sentinel arm and 5 (15%) in the No Sentinel Arm; RR 0.21 [0.46-0.55].** 	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☒ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline

References:

1. Haussig, S., et al. (2016). "Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial." JAMA **316**(6): 592-601.
2. Kapadia, S. R., et al. (2017). "Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement." Journal of the American College of Cardiology **69**(4): 367-377.
3. Kroon, H. G., et al. (2019). "Early Clinical Impact of Cerebral Embolic Protection in Patients Undergoing Transcatheter Aortic Valve Replacement." **12**(6): e007605.

4. Ndunda, P. M., et al. (2019). "Clinical outcomes of sentinel cerebral protection system use during transcatheter aortic valve replacement: A systematic review and meta-analysis." Cardiovasc Revasc Med.
5. Seeger, J., et al. (2019). "Rate of peri-procedural stroke observed with cerebral embolic protection during transcatheter aortic valve replacement: a patient-level propensity-matched analysis." Eur Heart J **40**(17): 1334-1340.
6. Seeger, J., et al. (2017). "Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement Significantly Reduces Death and Stroke Compared With Unprotected Procedures." **10**(22): 2297-2303.
7. Van Mieghem, N.M., et al. (2016). "Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial." EuroIntervention **12**(4): 499-507.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic
Modality: Sentinel Cerebral Protection System (Sentinel CPS)
Outcome: New Lesion Volume

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☒ Low
☐ Very Low

Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☐ High ☐ Medium ☒ Low	☐ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Kapadia, S.R., et al. Year Published: 2017 Location: Cleveland Clinic Journal: *Journal of the American College of Cardiology* *Note: Delivery and Retrieval of both filters were successful in 94.4% of patients. In the device arm vs the control arm, there was an increase in total procedure time (P = 0.01) and fluoroscopy time (P = 0.007).*	To evaluate the safety and efficacy of TCEP during TAVR. Methods Nineteen centers randomized patients undergoing TAVR to a safety arm, device imaging, and control imaging.	**Size:** 363 patients undergoing TAVR to a safety arm (n = 123), device imaging (n = 121), and control imaging (n = 119). **Inclusion Criteria**: Patients with severe symptomatic aortic stenosis and planned TAVR who were at high surgical risk. **Exclusion Criteria:** Known contraindications for right radial or brachial artery access	**Type:** RCT **Methods:** Patients undergoing TAVR at 17 centers in US and Germany were prospectively randomized 1:1:1 into a safety arm (TCEP only) and 2 imaging cohorts, in which patients were randomly treated with TCEP (device arm) or without TCEP (control arm). 4 different TAVR devices were used in the trial.	**Results:** 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* = 0.25). Total new lesion volume in all territories was also not statistically different in device versus control arms (294 mm^3	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☒ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U

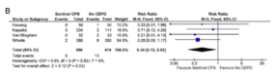
		and inability to undergo MRI brain evaluation for any reason.	Blinded diffusion-weighted MRI and neurocognitive function assessments were performed in the device and control arms. Particulate debris from the extracted filters was studied in the device arms. All patients underwent rigorous neurological evaluations post-TAVR at 30 and 90 days. The primary safety endpoint consisted of major adverse cardiac and cerebrovascular events (MACCE) at 30 days, and the primary efficacy endpoint was reduction in new lesion volume in protected brain territories on magnetic resonance imaging scans at 2 to 7 days.	vs. 309.8 mm^3; *P* 0.81). New lesion number in device versus control arms in both protected and all territories was unchanged.  When analyzed by valve type, new lesion volume and number of both protected and all territories had significant differences. The median total new lesion volume at 30 days was 0 for both protected and all territories in the device and control arm.	☒ Difference in important prognostic factors at baseline
Author: Haussig, S., et al. Year Published: 2016 Location: University of Leipzig, Germany Journal: *JAMA*	To determine the effect of a cerebral protection device on the number and volume of cerebral lesions in patients undergoing TAVI.	**Size:** 100 (50 control and 50 intervention) **Inclusion Criteria**: Symptomatic patients with severe aortic stenosis considered at increased risk for SAVR as determined by the heart team. **Exclusion Criteria:** Anatomy unsuitable for a safe TAVI, preexisting permanent pacemaker, stroke within the last 12 months, carotid artery stenosis of more than 70%, significant stenosis of the right subclavian artery or the brachiocephalic trunk, expected nonadherence to follow-up visits, participation in another clinical study, severe renal failure or pregnancy	**Type:** RCT **Methods:** Patients were randomly assigned (1:1) to the control or filter group using the Claret Montage Dual Filter System. Follow-up assessments were performed at 2 days and 7 days after TAVI and were identical to the preprocedural tests. In addition to MRI, follow-up included serial neurological and neurocognitive assessments, New York Heart Association classification, echocardiography, and documentation of adverse events and study end points. The primary end point was the numerical reduction in positive postprocedure DWMRI brain	**Results: The number of new lesions was lower in the filter group, 4.00 (interquartile range {IQR], 3.00-7.25) vs 10.00 (IQR, 6.75-17.00) in the control group (different, 5.00 [IQR 2.00-8.00] *P* < .001).** For the first hierarchical secondary endpoint, new lesion volume after TAVI was lower in the filter group (242mm3 [95%CI, 159-353]) vs in the control group (527 mm^3 [95% CI, 364-830]) (difference, 234 mm^3 [95% CI, 91-406]; P=.001).	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☒ Difference in important prognostic factors at baseline

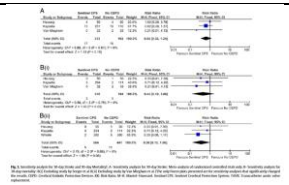
			lesions relative to baseline and 2 days following TAVI in potentially protected territories. Only new lesions that were visible at 2 days, 7 days, or both but not present in the baseline scans were analyzed. Secondary end points included serial volumetric and numerical reductions in positive postprocedure DWMRI-perfused brain lesions at 2 and 7 days, as well as the results of serial neurological and neurocognitive assessments.		
Author: Van Mieghem, N.M., et al. Year Published: 2016 Location: Erasmus Medical Center, the Netherlands Journal: *Euro Intervention*	To determine whether use of the filter-based Sentinel™ Cerebral Protection System (CPS) during transcatheter aortic valve implantation (TAVI) can affect the early incidence of new brain lesions, as assessed by diffusion-weighted magnetic resonance imaging (DW-MRI), and neurocognitive performance	**Size:** 65 patients **Inclusion Criteria**: Patients deemed at high risk for SAVR by the Heart Team **Exclusion Criteria**: Presence of a permanent pacemaker or automated internal cardiac defibrillator (AICD) at baseline, a history of prior stroke with sequelae and dementia.	**Type:** RCT **Methods:** Patients were randomized 1:1 to transfemoral TAVI with or without the Sentinel CPS. Patients underwent DW-MRI and extensive neurological examination, including neurocognitive testing was completed in 57% and 80%, respectively.	**Results:** **New brain lesions were found in 78% of patients with follow-up MRI. Patients with the Sentinel CPS had numerically fewer new lesions and a smaller total lesion volume (95 mm3 [IQR 10-257] vs. 197 mm3 [95-525]). Overall, 27% of Sentinel CPS patients and 13% of control patients had no new lesions. Ten or more new brain lesions were found only in the control cohort (in 20% vs. 0% in the Sentinel CPS cohort, p=0.03).**	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☒ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline

References:

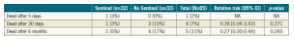
1. Haussig, S., et al. (2016). "Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial." JAMA **316**(6): 592-601.
2. Kapadia, S. R., et al. (2017). "Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement." Journal of the American College of Cardiology **69**(4): 367-377.
3. Van Mieghem, N.M., et al. (2016). "Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial." EuroIntervention **12**(4): 499-507.

BODY OF EVIDENCE APPRAISAL TABLE FOR:
Population: Symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic
Modality: Sentinel Cerebral Protection System (Sentinel CPS)
Outcome: Mortality

Quality (certainty) of evidence for: (outcome) ☐High ☐ Moderate ☒ Low ☐ Very Low					
Risk of Bias across studies: ☐ High ☒ Medium ☐ Low		**Lower Quality Rating if:** ☒ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) – ***Length for tracking outcomes varied*** ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*		**Other Considerations:** Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect	
Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Ndunda, P.M., et al. Year Published: 2019 Location: University of Kansas School of Medicine Journal: *Cardiovasc Revasc Med.*	To compare the clinical outcomes following transcatheter aortic valve replacement (TAVR) with and without the use of the Sentinel Cerebral Protection System (Sentinel CPS)	**Size:** 4 studies (3 RCTs and 1 cohort study). These studies had a total of 1330 patients with 606 assigned to the Sentinel CPS arms and 724 to the arms without cerebral embolic protection devices (CEPD) **Inclusion Criteria**: Studies were included if they were randomized controlled trials (RCTs) or controlled observational studies and compared TAVR using the Sentinel CPS versus TAVR without any embolic protection device. All studies included symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic valve replacement as determined by the heart team.	**Type:** Systematic review with meta-analysis	**Results: The risk of death at 30 days was lower in the Sentinel CPS arm [0.8% vs 2.7%; RR 0.34 (95% CI: 0.12-0.92) I^2 = 0%]**  Sensitivity analyses were done for 30-day stroke and mortality by removing one study at a time. When only RCTs were included, there was only a trend to lower 30-day mortality [0.9% vs 2.6% RR 0.44 (95% CI: 0.12-1.68) I^2 0%]. When the study by Van Miegham was excluded, there was only a trend to lower 30-day mortality in the Sentinel CPS patients [0.9% vs 2.5% RR 0.36 (95% CI: 0.12-1.06) I^2 = 0%].	**Study Limitations:** ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised ☒ Inappropriate pooled analysis **Haussig reported mortality at 7 days, the other three studies reported up to 30 days*

		Exclusion Criteria: Individual studies specifically stated that they excluded patients with the listed characteristics as follows: an unsuitable anatomy for TAVR (Haussing, Van Mieghem, Seeger, Kapadia), permanent pacemaker or automated internal cardiac defibrillator (Haussig, Van Miegham), history of prior stroke (Haussig, Van Mieghem), carotid artery stenosis >70%, Stage IV – V chronic kidney disease, pregnancy (Haussig), inability to undergo MRI (Kapadia), patients undergoing valve-in-valve procedures (Seeger) and dementia (Van Mieghem).			
Appraisal of studies included in meta-analysis					
Author: Haussig, S., et al. Year Published: 2016 Location: University of Leipzig, Germany Journal: *JAMA*	To determine the effect of a cerebral protection device on the number and volume of cerebral lesions in patients undergoing TAVI.	**Size:** 100 (50 control and 50 intervention) **Inclusion Criteria**: Symptomatic patients with severe aortic stenosis considered at increased risk for SAVR as determined by the heart team. **Exclusion Criteria:** Anatomy unsuitable for a safe TAVI, preexisting permanent pacemaker, stroke within the last 12 months, carotid artery stenosis of more than 70%, significant stenosis of the right subclavian artery or the brachiocephalic trunk, expected nonadherence to follow-up visits, participation in another clinical study, severe renal failure or pregnancy	**Type:** RCT **Methods:** Patients were randomly assigned (1:1) to the control or filter group using the Claret Montage Dual Filter System. Follow-up assessments were performed at 2 days and 7 days after TAVI and were identical to the preprocedural tests. In addition to MRI, follow-up included serial neurological and neurocognitive assessments, New York Heart Association classification, echocardiography, and documentation of adverse events and study end points. The primary end point was the numerical reduction in positive postprocedure DWMRI brain lesions relative to baseline and	**Results: 1 patient in the control group died in the 30-day visit. Therefore, 30-day mortality for the control group was 2% and 0% for the filter group.**	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☒ Difference in important prognostic factors at baseline

			2 days following TAVI in potentially protected territories. Only new lesions that were visible at 2 days, 7 days, or both but not present in the baseline scans were analyzed. Secondary end points included serial volumetric and numerical reductions in positive postprocedure DWMRI-perfused brain lesions at 2 and 7 days, as well as the results of serial neurological and neurocognitive assessments.		
Author: Seeger, J., et al. Year Published: 2017 Location: University of Ulm, Germany Journal: *JACC: Cardiovascular Interventions*	To evaluate the impact of cerebral embolic protection on stroke-free survival in patients undergoing transcatheter aortic valve replacement (TAVR)	**Size:** 802 consecutive patients. 280 with Sentinel cerebral embolic protection device, 522 in patients without cerebral embolic protection **Inclusion Criteria**: Patients undergoing TAVR	**Type:** Prospective cohort study **Intervention**: Enrolled patients underwent diagnostic evaluation with routine laboratory testing, medical history with current medication, Society of Thoracic Surgeons (STS) score, New York Heart Association functional class, electrocardiography, echocardiography, heart catheterization, and multislice computed tomography. Neurological follow-up was done within 7 days post-procedure. The primary endpoint was a composite of all-cause mortality or all-stroke according to Valve Academic Research Consortium-2 criteria within 7 days.	**Results:** Mortality occurred less frequently with 2 (0.7%) in the protected group compared with 8 (2.9%) in the unprotected group (OR 0.25 [0.05-1.20]; p = 0.06.	**Study Limitations:** ☐ None **\Non-randomized Studies** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up
Author: Van Mieghem, N.M., et al. Year Published: 2016 Location: Erasmus Medical Center, the Netherlands Journal: *Euro Intervention*	To determine whether use of the filter-based Sentinel™ Cerebral Protection System (CPS) during transcatheter aortic valve implantation (TAVI) can affect the early incidence of new brain lesions, as	**Size:** 65 patients **Inclusion Criteria**: Patients deemed at high risk for SAVR by the Heart Team	**Type:** RCT **Methods:** Patients were randomized 1:1 to transfemoral TAVI with or without the Sentinel CPS. Patients underwent DW-MRI	**Results:** **1 (3%) was dead after 5 days in the Sentinel arm, compared to 0 (0%) in the No Sentinel arm. 1 (3%) was dead after 30 days in the Sentinel arm compared to 3 (10%) in the**	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment

	assessed by diffusion-weighted magnetic resonance imaging (DW-MRI), and neurocognitive performance	**Exclusion Criteria**: Presence of a permanent pacemaker or automated internal cardiac defibrillator (AICD) at baseline, a history of prior stroke with sequelae and dementia.	and extensive neurological examination, including neurocognitive testing was completed in 57% and 80%, respectively.	**No Sentinel arm; RR 0.36 [CI 95% 0.04-3.43] p = 0.371. 1 (5%) patient was dead after 6 months in the Sentinel arm, compared to 4 (17%) in the No Sentinel arm; RR 0.27 [0.30-2.44] p = 0.245.** 	☒ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline

References:

1. Haussig, S., et al. (2016). "Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial." JAMA **316**(6): 592-601.
2. Ndunda, P. M., et al. (2019). "Clinical outcomes of sentinel cerebral protection system use during transcatheter aortic valve replacement: A systematic review and meta-analysis." Cardiovasc Revasc Med.
3. Seeger, J., et al. (2017). "Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement Significantly Reduces Death and Stroke Compared With Unprotected Procedures." **10**(22): 2297-2303.
4. Van Mieghem, N.M., et al. (2016). "Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial." EuroIntervention **12**(4): 499-507.

BODY OF EVIDENCE APPRAISAL TABLE FOR:

Population: Symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic

Modality: Sentinel Cerebral Protection System (Sentinel CPS)

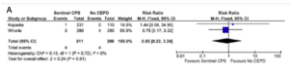
Outcome: Acute kidney injury

Quality (certainty) of evidence for: (outcome)

☐ High
☐ Moderate
☐ Low
☒ Very Low

Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☒ High ☐ Medium ☐ Low	☒ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) - **UNKOWN** ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**

Author: Ndunda, P.M., et al. Year Published: 2019 Location: University of Kansas School of Medicine Journal: *Cardiovasc Revasc Med.*	To compare the clinical outcomes following transcatheter aortic valve replacement (TAVR) with and without the use of the Sentinel Cerebral Protection System (Sentinel CPS)	**Size:** 4 studies (3 RCTs and 1 cohort study). These studies had a total of 1330 patients with 606 assigned to the Sentinel CPS arms and 724 to the arms without cerebral embolic protection devices (CEPD) **Inclusion Criteria**: Studies were included if they were randomized controlled trials (RCTs) or controlled observational studies and compared TAVR using the Sentinel CPS versus TAVR without any embolic protection device. All studies included symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic valve replacement as determined by the heart team. **Exclusion Criteria:** Individual studies specifically stated that they excluded patients with the listed characteristics as follows: an unsuitable anatomy for TAVR (Haussing, Van Mieghem, Seeger, Kapadia), permanent pacemaker or automated internal cardiac defibrillator (Haussig, Van Miegham), history of prior stroke (Haussig, Van Mieghem), carotid artery stenosis >70%, Stage IV – V chronic kidney disease, pregnancy (Haussig), inability to undergo MRI (Kapadia), patients undergoing valve-in-valve procedures (Seeger) and dementia (Van Mieghem).	**Type:** Systematic review with meta-analysis	**Results: There was no significant difference in the risk of acute kidney injury [0.8% vs 1%; RR 0.85 (95% CI 0.22, 3.24) I^2 = 0%].**  **Due to the need for separate vascular access site for the Sentinel CPS and use of extra iodinated contrast, theoretically, a higher risk of vascular access and contrast-related complications would be expected in the intervention group. However, there were relatively low rates of acute kidney injury complications in both group. Even though there was no significant difference between the two groups, the studies may not have been powered to detect differences in the endpoints.*	**Study Limitations:** ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised ☐ Inappropriate pooled analysis
Appraisal of studies included in meta-analysis					

Author: Haussig, S., et al. Year Published: 2016 Location: University of Leipzig, Germany Journal: *JAMA*	To determine the effect of a cerebral protection device on the number and volume of cerebral lesions in patients undergoing TAVI.	**Size:** 100 (50 control and 50 intervention) **Inclusion Criteria**: Symptomatic patients with severe aortic stenosis considered at increased risk for SAVR as determined by the heart team. **Exclusion Criteria:** Anatomy unsuitable for a safe TAVI, preexisting permanent pacemaker, stroke within the last 12 months, carotid artery stenosis of more than 70%, significant stenosis of the right subclavian artery or the brachiocephalic trunk, expected nonadherence to follow-up visits, participation in another clinical study, severe renal failure or pregnancy	**Type:** RCT **Methods:** Patients were randomly assigned (1:1) to the control or filter group using the Claret Montage Dual Filter System. Follow-up assessments were performed at 2 days and 7 days after TAVI and were identical to the preprocedural tests. In addition to MRI, follow-up included serial neurological and neurocognitive assessments, New York Heart Association classification, echocardiography, and documentation of adverse events and study end points. The primary end point was the numerical reduction in positive postprocedure DWMRI brain lesions relative to baseline and 2 days following TAVI in potentially protected territories. Only new lesions that were visible at 2 days, 7 days, or both but not present in the baseline scans were analyzed. Secondary end points included serial volumetric and numerical reductions in positive postprocedure DWMRI-perfused brain lesions at 2 and 7 days, as well as the results of serial neurological and neurocognitive assessments.	**Results: One patient (2%) in the filter group and 5 (10%) in the control group had acute kidney injury.**	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☒ Difference in important prognostic factors at baseline
Author: Seeger, J., et al. Year Published: 2017 Location: University of Ulm, Germany	To evaluate the impact of cerebral embolic protection on stroke-free survival in patients undergoing transcatheter	**Size:** 802 consecutive patients. 280 with Sentinel cerebral embolic protection device, 522 in patients without cerebral embolic protection	**Type:** Prospective cohort study **Intervention**: Enrolled patients underwent diagnostic evaluation with routine	**Results:** Acute kidney injury occurred less frequently with 3 (1.1%) in the protected group compared with 4 (1.4%) in the	**Study Limitations:** ☐ None **\Non-randomized Studies**

Journal: *JACC: Cardiovascular Interventions*	aortic valve replacement (TAVR)	**Inclusion Criteria**: Patients undergoing TAVR	laboratory testing, medical history with current medication, Society of Thoracic Surgeons (STS) score, New York Heart Association functional class, electrocardiography, echocardiography, heart catheterization, and multislice computed tomography. Neurological follow-up was done within 7 days post-procedure. The primary endpoint was a composite of all-cause mortality or all-stroke according to Valve Academic Research Consortium-2 criteria within 7 days.	unprotected group (OR 0.64 [0.15-2.71]; p = 0.54.	☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up

References:

1. Haussig, S., et al. (2016). "Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial." JAMA **316**(6): 592-601.
2. Ndunda, P. M., et al. (2019). "Clinical outcomes of sentinel cerebral protection system use during transcatheter aortic valve replacement: A systematic review and meta-analysis." Cardiovasc Revasc Med.
3. Seeger, J., et al. (2017). "Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement Significantly Reduces Death and Stroke Compared With Unprotected Procedures." **10**(22): 2297-2303.

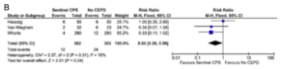
BODY OF EVIDENCE APPRAISAL TABLE FOR:

Population: Symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic

Modality: Sentinel Cerebral Protection System (Sentinel CPS)

Outcome: Major or life-threatening bleeding

Quality (certainty) of evidence for: (outcome)		
☐High ☐ Moderate ☐ Low ☒ Very Low		
Risk of Bias across studies: ☒ High ☐ Medium ☐ Low	**Lower Quality Rating if:** ☒ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) - **UNKOWN** ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)*	**Other Considerations:** Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient

		☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*		☐ Plausible confounders or other biases increase certainty of effect	
Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Ndunda, P.M., et al. Year Published: 2019 Location: University of Kansas School of Medicine Journal: *Cardiovasc Revasc Med.*	To compare the clinical outcomes following transcatheter aortic valve replacement (TAVR) with and without the use of the Sentinel Cerebral Protection System (Sentinel CPS)	**Size:** 4 studies (3 RCTs and 1 cohort study). These studies had a total of 1330 patients with 606 assigned to the Sentinel CPS arms and 724 to the arms without cerebral embolic protection devices (CEPD) **Inclusion Criteria**: Studies were included if they were randomized controlled trials (RCTs) or controlled observational studies and compared TAVR using the Sentinel CPS versus TAVR without any embolic protection device. All studies included symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic valve replacement as determined by the heart team. **Exclusion Criteria:** Individual studies specifically stated that they excluded patients with the listed characteristics as follows: an unsuitable anatomy for TAVR (Haussing, Van Mieghem, Seeger, Kapadia), permanent pacemaker or automated internal cardiac defibrillator (Haussig, Van Miegham), history of prior stroke (Haussig, Van Mieghem), carotid artery stenosis >70%,	**Type:** Systematic review with meta-analysis	**Results: The risk of major or life-threatening bleeding was lower in the Sentinel CPS group [3.3% vs 6.6%; RR 0.50 (0.26, 0.98) I^2 = 16%].**  **Data on the site and timing of the bleeding events relative to the procedure and the rate of hemorrhagic conversation of ischemic stroke was unavailable and the rate of hemorrhagic conversion of ischemic stroke was unavailable, therefore the reason for lower risk of bleeding is unclear.*	**Study Limitations:** ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised ☐ Inappropriate pooled analysis

		Stage IV – V chronic kidney disease, pregnancy (Haussig), inability to undergo MRI (Kapadia), patients undergoing valve-in-valve procedures (Seeger) and dementia (Van Mieghem).			
Appraisal of studies included in meta-analysis					
Author: Seeger, J., et al. Year Published: 2017 Location: University of Ulm, Germany Journal: *JACC: Cardiovascular Interventions*	To evaluate the impact of cerebral embolic protection on stroke-free survival in patients undergoing transcatheter aortic valve replacement (TAVR)	**Size:** 802 consecutive patients. 280 with Sentinel cerebral embolic protection device, 522 in patients without cerebral embolic protection **Inclusion Criteria**: Patients undergoing TAVR	**Type:** Prospective cohort study **Intervention**: Enrolled patients underwent diagnostic evaluation with routine laboratory testing, medical history with current medication, Society of Thoracic Surgeons (STS) score, New York Heart Association functional class, electrocardiography, echocardiography, heart catheterization, and multislice computed tomography. Neurological follow-up was done within 7 days post-procedure. The primary endpoint was a composite of all-cause mortality or all-stroke according to Valve Academic Research Consortium-2 criteria within 7 days.	**Results:** Major bleeding occurred less frequently with 4 (1.4%) in the protected group compared with 12 (4.3%) in the unprotected group (OR 0.33 [0.11-1.05]; p = 0.05.	**Study Limitations:** ☐ None **\Non-randomized Studies** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up
Author: Haussig, S., et al. Year Published: 2016 Location: University of Leipzig, Germany Journal: *JAMA*	To determine the effect of a cerebral protection device on the number and volume of cerebral lesions in patients undergoing TAVI.	**Size:** 100 (50 control and 50 intervention) **Inclusion Criteria**: Symptomatic patients with severe aortic stenosis considered at increased risk for SAVR as determined by the heart team. **Exclusion Criteria:** Anatomy unsuitable for a safe TAVI, preexisting permanent pacemaker, stroke within the last 12 months, carotid artery	**Type:** RCT **Methods:** Patients were randomly assigned (1:1) to the control or filter group using the Claret Montage Dual Filter System. Follow-up assessments were performed at 2 days and 7 days after TAVI and were identical to the preprocedural tests. In addition to MRI, follow-up included serial neurological and	**Results: Life-threatening hemorrhages occurred in 1 (2%) patient in the filter group and 1 (2%) in the control group.**	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U

		stenosis of more than 70%, significant stenosis of the right subclavian artery or the brachiocephalic trunk, expected nonadherence to follow-up visits, participation in another clinical study, severe renal failure or pregnancy	neurocognitive assessments, New York Heart Association classification, echocardiography, and documentation of adverse events and study end points. The primary end point was the numerical reduction in positive postprocedure DWMRI brain lesions relative to baseline and 2 days following TAVI in potentially protected territories. Only new lesions that were visible at 2 days, 7 days, or both but not present in the baseline scans were analyzed. Secondary end points included serial volumetric and numerical reductions in positive postprocedure DWMRI-perfused brain lesions at 2 and 7 days, as well as the results of serial neurological and neurocognitive assessments.		☒ Difference in important prognostic factors at baseline

References:

1. Haussig, S., et al. (2016). "Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial." JAMA **316**(6): 592-601.
2. Ndunda, P. M., et al. (2019). "Clinical outcomes of sentinel cerebral protection system use during transcatheter aortic valve replacement: A systematic review and meta-analysis." Cardiovasc Revasc Med.
3. Seeger, J., et al. (2017). "Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement Significantly Reduces Death and Stroke Compared With Unprotected Procedures." **10**(22): 2297-2303.

BODY OF EVIDENCE APPRAISAL TABLE FOR:

Population: Symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic

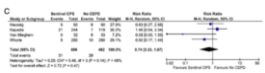
Modality: Sentinel Cerebral Protection System (Sentinel CPS)

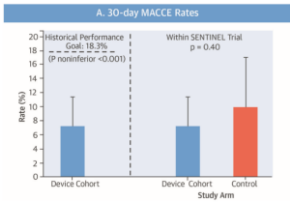
Outcome: Major Vascular Complications

Quality (certainty) of evidence for: (outcome)

☐ High
☐ Moderate
☐ Low
☒ Very Low

Risk of Bias across studies: ☒ High ☐ Medium ☐ Low	**Lower Quality Rating if:** ☒ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	**Other Considerations:** Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Ndunda, P.M., et al. Year Published: 2019 Location: University of Kansas School of Medicine Journal: *Cardiovasc Revasc Med.*	To compare the clinical outcomes following transcatheter aortic valve replacement (TAVR) with and without the use of the Sentinel Cerebral Protection System (Sentinel CPS)	**Size:** 4 studies (3 RCTs and 1 cohort study). These studies had a total of 1330 patients with 606 assigned to the Sentinel CPS arms and 724 to the arms without cerebral embolic protection devices (CEPD) **Inclusion Criteria**: Studies were included if they were randomized controlled trials (RCTs) or controlled observational studies and compared TAVR using the Sentinel CPS versus TAVR without any embolic protection device. All studies included symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic valve replacement as determined by the heart team. **Exclusion Criteria:** Individual studies specifically stated that they excluded patients with the listed characteristics as follows: an unsuitable anatomy for TAVR (Haussing, Van Mieghem, Seeger, Kapadia),	**Type:** Systematic review with meta-analysis	**Results: No significant difference was found between both groups in major vascular complications [5.1% vs 6%; RR 0.74 (0.33, 1.67) I^2 = 45%].**  **Due to the need for separate vascular access site for the Sentinel CPS and use of extra iodinated contrast, theoretically, a higher risk of vascular access and contrast-related complications would be expected in the intervention group. However, there were relatively low rates of major vascular complications in both group. Even though there was no significant difference between the two groups, the studies may not have been powered to detect differences in the endpoints.*	**Study Limitations:** ☐ None ***Systematic Review*** ☐ Review did not address focused clinical question ☐ Search was not detailed or exhaustive ☒ Quality of the studies was not appraised ☐ Inappropriate pooled analysis

		permanent pacemaker or automated internal cardiac defibrillator (Haussig, Van Miegham), history of prior stroke (Haussig, Van Mieghem), carotid artery stenosis >70%, Stage IV – V chronic kidney disease, pregnancy (Haussig), inability to undergo MRI (Kapadia), patients undergoing valve-in-valve procedures (Seeger) and dementia (Van Mieghem).			
Appraisal of studies included in meta-analysis					
Author: Kapadia, S.R., et al. Year Published: 2017 Location: Cleveland Clinic Journal: *Journal of the American College of Cardiology* *Note: The study population was older (median age 83.4 years), the majority (52.1%) consisted of female patients, the median Society of Thoracic Surgeons score was 6.0%, and frequent comorbidities included atrial fibrillation (31.7%) and previous strokes (5.8%).* *Delivery and Retrieval of both filters were successful in 94.4% of patients. In the device arm vs the control arm, there was an increase in total procedure time (P = 0.01) and fluoroscopy time (P = 0.007).*	To evaluate the safety and efficacy of TCEP during TAVR. Methods Nineteen centers randomized patients undergoing TAVR to a safety arm, device imaging, and control imaging.	**Size:** 363 patients undergoing TAVR to a safety arm (n = 123), device imaging (n = 121), and control imaging (n = 119). **Inclusion Criteria**: Patients with severe symptomatic aortic stenosis and planned TAVR who were at high surgical risk. **Exclusion Criteria:** Known contraindications for right radial or brachial artery access and inability to undergo MRI brain evaluation for any reason.	**Type:** RCT **Methods:** Patients undergoing TAVR at 17 centers in US and Germany were prospectively randomized 1:1:1 into a safety arm (TCEP only) and 2 imaging cohorts, in which patients were randomly treated with TCEP (device arm) or without TCEP (control arm). 4 different TAVR devices were used in the trial. Blinded diffusion-weighted MRI and neurocognitive function assessments were performed in the device and control arms. Particulate debris from the extracted filters was studied in the device arms. All patients underwent rigorous neurological evaluations post-TAVR at 30 and 90 days. The primary safety endpoint consisted of major adverse cardiac and cerebrovascular events (MACCE) at 30 days, and the primary efficacy endpoint was reduction in new lesion volume in protected brain territories on magnetic	**Results:** **The rate of MACCE (7.3%) was noninferior to the performance goal (18.3%, pnoninferior < 0.001) and not statistically different from that of the control group (9.9%; p = 0.41).** 	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☒ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☒ Difference in important prognostic factors at baseline

			resonance imaging scans at 2 to 7 days.		
Author: Seeger, J., et al. Year Published: 2017 Location: University of Ulm, Germany Journal: *JACC: Cardiovascular Interventions*	To evaluate the impact of cerebral embolic protection on stroke-free survival in patients undergoing transcatheter aortic valve replacement (TAVR)	**Size:** 802 consecutive patients. 280 with Sentinel cerebral embolic protection device, 522 in patients without cerebral embolic protection **Inclusion Criteria**: Patients undergoing TAVR	**Type:** Prospective cohort study **Intervention**: Enrolled patients underwent diagnostic evaluation with routine laboratory testing, medical history with current medication, Society of Thoracic Surgeons (STS) score, New York Heart Association functional class, electrocardiography, echocardiography, heart catheterization, and multislice computed tomography. Neurological follow-up was done within 7 days post-procedure. The primary endpoint was a composite of all-cause mortality or all-stroke according to Valve Academic Research Consortium-2 criteria within 7 days.	**Results:** Major vascular complications occurred less frequently with 5 (1.8%) in the protected group compared with 10 (3.6%) in the unprotected group (OR 0.64 [0.23-1.78]; p = 0.19.	**Study Limitations:** ☐ None **\Non-randomized Studies** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☐ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up
Author: Haussig, S., et al. Year Published: 2016 Location: University of Leipzig, Germany Journal: *JAMA*	To determine the effect of a cerebral protection device on the number and volume of cerebral lesions in patients undergoing TAVI.	**Size:** 100 (50 control and 50 intervention) **Inclusion Criteria**: Symptomatic patients with severe aortic stenosis considered at increased risk for SAVR as determined by the heart team. **Exclusion Criteria:** Anatomy unsuitable for a safe TAVI, preexisting permanent pacemaker, stroke within the last 12 months, carotid artery stenosis of more than 70%, significant stenosis of the right subclavian artery or the brachiocephalic trunk, expected nonadherence to	**Type:** RCT **Methods:** Patients were randomly assigned (1:1) to the control or filter group using the Claret Montage Dual Filter System. Follow-up assessments were performed at 2 days and 7 days after TAVI and were identical to the preprocedural tests. In addition to MRI, follow-up included serial neurological and neurocognitive assessments, New York Heart Association classification, echocardiography, and	**Results: Major vascular complications occurred in 5 (10%) patients in the filter group and 6 (12%) patients in the control group.**	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☐ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☐ Large losses to F/U ☒ Difference in important prognostic factors at baseline

		follow-up visits, participation in another clinical study, severe renal failure or pregnancy	documentation of adverse events and study end points. The primary end point was the numerical reduction in positive postprocedure DWMRI brain lesions relative to baseline and 2 days following TAVI in potentially protected territories. Only new lesions that were visible at 2 days, 7 days, or both but not present in the baseline scans were analyzed. Secondary end points included serial volumetric and numerical reductions in positive postprocedure DWMRI-perfused brain lesions at 2 and 7 days, as well as the results of serial neurological and neurocognitive assessments.		

References:

1. Haussig, S., et al. (2016). "Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial." JAMA **316**(6): 592-601.
2. Kapadia, S. R., et al. (2017). "Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement." Journal of the American College of Cardiology **69**(4): 367-377.
3. Ndunda, P. M., et al. (2019). "Clinical outcomes of sentinel cerebral protection system use during transcatheter aortic valve replacement: A systematic review and meta-analysis." Cardiovasc Revasc Med.
4. Seeger, J., et al. (2017). "Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement Significantly Reduces Death and Stroke Compared With Unprotected Procedures." **10**(22): 2297-2303.

BODY OF EVIDENCE APPRAISAL TABLE FOR:

Population: Symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic

Modality: Sentinel Cerebral Protection System (Sentinel CPS)

Outcome: Neurocognitive function

Quality (certainty) of evidence for: (outcome)

☐ High
☐ Moderate
☐ Low
☒ Very Low

Risk of Bias across studies: ☐ High ☒ Medium ☐ Low	**Lower Quality Rating if:** ☒ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	**Other Considerations:** Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	**Aim of Study**	**Patient Population**	**Study Methods**	**Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)**	**Design Limitations**
Author: Kapadia, S.R., et al. Year Published: 2017 Location: Cleveland Clinic Journal: *Journal of the American College of Cardiology* *Note: The study population was older (median age 83.4 years), the majority (52.1%) consisted of female patients, the median Society of Thoracic Surgeons score was 6.0%, and frequent comorbidities included atrial fibrillation (31.7%) and previous strokes (5.8%).* *Delivery and Retrieval of both filters were successful in 94.4% of patients. In the device arm vs the control arm, there was an increase in total procedure time (P = 0.01) and fluoroscopy time (P = 0.007).*	To evaluate the safety and efficacy of TCEP during TAVR. Methods Nineteen centers randomized patients undergoing TAVR to a safety arm, device imaging, and control imaging.	**Size:** 363 patients undergoing TAVR to a safety arm (n = 123), device imaging (n = 121), and control imaging (n = 119). **Inclusion Criteria**: Patients with severe symptomatic aortic stenosis and planned TAVR who were at high surgical risk. **Exclusion Criteria:** Known contraindications for right radial or brachial artery access and inability to undergo MRI brain evaluation for any reason.	**Type:** RCT **Methods:** Patients undergoing TAVR at 17 centers in US and Germany were prospectively randomized 1:1:1 into a safety arm (TCEP only) and 2 imaging cohorts, in which patients were randomly treated with TCEP (device arm) or without TCEP (control arm). 4 different TAVR devices were used in the trial. Blinded diffusion-weighted MRI and neurocognitive function assessments were performed in the device and control arms. Particulate debris from the extracted filters was studied in the device arms. All patients underwent rigorous neurological evaluations post-TAVR at 30 and 90 days. The primary safety endpoint consisted of major adverse cardiac and cerebrovascular events (MACCE) at 30 days, and the primary efficacy endpoint was reduction in new lesion volume in protected brain territories on magnetic	**Results:** **Neurocognitive function was similar in control subjects and patients with devices, but there was a correlation between lesion volume and neurocognitive decline (p = 0.0022).**	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☒ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☒ Difference in important prognostic factors at baseline

			resonance imaging scans at 2 to 7 days.		
Author: Van Mieghem, N.M., et al. Year Published: 2016 Location: Erasmus Medical Center, the Netherlands Journal: *Euro Intervention*	To determine whether use of the filter-based Sentinel™ Cerebral Protection System (CPS) during transcatheter aortic valve implantation (TAVI) can affect the early incidence of new brain lesions, as assessed by diffusion-weighted magnetic resonance imaging (DW-MRI), and neurocognitive performance	**Size:** 65 patients **Inclusion Criteria**: Patients deemed at high risk for SAVR by the Heart Team **Exclusion Criteria**: Presence of a permanent pacemaker or automated internal cardiac defibrillator (AICD) at baseline, a history of prior stroke with sequelae and dementia.	**Type:** RCT **Methods:** Patients were randomized 1:1 to transfemoral TAVI with or without the Sentinel CPS. Patients underwent DW-MRI and extensive neurological examination, including neurocognitive testing was completed in 57% and 80%, respectively.	**Results:** **Neurocognitive deterioration was present in 4% of patients with Sentinel CPS vs. 27% of patients without (p=0.017).**	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☒ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline

References:

1. Kapadia, S. R., et al. (2017). "Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement." Journal of the American College of Cardiology **69**(4): 367-377.
2. Van Mieghem, N.M., et al. (2016). "Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial." EuroIntervention **12**(4): 499-507.

BODY OF EVIDENCE APPRAISAL TABLE FOR:

Population: Symptomatic patients with severe aortic stenosis who were at high risk for surgical aortic
Modality: Sentinel Cerebral Protection System (Sentinel CPS)
Outcome: Debris

Quality (certainty) of evidence for: (outcome)
☐ High
☐ Moderate
☒ Low
☐ Very Low

Risk of Bias across studies:	**Lower Quality Rating if:**	**Other Considerations:**
☐ High ☒ Medium ☐ Low	☒ Studies inconsistent (*wide variation of treatment effect across studies, population, interventions, or outcomes varied*) – ***Methods for tracking outcomes varied*** ☐ Studies are indirect (*PICO question is quite different from the available evidence in regard to population, intervention, comparison, or outcome)* ☒ Studies are imprecise (*when studies include few patients and few events, and thus have wide confidence intervals, and the results are uncertain)*	Lower Quality Rating if: ☐ Publication Bias (*e.g. pharmaceutical company sponsors study on effectiveness of drug only small, positive studies found)* Increase Quality Rating if: ☐ Large effect ☐ Dose-response gradient ☐ Plausible confounders or other biases increase certainty of effect

Study Acronym; Author; Year Published; Location	Aim of Study	Patient Population	Study Methods	Endpoint Results / Outcome (Absolute Event Rates, P values; OR or RR; & 95% CI)	Design Limitations
Author: Seeger, J., et al. Year Published: 2018 Location: University of Ulm, Germany Journal: *JACC Cardivasc Interv*	To evaluate the debris captured by the Claret Sentinel cerebral embolic dual-filter protection device during transfemoral transcatheter aortic valve replacement (TAVR) with different valve types	**Size:** 100 patients, **Inclusion Criteria**: Patients undergoing protected TAVR for symptomatic severe native aortic stenosis	**Type:** Prospective Study **Methods:** The filers of consecutive patients were collected and captured debris was analyzed by histopathology and histomorphometry. Three valve types were implanted: the balloon-expanded Edwards SAPIEN 3 (n=42), the self-expanded Medtronic Evolut R (n=35), and the mechanically implantable Boston Scientific Lotus (n=23).	**Results:** With the balloon-expandable valve, there were significantly more patients with large debris measuring >/= 1,000 um. The number of particles in the proximal filter was significantly power with the Lotus (89.8 +/- 106.3) compared with the Evolut R (187.3 +/- 176.9) and Edwards SAPIEN 3 (172.3 +/- 133.5) valves (*P* = 0.035). Total tissue area in the proximal filter was significantly smaller for the Lotus compared with the other 2 valve types (7.1 +/- 6.3, 20.1 +/- 19.0, and 21.3 +/- 15.1 mm^2; *P* = 0.0014). In contrast, for the distal filter, there was no differences with respect to valve type for total tissue area, particle size, and number of particles.	**Study Limitations:** ☐ None **Non-randomized Studies** ☒ Failure to develop and apply appropriate eligibility criteria ☐ Flawed measurement of both exposure and outcome ☒ Failure to adequately control confounding ☐ Incomplete or inadequately short follow-up
Author: Kapadia, S.R., et al. Year Published: 2017 Location: Cleveland Clinic Journal: *Journal of the American College of Cardiology* *Note: The study population was older (median age 83.4 years), the majority (52.1%) consisted of female patients, the median Society of Thoracic Surgeons score was 6.0%, and frequent comorbidities included atrial fibrillation (31.7%) and previous strokes (5.8%).* *Delivery and Retrieval of both filters were successful in 94.4% of patients. In the device arm vs*	To evaluate the safety and efficacy of TCEP during TAVR. Methods Nineteen centers randomized patients undergoing TAVR to a safety arm, device imaging, and control imaging.	**Size:** 363 patients undergoing TAVR to a safety arm (n = 123), device imaging (n = 121), and control imaging (n = 119). **Inclusion Criteria**: Patients with severe symptomatic aortic stenosis and planned TAVR who were at high surgical risk. **Exclusion Criteria:** Known contraindications for right radial or brachial artery access and inability to undergo MRI brain evaluation for any reason.	**Type:** RCT **Methods:** Patients undergoing TAVR at 17 centers in US and Germany were prospectively randomized 1:1:1 into a safety arm (TCEP only) and 2 imaging cohorts, in which patients were randomly treated with TCEP (device arm) or without TCEP (control arm). 4 different TAVR devices were used in the trial. Blinded diffusion-weighted MRI and neurocognitive function assessments were performed in the device and control arms. Particulate debris from the extracted filters was studied in the device arms. All	**Results:** **Debris found within filters in 99% of patients included thrombus, calcification, valve tissue, artery wall, and foreign material. Conclusions TCEP was safe, captured embolic debris in 99% of patients, and did not change neurocognitive function.**	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☒ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☒ Difference in important prognostic factors at baseline

the control arm, there was an increase in total procedure time (P = 0.01) and fluoroscopy time (P = 0.007).			patients underwent rigorous neurological evaluations post-TAVR at 30 and 90 days. The primary safety endpoint consisted of major adverse cardiac and cerebrovascular events (MACCE) at 30 days, and the primary efficacy endpoint was reduction in new lesion volume in protected brain territories on magnetic resonance imaging scans at 2 to 7 days.		
Author: Van Mieghem, N.M., et al. Year Published: 2016 Location: Erasmus Medical Center, the Netherlands Journal: *Euro Intervention*	To determine whether use of the filter-based Sentinel™ Cerebral Protection System (CPS) during transcatheter aortic valve implantation (TAVI) can affect the early incidence of new brain lesions, as assessed by diffusion-weighted magnetic resonance imaging (DW-MRI), and neurocognitive performance	**Size:** 65 patients **Inclusion Criteria**: Patients deemed at high risk for SAVR by the Heart Team **Exclusion Criteria**: Presence of a permanent pacemaker or automated internal cardiac defibrillator (AICD) at baseline, a history of prior stroke with sequelae and dementia.	**Type:** RCT **Methods:** Patients were randomized 1:1 to transfemoral TAVI with or without the Sentinel CPS. Patients underwent DW-MRI and extensive neurological examination, including neurocognitive testing was completed in 57% and 80%, respectively.	**Results:** **The filters captured debris in all patients with Sentinel CPS protection.**	**Study Limitations:** ☐ None ***RCTs*** ☐ Lack of blinding ☐ Lack of allocation concealment ☒ Unknown allocation concealment ☐ Stopped early for benefit ☐ Incorrect analysis of ITT ☐ Selective reporting of measures (e.g., no effect outcome) ☒ Large losses to F/U ☐ Difference in important prognostic factors at baseline

References:

1. Kapadia, S. R., et al. (2017). "Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement." Journal of the American College of Cardiology **69**(4): 367-377.
2. Seeger, J., et al. (2018). "Significant Differences in Debris Captured by the Sentinel Dual-Filter Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement Among Different Valve Types." JACC Cardiovasc Interv **11**(17): 1683-1693.
3. Van Mieghem, N.M., et al. (2016). "Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial." EuroIntervention **12**(4): 499-507.

REFERENCES:

1. Testa, L., et al. (2018). "Cerebral Protection During Transcatheter Aortic Valve Implantation: An Updated Systematic Review and Meta‐Analysis." **7**(10): e008463.
2. Leon, M. B., et al. (2010). "Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery." New England Journal of Medicine **363**(17): 1597-1607.
3. Smith, C. R., et al. (2011). "Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients." **364**(23): 2187-2198.
4. Adams, D. H., et al. (2014). "Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis." **370**(19): 1790-1798.
5. Popma, J. J., et al. (2014). "Transcatheter Aortic Valve Replacement Using a Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis at Extreme Risk for Surgery." Journal of the American College of Cardiology **63**(19): 1972-1981.
6. Leon, M. B., et al. (2016). "Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients." **374**(17): 1609-1620.
7. Reardon, M. J., et al. (2017). "Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients." New England Journal of Medicine **376**(14): 1321-1331.
8. Kroon, H. G., et al. (2019). "Early Clinical Impact of Cerebral Embolic Protection in Patients Undergoing Transcatheter Aortic Valve Replacement." **12**(6): e007605.
9. Kapadia, S. R., et al. (2017). "Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement." Journal of the American College of Cardiology **69**(4): 367-377.
10. Seeger, J., et al. (2019). "Rate of peri-procedural stroke observed with cerebral embolic protection during transcatheter aortic valve replacement: a patient-level propensity-matched analysis." Eur Heart J **40**(17): 1334-1340.
11. Thourani, V. H., et al. (2016). "Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis." Lancet **387**(10034): 2218-2225.
12. Eggebrecht, E., et al. (2012). "Risk of stroke after transcatheter aortic valve implantation (TAVI): a meta-analysis of 10,037 published patients." EuroIntervention **8**(1): 129-138.
13. Ndunda, P. M., et al. (2019). "Clinical outcomes of sentinel cerebral protection system use during transcatheter aortic valve replacement: A systematic review and meta-analysis." Cardiovasc Revasc Med.
14. Vlastra, W., et al. (2018). "Cerebral protection devices during transcatheter aortic valve implantation." Trends Cardiovasc Med **28**(6): 412-418.
15. Salaun, E., et al. (2020). "Transcatheter Aortic Valve Replacement: Procedure and Outcomes." Cardiology Clinics **38**(1): 115-128.

16. Huded, C. P., et al. (2019). "Association Between Transcatheter Aortic Valve Replacement and Early Postprocedural Stroke." JAMA **321**(23): 2306-2315.
17. Mack, M. J., et al. (2019). "Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients." **380**(18): 1695-1705.
18. Giustino, G., et al. (2017). "Cerebral Embolic Protection During TAVR: A Clinical Event Meta-Analysis." J Am Coll Cardiol **69**(4): 465-466.
19. U.S. Food and Drug Administration. https://www.fda.gov/media/102984/download. Accessed December 26th, 2019.
20. Van Gils, L., et al. (2018). "Complete filter-based cerebral embolic protection with transcatheter aortic valve replacement." Catheterization & Cardiovascular Interventions **91**(4): 790-797.
21. Haussig, S., et al. (2016). "Effect of a Cerebral Protection Device on Brain Lesions Following Transcatheter Aortic Valve Implantation in Patients With Severe Aortic Stenosis: The CLEAN-TAVI Randomized Clinical Trial." JAMA **316**(6): 592-601.
22. Seeger, J., et al. (2017). "Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement Significantly Reduces Death and Stroke Compared With Unprotected Procedures." **10**(22): 2297-2303.
23. Van Mieghem, N.M., et al. (2016). "Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial." EuroIntervention **12**(4): 499-507.

Appendix A. GRADE criteria for rating a body of evidence on an intervention

Developed by the GRADE Working Group

Grades and interpretations:

High: Further research is very unlikely to change our confidence in the estimate of effect. Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low: Any estimate of effect is very uncertain.

Type of evidence and starting level

Randomized trial–high Observational study–low Any other evidence–very low

Criteria for increasing or decreasing level

Reductions Study quality has serious (–1) or very serious (–2) problems Important inconsistency in evidence (–1) Directness is somewhat (–1) or seriously (–2) uncertain Sparse or imprecise data (–1) Reporting bias highly probable (–1) **Increases** Evidence of association† strong (+1) or very strong (+2) †Strong association defined as significant relative risk (factor of 2) based on consistent evidence from two or more studies with no plausible confounders Very strong association defined as significant relative risk (factor of 5) based on direct evidence with no threats to validity.

Appendix B. Trustworthy Guideline rating scale

The University of Pennsylvania's Center for Evidence-Based Practice Trustworthy Guideline rating scale is based on the Institute of Medicine's "Standards for Developing Trustworthy Clinical Practice Guidelines" (IOM), as well as a review of the AGREE Enterprise and Guidelines International Network domains.

The purpose of this scale is to focus on the weaknesses of a guideline that may reduce the trust a clinical user can have in the guideline, and distinguish weaknesses in documentation (e.g. guide-line does not have a documented updating process) from weaknesses in the guidance itself (e.g. recommendations are outdated). Current quality scales like AGREE emphasize documentation. They are important checklists for developers of new guidelines, but are less useful for grading existing guidelines. These scales also are harder for clinicians and other persons who are not methodology experts to apply, and their length discourages their use outside formal technology assessment reports. This new scale is brief, balanced, and easy and consistent to apply.

We do not attempt to convert the results of this assessment into a numeric score. Instead we present a table listing the guidelines and how they are rated on each standard. This facilitates qualitative understanding by the reader, who can see for what areas the guideline base as a whole is weak or strong as well as which guidelines are weaker or stronger.

1. Transparency

A	Guideline development methods are fully disclosed.
B	Guideline development methods are partially disclosed.
C	Guideline development methods are not disclosed.

The grader must refer to any cited methods supplements or other supporting material when evaluating the guideline. Methods should include:

Who wrote the initial draft
How the committee voted on or otherwise approved recommendations

Evidence review, external review and methods used for updating are not addressed in this standard.

2. Conflict of interest

A	Funding of the guideline project is disclosed, disclosures are made for each individual panelist, and financial or other conflicts do not apply to key authors of the guideline or to more than 1 in 10 panel members).
B	Guideline states that there were no conflicts (or fewer than 1 in 10 panel members), but does not disclose funding source.
C	Lead author, senior author, or guideline panel members (at least 1 in 10) have conflict of interest, or guideline project was funded by industry sponsor with no assurance of independence.

NR	Guideline does not report on potential conflict of interests.

For purposes of this checklist, conflicts of interest include employment by, consulting for, or holding stock in companies doing business in fields affected by the guideline, as well as related financial conflicts. This definition should not be considered exclusive. As much as anything, this is a surrogate marker for thorough reporting, since it may be assumed that guideline projects are funded by the sponsoring organization and many authors think it unnecessary to report a non-conflict.

3. Guideline development group

A	Guideline development group includes 1) methodological experts and clinicians and 2) representatives of multiple specialties.
B	Guideline development group includes one of the above, but not both.
C	Guideline developers all from one specialty or organization, and no methodologists.
NR	Affiliations of guideline developers not reported

The purpose of this standard is to ensure that supporters of competing procedures, or clinicians with no vested interest in utilization of one procedure or another, are involved in development of the guideline. Both AGREE II and IOM call for patient or public involvement: very few guideline panels have done so to date, so this is not necessary for guidelines to be rated A. Involvement of methodologists or HTA specialists in the systematic review is sufficient involvement in the guideline development group for our purposes. In the absence of any description of the guideline group, assume the named authors are the guideline group.

4. Systematic review

A	Guideline includes a systematic review of the evidence or links to a current review.
B	Guideline is based on a review which may or may not meet systematic review criteria.
C	Guideline is not based on a review of the evidence.

In order to qualify as a systematic review, the review must do all of the following:

Describe itself as systematic or report search strategies using multiple databases
Define the scope of the review (including key questions and the applicable population)
Either include quantitative or qualitative synthesis of the data or explain why it is not indicated

Note: this element does not address the quality of the systematic review: simply whether or not it exists. Concerns about quality or bias of the review will be discussed in text, where the analyst will explain whether the weaknesses of the review weaken the validity or reliability of the guideline.

Note: a guideline may be rated B on this domain even if the review on which it is based is not available to us. This potential weakness of the guideline should be discussed in text of the report.

5. Grading the supporting evidence

A	Specific supporting evidence (or lack thereof) for each recommendation is cited and graded
B	Specific supporting evidence (or lack thereof) for each recommendation is cited but the recommendation is not graded.
C	Recommendations are not supported by specific evidence.

To score a B on this domain there should be specific citations to evidence tables or individual references for each relevant recommendation in the guideline, or an indication that no evidence was available. Any standardized grading system is acceptable for purposes of this rating. If a guideline reports that there is no evidence available despite a thorough literature search, it may be scored B on this domain, or even A if evidence for other recommendations is cited and graded.

6. Recommendations

A	Considerations for each recommendation are documented (i.e. benefits and harms of a particular action, and/or strength of the evidence); and recommendations are presented in an actionable form.
B	Either one or the other of the above criteria is met.
C	Neither of the above criteria are met

In order to be actionable, the guideline should specify the specific population to which the guideline applies, the specific intervention in question, and the circumstances under which it should be carried out (or not carried out). The language used in the recommendations should also be consistent with the strength of the recommendation (e.g. directive and active language like “should” or “should not” for strong recommendations, and passive language like “consider” for weak recommendations). A figure or algorithm is considered actionable as long as it is complete enough to incorporate all the applicable patients and interventions. Please see the forthcoming NICE manual (24) for a good discussion of actionability in guidelines.

7. External review

A	Guideline was made available to external groups for review.
B	Guideline was reviewed by members of the sponsoring body only.
C	Guideline was not externally reviewed.
NR	No external review process is described.

8. Updating and currency of guideline

A	Guideline is current and an expiration date or update process is specified.
B	Guideline is current but no expiration date or update process is specified.
C	Guideline is outdated.

A guideline is considered current if it is within the developers' stated validity period, or if no period or expiration data is stated, the guideline was published in the past three years (NOTE: the specific period may be changed at the analyst's discretion, based on whether the technology is mature and whether there is a significant amount of recent evidence). A guideline must address new evidence when it is updated. A guideline which is simply re-endorsed by the panel without searching for new evidence must be considered outdated

Appendix C. Search Strategy

Database: Ovid MEDLINE(R) without Revisions <1996 to December 2019>
Search Strategy:

Keywords:

1. Cerebral protection
2. Sentinel
3. Embolic protection filter
4. TAVI
5. TAVR