NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of percutaneous insertion of a cerebral protection device to prevent cerebral embolism during TAVI

Transcatheter aortic valve implantation (TAVI) places a new valve inside a faulty valve in the heart. It is inserted through a tube (catheter), by way of a large blood vessel (artery) at the top of the leg or in the arm. This can dislodge fatty deposits that may block arteries supplying blood to the brain (a cerebral embolism), causing a stroke. In this procedure, before the new valve is inserted, a cerebral protection device is placed inside an artery near the heart. It filters the debris from the blood or deflects it away from the brain. The device is removed at the end of the TAVI procedure. The aim is to reduce the risk of stroke.

Contents

Introduction

The National Institute for Health and Care Excellence (NICE) prepared this interventional procedure overview to help members of the interventional procedures advisory committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in September 2018 and updated in January 2019.

Procedure name

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

Specialist societies

- Royal College of Physicians
- Royal College of Physicians and Surgeons of Glasgow
- Royal College of Physicians of Edinburgh
- Society for Cardiothoracic Surgery in Great Britain and Ireland
- British Cardiovascular Intervention Society
- British Society of Echocardiography
- British Cardiovascular Society.

Description of the procedure

Indications

Transcatheter aortic valve implantation (TAVI) aims to provide a less invasive alternative to open cardiac surgery for treating aortic stenosis, avoiding the need for sternotomy and cardiopulmonary bypass. However debris may be dislodged during the TAVI procedure. This can enter the cerebral circulation and embolise, causing cerebral ischaemic events including a stroke.

What the procedure involves

Percutaneous insertion of a cerebral protection device aims to prevent debris dislodged during TAVI from passing into the cerebral circulation. The aim is to reduce the risk of cerebral ischaemic events including a stroke.

During the TAVI procedure, before the valve is inserted, a cerebral protection device is inserted percutaneously through the radial or femoral artery. Depending on the type of device used, it is placed into the aortic arch or into the brachiocephalic (innominate) and left common carotid arteries. It is deployed to protect the ostia of the brachiocephalic (innominate) artery and the left common carotid artery. It may also protect the left subclavian artery, depending on the type of device used. It works either by filtering dislodged debris from the blood, or by deflecting dislodged debris away from the cerebral circulation to the systemic circulation. The device is removed at the end of the TAVI procedure.

The evidence review identified 3 types of cerebral protection devices. One is a deflector system that covers all 3 main branches of the aortic arch. The 2 other types cover the brachiocephalic trunk and the left common carotid artery; 1 is a filter system, the other is a deflector system.

Efficacy summary

Peri-procedural stroke

In a systematic review and meta-analysis of 1225 patients having TAVI (570 patients having cerebral protection with all types of device, and 655 patients without cerebral protection) there was no statistically significant difference between groups for stroke occurring within 72 hours of the procedure: risk ratio (RR) 0.53, 95% confidence interval (CI) 0.27 to 1.07, p=0.08.[1]

In a non-randomised comparative study of 560 patients having cerebral protection with a dual filter device (n=280) or no cerebral protection (n=280) during TAVI, the stroke rate was significantly lower with the use of the protection

device compared with unprotected procedures within 48 hours (3.6% compared with 1.1%; p=0.03; odds ratio (OR) 0.29; 95% CI 0.10 to 0.93; number needed to treat [NNT] 31).[7]

In a prospective case series of 40 patients having cerebral protection with a dual filter device during TAVI, 1 major stroke happened 4 hours after the procedure.[8]

In a pooled analysis combining and comparing 1,066 propensity-matched patients from 3 studies (the SENTINEL US IDE trial, the CLEAN-TAVI and SENTINEL-Ulm studies), the all-stroke rate within 72 hours was statistically significantly lower in the group with cerebral protection (1.88% [10/533]) compared with the group without cerebral protection (5.44% [29/533]; OR 0.35, 95% CI 0.17 to 0.72, relative risk reduction 65%, absolute risk reduction 3.54%; p=0.0028). The disabling stroke rate within 72 hours was statistically significantly lower in the group with cerebral protection (0.38% [2/533]) compared with the group without cerebral protection (2.44% [13/533]; OR 0.14, 95% CI 0.03 to 0.66, p=0.0045). There was no statistically significant difference between groups for the non-disabling stroke rate within 72 hours: 1.50% (8/533) compared with 3.00% (16/533), OR 0.53, 95% CI 0.23 to 1.24, p=0.13.[9]

Stroke within 1 week (or in-hospital)

In the systematic review and meta-analysis of 1225 patients, the risk of strokes within the first week of TAVI was statistically significantly lower in the cerebral protection group compared with the control group (RR 0.56, 95% CI 0.33 to 0.96).[1]

All-stroke rates before hospital discharge were not statistically significantly different between groups in an RCT of 85 patients having TAVI (46 patients having cerebral protection using an embolic deflector covering the 3 main branches of the aorta, and 39 patients without cerebral protection): 2% (1/46) in the cerebral protection group compared with 5% (2/39) in the control group.[5]

Disabling and non-disabling stroke rates at 7 days were statistically significantly lower in the cerebral protection group compared with the control group in the non-randomised comparative study of 560 patients having cerebral protection with a dual filter device (n=280) or no cerebral protection (n=280) during TAVI: 1% (4/280) compared with 5% (13/280), odds ratio (OR) 0.29, 95% CI 0.10 to 0.93, p=0.03. The rates of disabling strokes only were statistically significantly different between groups (<1% [1/280] compared with 3% [9/280], p=0.01) but the rates of non-disabling strokes were similar between groups (1% [3/280] compared with 1% [4/280], p=0.70). [7]

Stroke at 30 days

In the systematic review and meta-analysis of 1225 patients, there was no statistically significant difference between groups for stroke at 30 days (RR 0.69, 95% CI 0.38 to 1.26).[1]

In a systematic review and meta-analysis of 1170 patients having TAVI (865 patients having cerebral protection with all types of device, and 305 patients without cerebral protection) there was no statistically significant difference between groups for clinically evident stroke at 30 days (RR 0.70, 95% CI 0.38 to 1.29; p=0.26). The stroke rate within 30 days of TAVI was 4% in the cerebral protection group (31/843, 15 studies) compared with 6% in the control group (18/296, 7 studies).[2]

In an RCT of 363 patients having TAVI (121 patients having cerebral protection with a dual filter device and control imaging, 123 patients having cerebral protection without imaging, and 119 patients without cerebral protection and with control imaging) the rate of stroke at 30 days was not statistically significantly different between the cerebral protection groups (6% [13/231]) and the control group (9% [10/110], p=0.25).[3]

In the RCT of 85 patients, all-stroke rates at 30 days were not statistically significantly different between groups: 4% (2/46) in the cerebral protection group compared with 6% (2/39) in the control group.[5]

In an RCT of 65 patients having TAVI (32 patients having cerebral protection with a dual filter device, and 33 patients without cerebral protection) disabling stroke within 30 days of the procedure was reported in none of the patients in the cerebral protection group and in 7% (2/33) of patients in the control group. Non-disabling stroke was not reported in either group. Stroke causing delirium was reported in 3% (1/32) of patients in the cerebral protection group compared with 15% (5/33) of patients in the control group (RR 0.21, 95% CI 0.02 to 1.77, p=0.150).[6]

In the prospective case series of 40 patients, 1 minor stroke was reported at 30 days and 1 major stroke at 27 days. [8]

Stroke or all-cause mortality at 72-hour follow-up (composite outcome)

In the pooled analysis combining and comparing 1,066 propensity-matched patients from 3 studies, the all-cause mortality or stroke rate within 72 hours was statistically significantly lower in patients with cerebral protection (2.06% [11/533]) compared with patients without cerebral protection (6.00% [32/533]; OR 0.34, 95% CI 0.17 to 0.68, relative risk reduction 66%, absolute risk reduction 3.94%, p=0.0013).[9]

Stroke or all-cause mortality at 7-day follow-up (composite outcome)

In the non-randomised comparative study of 560 patients, mortality or stroke at 7 days was statistically significantly lower in patients with cerebral protection than in the control group: 2% (6/280) compared with 7% (19/280), OR 0.30, 95% CI 0.12 to 0.77, p=0.01).[7]

Stroke or all-cause mortality at 30-day follow-up (composite outcome)

In the systematic review and meta-analysis of 1225 patients, there was no statistically significant difference between groups for stroke or all-cause mortality at 30-day follow-up (RR 0.70, 95% CI 0.40 to 1.21).[1]

Transient ischemic attack (TIA)

In the RCT of 363 patients, the rate of TIA at 30 days was not statistically significantly different between the cerebral protection groups (<1% [1/231]) and the control group (0%; p=1.00).[3]

Neurocognitive function

In the systematic review and meta-analysis of 1170 patients, 3 studies assessed neurocognitive function using the Montreal Cognitive Assessment scale. In the cerebral protection group, 11% to 27% of patients showed worsening neurocognitive function compared with 23% to 33% in the control group. In the same systematic review, 3 studies used the National Institutes of Health Stroke Scale and reported worsening of cognitive function in 0% to 18% of patients in the cerebral protection group, compared with 5% to 23% in the control group. One study using the mini-mental state examination scale found no difference between groups (no further details reported). [2]

In the RCT of 363 patients there was no statistically significant difference in neurocognitive function assessed with an overall composite score between the cerebral protection group and the control group at baseline (mean −0.66 compared with −0.63), at 2 to 7 days after TAVI (−1 compared with −0.81), after 30 days (−0.77 compared with 0.59), and after 90 days (−0.47 compared with −0.34). [3]

In an RCT of 100 patients having TAVI (50 patients having cerebral protection with a dual filter device, and 50 patients without cerebral protection), the number of patients with neurological symptoms indicative of stroke was 5 in each group at 2 and 7 days; all were minor and non-disabling in nature (no further details reported).[4]

In the RCT of 85 patients, 3% of patients in the cerebral protection group compared with 15% of patients in the control group had National Institutes of Health Stroke Scale scores that worsened at hospital discharge (p=0.16). At 30-

day follow-up, the scores had worsened in 4% of patients in the cerebral protection group compared with 5% of patients in the control group. In the same study, 28% of patients in the cerebral protection group compared with 37% of patients in the control group had Montreal Cognitive Assessment scores that worsened at hospital discharge, and at 30 days this was 27% compared with 33%.[5]

In the RCT of 65 patients, the difference in neurocognitive deterioration (worsening of mini-mental state examination [MMSE] score) 5 to 7 days after the procedure was statistically significantly different between groups: 4% (1/28) of patients in the cerebral protection group compared with 27% (6/22) of patients in the control group (p=0.017). The MMSE score increased by 0.25±1.6 in patients who had cerebral protection and decreased by 0.77±2.5 in the control group (p=0.086).[6]

Development of new cerebral lesions

In the systematic review and meta-analysis of 1170 patients, there were no statistically significant differences in new-single, multiple, or total number of lesions between groups. But cerebral protection was associated with a statistically significantly smaller ischemic volume per lesion (standardised mean difference −0.52; 95% CI −0.85 to −0.20; p=0.002) and a smaller total volume of lesions (standardised mean difference −0.23; 95% CI −0.42 to −0.03; p=0.02) compared with the control group.[2]

In the RCT of 363 patients there were no statistically significant differences between groups in the median total new-lesion volumes in protected territories (p=0.33) and in all territories (p=0.81), and in the median number of new lesions in protected territories (p=0.90) and in all territories (p=0.77). [3]

In the RCT of 100 patients the median number of new lesions in potentially protected areas 2 days after the procedure was statistically significantly lower in the cerebral protection group (4.00, interquartile range [IQR] 3.00 to 7.25) compared with the control group (10.00, IQR 6.75 to 17.00; difference 5.00, IQR 2.00 to 8.00, p<0.001. It was still statistically significantly lower after 7 days (p=0.003). In the same study, the median volume of new lesions in potentially protected areas 2 days after the procedure was statistically significantly smaller in the cerebral protection group (242 mm^3, 95% CI 159 mm^3 to 353 mm^3) compared with the control group (527 mm^3, 95% CI 364 mm^3 to 830mm^3), difference 234 mm^3, 95% CI 91mm^3 to 406 mm^3, p=0.001. It was still statistically significantly smaller 7 days after the procedure (p=0.002). The number of new lesions and the volume of new lesions in the entire brain were also statistically significantly lower in the cerebral protection group after 2 days (p=0.002 and p=0.02 respectively) and after 7 days (p=0.002 and p=0.02 respectively). [4]

In the RCT of 85 patients, 21% of patients in the cerebral protection group compared with 12% of patients in the control group were free from new ischaemic brain lesions after the procedure (intention-to-treat population). In the same study, the median single-lesion volume per patient was 30.9 mm^3 in the cerebral protection group compared with 34.8 mm^3 in the control group. At 30 days, 12% (3/26) of patients in the cerebral protection group compared with 9% (2/22) of patients in the control group had new ischaemic lesions (level of significance not reported).[5]

In the RCT of 65 patients, there was no statistically significantly difference between groups in the rate of patients without any new brain lesions overall on MRI 5 to 7 days after the procedure (27% [6/22] compared with 13% [2/15], p=0.31) and in unprotected lobes (32% [7/22] compared with 33% [5/15], p=0.92). There was a statistically significantly difference between groups in the rate of patients without any new brain lesions in protected lobes (55% [12/22] compared with 20% [3/15], p=0.04). There was also a statistically significant difference between groups in the rate of patients with 10 or more new brain lesions on MRI 5 to 7 days after the procedure (0% [0/22] compared with 20% [3/15], p=0.03). The total lesion volume was similar between groups: 95 mm^3 (IQR 10 to 257) compared with 197 mm^3 (IQR 95 to 525), p=0.171.[6]

Safety summary

Mortality

Mortality at 30 days was similar between groups in a systematic review and meta-analysis of 1225 patients having TAVI (570 patients having cerebral protection with all types of devices, and 655 patients without cerebral protection): risk ratio (RR) 0.59, 95% confidence interval (CI) 0.22 to 1.59.[1]

In a systematic review and meta-analysis of 1170 patients having TAVI (865 patients having cerebral protection with all types of device, and 305 patients without cerebral protection), there was no statistically significant difference between groups for 30-day mortality (RR 0.58, 95% CI 0.20 to 1.64; p=0.30). Death occurred in 2% of patients in the cerebral protection group (15/626, 9 studies) compared with 3% of patients in the control group (8/281, 6 studies) within 30 days of TAVI.[2]

Death rate at 30 days was not statistically significantly different between the cerebral protection groups (1% [3/234]) and the control arm (2% [2/111]) in a randomised controlled trial (RCT) of 363 patients having TAVI (121 patients having cerebral protection with a dual filter device and control imaging, 123 patients having cerebral protection without imaging, and 119 patients without cerebral protection and with control imaging); p=0.65.[3]

Mortality rate at 30 days was 0% (0/50) in the cerebral protection group compared with 2% (1/50) in the control group in an RCT of 100 patients having TAVI (50 patients with cerebral protection using a dual filter device, and 50 patients without cerebral protection). [4]

All-cause death rate before hospital discharge and at 30 days were not statistically significantly different between groups in an RCT of 85 patients having TAVI (46 patients having cerebral protection using an embolic deflector that covers the 3 main branches of the aorta, and 39 patients without cerebral protection): 2% [1/46] in the cerebral protection group compared with 5% [2/39] in the control group. The deaths were caused by pneumonia in the cerebral protection group and by aortic ring ruptures in the control group. [5]

Death within 5 days of the procedure was reported in 1 patient in the cerebral protection group and in none of the patients in the control group in an RCT of 65 patients having TAVI (32 patients having cerebral protection with a dual filter device, and 33 patients without cerebral protection). The level of statistical significance was not reported. After 30 days, death rates were 3% (1/32) compared with 10% (3/33): RR 0.36, 95% CI 0.04 to 3.43; p=0.371). After 6 months the rates were 5% (1/32) compared with 17% (4/33): RR 0.27, 95% CI 0.30 to 2.44; p=0.245. [6]

Mortality rates at 7 days were similar between groups in a non-randomised comparative study of 560 patients having TAVI (280 patients having cerebral protection with a dual filter device, and 280 patients with no cerebral protection): less than 1% [2/280] compared with 3% [8/280], odds ratio (OR) 0.25, 95% CI 0.05 to 1.20; p=0.06). [7]

Major adverse cardiac and cerebrovascular events (MACCE)

In the RCT of 363 patients the rate of MACCE (defined as death from any cause, any type of stroke, or stage-3 acute kidney injury [AKI]) in the cerebral protection group (7% [17/234]) was not statistically significantly different from that of the control group (10% [11/111]) at 30 days; p=0.40.[3]

In the RCT of 85 patients, the rate of in-hospital MACCE (defined as all-cause mortality, all stroke, life-threatening or disabling bleeding, stage-2 or stage-3 AKI, or major vascular complications) was similar in both groups: 22% compared with 31%, RR 0.71, 95% CI 0.34 to 1.46; p=0.34. The rates of 30-day MACCE were also similar: 26% compared with 31%, RR 0.83, 95% CI 0.37 to 1.84; p=0.62. [5]

In the non-randomised comparative study of 560 patients the composite outcome (defined as all-cause mortality, all types of stroke or stage-3 AKI) at 7 days was statistically significantly lower in the cerebral protection group compared with the

control group: 2% (7/280) compared with 8% (22/280), OR 0.32, 95% CI 0.14 to 0.77; p=0.01. [7]

Acute kidney injury (AKI)

The risk of AKI after TAVI was similar between groups in the systematic review and meta-analysis of 1225 patients: RR 0.68, 95% CI 0.28 to 1.62. [1]

The rate of stage-3 AKI at 30 days was not statistically significantly different between the cerebral protection groups (<1% [1/231]) and the control arm (0%) in the RCT of 363 patients (p=1.00).[3]

AKI after the procedure was reported in 2% (1/50) of patients in the cerebral protection group compared with 10% (5/50) of patients in the control group in the RCT of 100 patients.[4]

The rates of stage-2 and stage-3 AKI before hospital discharge and at 30 days were not statistically significantly different between the cerebral protection group (2% [1/46]) and the control group (0%) in the RCT of 85 patients.[5]

AKI within 30 days of the procedure was reported in none of the patients in the cerebral protection group and in 1 patient in the control group in the RCT of 65 patients. [6]

AKI (stage 2 or 3) was reported in 1% (3/280) of patients in the cerebral protection group compared with 1% (4/280) of patients in the control group in the non-randomised controlled study of 560 patients (not statistically significant).[7]

Bleeding

There were no statistically significant differences between groups for the risk of major bleeding (RR 0.56, 95% CI 0.26 to 1.18) or life-threatening bleeding (RR 0.54, 95% CI 0.19 to 1.53) after TAVI in the systematic review and meta-analysis of 1225 patients.[1]

Life-threatening haemorrhage during the procedure was reported in 1 patient in the cerebral protection group and 1 patient in the control group in the RCT of 100 patients. [4]

The rates of life-threatening bleeding were similar between groups before hospital discharge (2% [1/46] compared with 5% [2/39]) and after 30 days (4% [2/46] compared with 8% [3/39]) in the RCT of 85 patients.[5]

Any bleeding within 1 day was reported in 32% (10/32) of patients in the cerebral protection group compared with 44% (14/33) of patients in the control group in the RCT of 65 patients (RR 0.74, 95% CI 0.33 to 1.66; p=0.462). Any bleeding

after 1 day was reported in 29% (9/32) of patients compared with 41% (13/33) of patients respectively (RR 0.72, CI 0.31 to 1.67; p=0.438). Life-threatening bleeding within 1 day was not reported in any patients in the cerebral protection group compared with 16% (5/33) of patients in the control group. Life-threatening bleeding after 1 day was reported in 1 patient in the cerebral protection group compared with none of the patients in the control group.[6]

Major bleeding was reported in 1% (4/280) of patients in the cerebral protection group compared with 4% (12/280) of patients in the control group in the non-randomised comparative study of 560 patients (p=0.05).[7]

Vascular complications

There was no statistically significant difference between groups for the risk of major vascular complications (RR 0.80, 95% CI 0.52 to 1.24) after TAVI in the systematic review and meta-analysis of 1225 patients.[1]

There was no statistically significant difference in the major vascular complications rate at 30 days between the cerebral protection groups (9% [21/244]) and the control group (6% [7/119]) in the RCT of 363 patients.[3]

Major vascular complications during the procedure were reported in 10% (5/50) of patients in the cerebral protection group compared with 12% (6/50) of patients in the control group in the RCT of 100 patients.[4]

The rates of major vascular complications were similar between groups before hospital discharge (15% [7/46] compared with 15% [6/39]) and after 30 days (17% [8/46] compared with 21% [8/39]) in the RCT of 85 patients.[5]

Any vascular complication was reported in 39% (12) of patients in the cerebral protection group compared with 59% (19) of patients in the control group in the RCT of 65 patients (RR 0.65, 95% CI 0.32 to 1.34; p=0.246). Major vascular complication was not reported in any patients in the cerebral protection group compared with 19% (6) of patients in the control group.[6]

Major vascular complications were reported in 2% (5/280) of patients in the cerebral protection group compared with 4% (10/280) of patients in the control group in the non-randomised comparative study of 560 patients (not statistically significant).[7]

Dissection of the radial artery was reported in 1 patient, rupture of a minor branch of the radial artery was reported in 1 patient and brachial pseudo-aneurysm was reported in 2 patients in a prospective case series of 40 patients having TAVI with cerebral protection. The dissection of the radial artery was caused by the manipulation of a first-generation device and it had to be treated surgically. The

rupture of a branch of the radial artery also happened with a first-generation device that lacked a guidewire. This led to a minor haematoma that was treated with manual compression without any clinical consequence for the patient during the follow-up period. The brachial pseudo-aneurysms developed after removal of the vascular sheath and mechanical compression of the puncture site. Both were treated surgically. [8]

Coronary obstruction

Coronary obstruction with intervention within 30 days of the procedure was reported in 1 patient in the cerebral protection group compared with none in the control group in the RCT of 85 patients (not statistically significant).[5]

Coronary obstruction was reported in none of the patients in the cerebral protection group compared with 1 patient in the control group in the RCT of 65 patients.[6]

Need for a thoracotomy

Need for a thoracotomy during the procedure was reported in 6% (3/50) of patients in the cerebral protection group compared with none of the patients in the control group in the RCT of 100 patients (p=0.24). None of the thoracotomies appeared to be related to the cerebral protection device. All 3 patients recovered and were alive at 30 days.[4]

Anecdotal and theoretical adverse events

In addition to safety outcomes reported in the literature, specialist advisers are asked about anecdotal adverse events (events which they have heard about) and about theoretical adverse events (events which they think might possibly occur, even if they have never happened). For this procedure, specialist advisers did not list any anecdotal adverse events. They considered that the following were theoretical adverse events: stroke or systemic embolisation induced as a result of introducing the cerebral protection device, vascular injury from access site used for introducing the cerebral protection device, and device fracture.

The evidence assessed

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to percutaneous insertion of a cerebral protection device to prevent cerebral embolism during transcatheter aortic valve implantation. The following databases were searched, covering the period from their start to 16 January 2019:

MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see the literature search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients having TAVI.
Intervention/test	Percutaneous insertion of a cerebral protection device
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the IP overview

This IP overview is based on 2,815 patients from 2 systematic reviews and meta-analyses[1,2], 4 RCTs[3-6], 1 non-randomised comparative study[7], 1 patient-level pooled analysis[9] and 1 case series[8].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) are listed in the appendix.

Table 2 Summary of key efficacy and safety findings on percutaneous insertion of a cerebral protection device to prevent cerebral embolism during TAVI

Study 1 Mohananey D (2018)

Details

Study type	**Systematic review and meta-analysis**
Country	USA
Recruitment period	Literature search up to 01/09/2017.
Study population and number	n=**1225 (570 with a cerebral protection device [CPD], 655 without CPD)** patients from 6 studies (4 RCTs and 2 prospective observational studies) having a TAVI procedure
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: Studies in adult patients undergoing TAVI which compared the outcomes in patients with and without CPD; all valves and access types for TAVI were included; all types of cerebral protection devices; prospective studies and RCT. Exclusion criteria: Case reports and case series; conference abstracts; non-English literature; retrospective studies; studies where a direct comparison was not available between patients undergoing TAVI with and without CPD; studies evaluating pathological (histology related) or imaging endpoints which did not contain enough information to extract data on clinical outcomes.
Technique	The Embrella embolic deflector was used in 1 study, the Triguard cerebral protection device in 1 study and the Claret Sentinel device in 4 studies.
Follow-up	**30 days**
Conflict of interest/source of funding	None

Analysis

Study design issues:

- The PRISMA statement was applied to this study.
- The primary outcome was a composite of all-cause mortality and stroke at 30 days of follow-up. Secondary outcomes included: periprocedural stroke defined as stroke occurring within 72 h of follow-up, stroke within 1 week of follow-up (or in-hospital stroke), stroke at 30 days of follow-up, mortality at 30 days of follow-up, acute kidney injury, major vascular complications, major bleeding, and life-threatening bleeding.
- Categorical dichotomous data were summarized across treatment arms using Mantel-Haenszel risk ratio along with 95% confidence intervals. Heterogeneity of effects was assessed using the Higgins´ I-squared statistic. Fixed effects model was used for all the analyses as heterogeneity was <25% for all the comparisons. Several sensitivity analyses were conducted for each analysis: using the “one-study-removal” method where the effect of removal of each study was studied on the overall effect limiting the analysis to RCTs only. Assessment of bias was done using the Newcastle Ottawa Scale for prospective studies and the Risk of Bias tool provided by Cochrane Collaboration for RCTs. To address publication bias, the visual inspection of funnel plots and the Egger's test were used. Comprehensive Meta-analysis v3.3.070 was used for meta-analysis.

Study population issues: This meta-analysis was done on study-level data and therefore individual patient risk could not be addressed.

Other issues: All the studies were included in the Bagur (2017) systematic review and meta-analysis (study 2) except the Seeger (2017) prospective observational study.

Key efficacy and safety findings

Efficacy
Number of patients analysed: **1225 (570 with CPD, compared with 655 without CPD)** **Stroke or all-cause mortality at 30 days of follow-up** There was no statistically significant difference between patients with and without CPD: RR 0.70 (95% CI 0.40 to 1.21). Analysis of only randomised trials did not change the overall effect. **Peri-procedural stroke** There was no statistically significant difference between groups for peri-procedural strokes: RR 0.53 (95% CI 0.27 to 1.07), p=0.08. While this effect did not change with analysis of only RCTs (p = 0.07), sensitivity analysis using the "one-study-removal" method revealed that removal of study by Haussig et al. moves the overall effect in favour of CPD [RR 0.37 (0.15–0.90)]. **Stroke within 1 week (or in-hospital)** Within 1 week of follow-up, the risk of strokes was statistically significantly lower in the CPD group: RR 0.56 (95% CI 0.33 to 0.96). While the overall risk remains lower, this effect loses significance if only RCTs are considered. Also, sensitivity analysis reveals that removal studies by Seeger et al. or Kapadia et al. makes the overall stroke incidence comparable between the 2 groups. **Stroke at 30 days** At 30 days, incidence of stroke was comparable between the 2 groups [RR 0.69 (95% CI 0.38 to 1.26)]. Analysis of only RCTs did not change the overall effect for these outcomes.
Safety
Mortality at 30 days and acute kidney injury There was no statistically significant difference between groups for mortality at 30 days [RR 0.59 (95% CI 0.22 to 1.59) (Forest plot A) and acute kidney injury [RR 0.68 (95% CI 0.28 to 1.62)] (Forest plot B). Results did not change when only RCTs were analysed. **Major bleeding, life-threatening bleeding and major vascular events** There was no statistically significant difference between groups for major bleeding [RR 0.56 (95% CI 0.26 to 1.18)] (Forest plot A), life-threatening bleeding [0.54 (95% CI 0.19 to 1.53)] (Forest plot B) or major vascular complications [RR 0.80 (95% CI 0.52 to 1.24)] (Forest plot C). The effect was consistent when analysing only RCTs. Analysis of the funnel plots revealed asymmetry for the following outcomes: stroke or mortality at 30 days, peri-procedural stroke, stroke at 1 week, stroke at 30 days, acute kidney injury, major bleeding and life-threatening bleeding. Egger's test did not reveal any evidence of publication bias for any of the outcomes.
Abbreviations used: CI, confidence interval; CPD, cerebral protection device; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RR, risk ratio; TAVI, transcatheter aortic valve implantation

Study 2 Bagur R (2017)

Details

Study type	**Systematic review and meta-analysis**
Country	Canada
Recruitment period	Literature search conducted up to 15 August 2016.
Study population and number	n=**1170 (865 with CPD, 305 without CPD)** patients from 16 studies having a TAVI procedure
Age and sex	Mean 82 years; 50% female in 14 studies that reported both age and sex
Patient selection criteria	Inclusion criteria: studies that evaluated patients who had TAVI with and without CPD. Studies included in the meta-analysis had to be parallel group in design, with 1 group having TAVI with CPD and the other having TAVI without CPD. To increase power of the feasibility analysis, single-arm studies that evaluated the feasibility of performing TAVI with CPD were also included. Studies that evaluated 1 or more of the following outcomes within the 30 days after TAVI: CPD delivery success, stroke or transient ischemic attack, death, new-silent ischemic lesions as assessed by DW-MRI or high-intensity transient signals, neurocognitive function as assessed by Mini-Mental State Examination, Montreal Cognitive Assessment, centre for epidemiological studies- depression scale, or National Institutes of Health Stroke Scale. Reporting of outcomes had to include either crude events in each group or any risk/odds estimate with 95% CI. There was no restriction based on language of study, and both abstracts and unpublished studies presented in conferences were included.
Technique	The Embrella Embolic Deflector system (Edwards Lifesciences, Irvine, CA) was used in 3 studies, the TriGuard HDH (Keystone Heart, Caesarea, Israel) in 3 studies, the SMT Embolic Deflection Device (SMT Research and Development Ltd., Herzliya, Israel) in 1 study, the Claret CE Pro (Claret Medical, Inc. Santa Rosa, CA, USA) in 1 study, the Montage (Claret Medical Inc., Santa Rosa, CA, USA) in 2 studies, the Sentinel (Claret Medical Inc., Santa Rosa, CA, USA) in 2 studies, and 2 studies used both Montage and Sentinel (Claret Medical Inc., Santa Rosa, CA, USA) dual filter devices. The EMBOL-X (Edwards Lifesciences, Irvine, CA) was used in 1 study, and the combination of the Sentinel® plus Wirion (Allium Medical, Israel) for posterior territory protection in 1 study.
Follow-up	**30 days**
Conflict of I nterest/source of funding	This study was supported in part by a Program of Experimental Medicine (POEM) Research Award, Department of Medicine, Western University.

Analysis
Follow-up issues: Loss to follow-up was frequent and most common reported causes were death, stroke, pacemaker implantation, logistical reasons, delirium, patient's refusal and withdrawal of consent.
Study design issues:

- End points, when available, were reported in accordance to Valve Academic Research Consortium-2.7.
- An additional study published after the systematic search was included because of its scientific relevance.
- Risk of bias in the eligible studies was assessed separately for randomised studies using ACROBAT (A Cochrane Collaboration Risk of Bias Tool) and non-randomised Studies of Intervention using the ACROBAT-NRSI. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system was used to determine the strength of evidence as high, moderate, low, or very low based on risk of bias, consistency, precision, directness, and publication bias.
- The quality of overall evidence was low-to-very low, with the main limitation being serious risk of bias and imprecision.
- The authors used the PRISMA checklist to report the outcomes of the systematic review and meta-analysis.

Study population issues: Baseline atrial fibrillation was reported in 9 studies, with a prevalence of 32% (285/902) of patients. Previous stroke was reported in 14 studies, with a prevalence of 11% (111/1028) of patients.
Other issues:

- Patient level data were not available to the authors.
- This systematic review included 1 study (Wendt 2015) in which the Embol-X device was used. This device is inserted through a different procedure (trans-aortic) and therefore is out of remit.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **1170 (865 with CPD, compared with 305 without CPD)**

CPD delivery success: 94% (804/851), range 64% to 100%; reported in 16 studies

All-cause mortality at 30 days: 3% (27/907, 9 studies)
2.4% (15/626, 9 studies with CPD) versus 2.8% (8/281, 6 studies without CPD)

Incidence of stroke at 30 days: 4% (23/1139, 15 studies)
3.7% (31/843, 15 studies with CPD) versus 6.1% (18/296) in 7 studies without CPD

Meta-analysis evaluating CPD compared with no CPD

There was no statistically significant difference in:

- **clinically evident stroke at 30 days (RR 0.70; 95% CI 0.38 to 1.29; p=0.26)**
- **30-day mortality (RR 0.58; 95% CI 0.20 to 1.64; p=0.30)**

Silent ischemic lesions

	All patients	TAVI with CPD	TAVI without CPD
New lesions (% patients)	89% (305/344) from 8 studies	87% (173/199) from 8 studies	91% (132/145) from 6 studies
Multiple lesions (% patients)	76% (101/133) from 4 studies	78% (58/74) from 4 studies	73% (43/59) from 3 studies
Total number of new lesions per patient (range)	-	2.2 to 8.3 (6 studies)	3.1 to 16.7 (6 studies)
Total volume of lesions per patient (average range)	-	88 to 466 mm^3 (6 studies)	168 to 800 mm^3 (6 studies)

- **The meta-analysis showed no statistically significant differences in new-single, multiple, or total number of lesions**.
- **The use of CPD was associated with a statistically significantly:**
  - **smaller ischemic volume per lesion (standardized mean difference, −0.52; 95% CI −0.85 to −0.20; p=0.002)**
  - **smaller total volume of lesions (standardized mean difference, −0.23; 95% CI −0.42 to −0.03; p=0.02).**

Neurocognitive function (Proportion of patients showing worsening neurocognitive function, range)

	Number of studies using the scale to assess this outcome	TAVI with CPD	TAVI without CPD
Montreal Cognitive Assessment	3	10.7% to 27.3%	22.7% to 33.3%
National Institutes of Health Stroke Scale	3	0% to 17.9%	4.5% to 22.5%
Mini-Mental State Examination	1	No difference shown between groups	

Safety

No safety outcomes were reported.

Abbreviations used: CI, confidence interval; CPD, cerebral protection device; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RR, risk ratio; TAVI, transcatheter aortic valve implantation

Study 3 Kapadia S R (2017) – The Sentinel trial

Details

Study type	**RCT**
Country	USA (17 centres) and Germany (2 centres)
Recruitment period	Not reported
Study population and number	n=**363 (121 device imaging compared with 123 device safety and 119 control imaging)** patients having TAVI
Age and sex	Median 83 years; 52% (189/363) female
Patient selection criteria	Inclusion criteria: All patients had multislice computed tomography scans that were analysed by a core laboratory and reviewed by a committee to determine treatment eligibility for the Sentinel TCEP device (Claret Medical). Exclusion criteria: known contraindications for right radial or brachial artery access and inability to have MRI brain evaluation for any reason.
Technique	The Sentinel TCEP device was used. It consists of 2 filters within a single 6-F delivery catheter percutaneously placed from the right radial or brachial artery over a 0.014- inch guidewire.
Follow-up	**90 days**
Conflict of interest/source of funding	The SENTINEL trial was funded by Claret Medical.

Analysis

Follow-up issues:

- Neurological evaluations post-TAVI were planned for all patients at 30 and 90 days.
- Brain MRI using a 3-T scanner was done in both imaging arms at baseline and post-TAVI at 2 to 7 days and at 30 days.
- Within the imaging cohort, MRI studies at baseline and 2 to 7 days post-TAVI were done in 189 (79%) patients, and neurocognitive assessments were completed at baseline and 30 days in 185 (77.1%) patients.

Study design issues:

- The primary safety endpoint consisted of MACCE at 30 days, and the primary efficacy endpoint was reduction in new lesion volume in protected brain territories on MRI scans at 2 to 7 days.
- Patients having TAVI were prospectively randomised 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). The safety arm was included to assess safety without increasing cost of the trial by eliminating MRI cost.
- Patients were blinded to treatment assignment. Blinded diffusion-weighted MRI and neurocognitive function assessments were done in the device and control arms. Particulate debris from the extracted filters was studied in the device arm.
- 72 patients per arm were needed for 80% power and an alpha of 0.05 (2-sided). With an estimated loss allowance of 35%, 120 patients were planned for randomisation to each imaging arm to achieve 75 evaluable patients.

Study population issues:

- The only baseline characteristics that differed between those with and without paired MRI were history of previous coronary artery bypass graft and mean gradient.
- Frequent comorbidities included atrial fibrillation (32%) and previous strokes (6%).
- 4 different TAVI devices were used in this trial: SAPIEN XT (18%) and SAPIEN 3 (52%) (Edwards Lifesciences), and CoreValve (3.9%) and Evolut R (25.9%) (Medtronic). TAVI systems were used with similar distribution across all 3 treatment groups.

Other issues: This study was included in both of the systematic reviews and meta-analyses included in Table 2.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **363 (121 device imaging compared with 123 device safety and 119 control imaging)**

Procedural details

- TAVI was done through the femoral artery in 95% of patients.
- The device was delivered from the radial and brachial arteries in 93% and 6% of patients, respectively.
- In the device arm compared with the control arm, there was an increase in total procedure time (p=0.01) and fluoroscopy time (p= 0.007)

Median total new lesion volume and number of new lesions (unadjusted analysis, day 2 to 7). Values are median (interquartile range).

	Device Arm (n= 91)	Control Arm (n=98)	Hodges-Lehmann Estimate of Location Shift (95% CI)	p Value
Median total new lesion volume in protected territories, mm^3**	102.8 (36.9–423.2)	178.0 (34.3–482.5)	-21.1 (-94.9 to 21.8)	0.3345*
Median total new lesion volume in all territories, mm^3	294.0 (69.2–786.4)	309.8 (105.5–859.6)	-8.6 (-110.7 to 68.6)	0.8076*
Median number of new lesions in protected territories	2 (1–6)	3 (1–6)	0 (-1 to 0)	0.8979†
Median number of new lesions in all territories	3 (2–10)	5 (2–10)	-1 (-2 to 1)	0.7667†

*On the basis of the Wilcoxon test. †On the basis of the negative binomial regression model.

**'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 mm3 vs. 178.0 mm3; p= 0.33).

When analysed by valve type, new lesion volume and number in both protected and all territories had statistically significant differences.

Neurocognitive function (overall composite score evaluating 7 domains: attention, executive function, processing speed, verbal and visual memory, mental status, and depression). Values are mean ± SD (n).

	Device Arm		Control Arm		
		Change From Baseline		Change From Baseline	p Value

Safety

Complications at 30 days

	Safety + Device Arm	Control Arm	p Value
Major vascular complication	8.6% (21/244)	5.9% (7/119)	0.53
Radial/brachial	0.4% (1/244)	NA	-
Femoral	8.2% (20/244)	5.9% (7/119)	-
Any MACCE*	7.3% (17/234)	9.9% (11/111)	0.40
Death (all cause)	1.3% (3/234)	1.8% (2/111)	0.65
Stroke	5.6%(13/231)	9.1% (10/110)	0.25
Disabling	0.9% (2/231)	0.9% (1/109)	1.00
Non-disabling	4.8% (11/231)	8.2% (9/110)	0.22
AKI (stage 3)	0.4% (1/231)	0	1.00
TIA	0.4% (1/231)	0	1.00

*MACCE was defined as death (any cause), stroke (any), AKI (stage 3).

The rate of MACCE in the safety and device arm was non-inferior to the performance goal (18.3%, p<0.001) and not statistically different from that of the control group.

Baseline	-0.66 ± 0.75 (117)	NA	-0.63 ± 0.79 (117)	NA	NA
2–7 days post-TAVI	-1.00 ±0.95 (66)	-0.33±0.65 (66)	-0.81 ± 0.93 (66)	-0.16 ± 0.58 (66)	0.1894
30-day follow-up	-0.77 ± 0.82 (93)	-0.09 ±0.44 (93)	0.59 ± 0.79 (92)	-0.03 ± 0.37 (92)	0.4207
90-day follow-up	-0.47 ± 0.76 (77)	0.18 ± 0.38 (77)	-0.34 ± 0.72 (76)	0.18 ± 0.35 (76)	0.9409

There was a correlation between lesion volume and neurocognitive decline (p= 0.0022).

Histopathological findings

Debris was found within filters in 99% of patients included thrombus, calcification, valve tissue, artery wall, and foreign material.

Abbreviations used: AKI, acute kidney injury; CI, confidence interval; MACCE, major adverse cardiac and cerebrovascular events; NA, not applicable; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack.

Study 4 Haussig S (2016) – The CLEAN-TAVI trial

Details

Study type	**RCT**
Country	Germany (1 centre)
Recruitment period	2013-14
Study population and number	n=**100 (50 filter compared with 50 control)** patients having transfemoral TAVI
Age and sex	Filter group: Mean 80 years; 58% (29/50) female Control group: Mean 79 years; 56% (28/50) female
Patient selection criteria	Inclusion criteria: symptomatic patients with severe aortic stenosis at increased risk for SAVR. Exclusion criteria: anatomy unsuitable for a safe TAVI, pre-existing 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.
Technique	Transfemoral TAVI using the Medtronic CoreValve (Medtronic) self-expanding prosthesis with or without a cerebral protection device using the Claret Montage Dual Filter System (Claret Medical Inc).
Follow-up	**1 month**
Conflict of interest/source of funding	The Leipzig Heart Center received a grant from Claret Medical and Medtronic.

Analysis

Follow-up issues:

- Follow-up assessments were done at 2 and 7 days after TAVI. Follow-up included MRI, serial neurological and neurocognitive assessments, New York Heart Association classification, echocardiography and documentation of adverse events and study end points.
- All brain MRI assessments were done on a 3T scanner (Magnetom Verio) except for 11 patients who were pacemaker dependant after TAVI. For these patients, a 1.5T system (Intera by Phillips), which has a lower sensitivity to detect smaller lesions, was used.
- 49 patients in the filter group and 45 patients in the control group were included in the primary analysis. In the filter group, 1 patient was in the intensive care unit and discontinued the study. In the control group, 2 patients withdrew consent, 1 died, 1 was in the intensive care unit and 1 was pacemaker-dependent.
- 45 patients in the filter group and 43 in the control group were included in the secondary end point analysis. In the filter group, 3 patients withdrew consent and 1 had delirium. In the control group, 1 withdrew consent and 1 had an implantable cardioverter defibrillator placed.

Study design issues:

- The primary end point was the numerical difference in new positive DWMRI brain lesions 2 days after TAVI in potentially protected territories.
- Secondary end point were only assessed if the primary efficacy end pint was met.
- Patients were randomly assigned (1:1) to the control or filter group using concealed and black laminated identical envelopes. Physicians and nurses doing the neurological and neurocognitive tests were otherwise not involved in the study or patient treatment and were blinded to group assignment. MRIs were anonymised and transferred to a central MRI core laboratory for analysis to ensure blinding of the core laboratory.
- 50 patients per arm were needed for 90% power and an alpha of 0.05 (2-sided).
- All the procedure were done by the same heart team.

Study population issues: There were more patients with insulin-dependent diabetes in the control group (30% [15/50]) compared to the filter group (10% [5/50]), more patients with pre-existing stage 3 kidney disease in the filter group (46% [23/50]) versus the control group (22% [11/50]) and more patients with prior coronary artery bypass surgery in the filter group (16% [8/50]) versus the control group (4% [2/50]).

Other issues: This study was included in both of the systematic reviews and meta-analyses included in Table 2.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **100 (50 filter compared with 50 control)**

Procedural outcomes (mean [95% CI])

	Filter group (n=50)	Control group (n=50)	p value
Procedural time (min)	72.1 (65.7 to 78.5)	54.1 (50.0 to 58.1)	<0.001
Device success*	92% (46/50)	NA	NA
Procedural success**	90% (45/50)	NA	NA

*Device success was defined as successful positioning and deployment of both filters in correct anatomical position.

**Procedural success was defined as successful positioning and deployment of both filters in correct anatomical position, correct positioning of both filters during TAVI and successful retrieval of both filters after TAVI.

New brain lesions assessed by MRI

	2 days				7 days			
	Filter (n=49)	Control (n=45)	Difference (95% CI)	p value	Filter (n=49)	Control (n=45)	Difference (95% CI)	p value
Potentially protected areas								
Number of new lesions, median (IQR)	4.00 (3.00 to 7.25)	10.00 (6.75 to 17.00)	5.00 (2.00 to 8.00)	**<0.001**	3.00 (1.00 to 5.25)	7.00 (3.00 to 13.50)	3.00 (1.00 to 5.00)	**0.003**
Volume of new lesions ,median (95% CI), mm^3	242 (159 to 353)	527 (364 to 830)	234 (91 to 406)	**0.001**	101 (60 to 174)	292 (181 to 515)	160 (57 to 281)	**0.002**
Partially protected areas								
Number of new lesions	2.00 (1.00 to 3.25)	4.00 (2.00 to 7.00)	2.00 (0.00 to 3.00)	**0.008**	1.00 (0.00 to 3.00)	3.00 (1.00 to 5.00)	1.00 (0.00 to 2.00)	**0.02**
Volume of new lesions	113 (72 to 164)	247 (147 to 399)	98 (18 to 194)	**0.01**	37 (11 to 70)	129 (67 to 227)	72 (3 to 129)	**0.008**
Entire brain								
Number of new lesions	8.00 (5.00 to 12.00)	16.00 (9.75 to 24.25)	6.00 (3.00 to 10.00)	**0.002**	5.00 (2.75 to 8.00)	10.00 (3.00 to 18.00)	4.00 (1.00 to 8.00)	**0.009**
Volume of new lesions	466 (349 to 711	800 (594 to 1407)	311 (66 to 580)	**0.02**	205 (115 to 338)	472 (385 to 909)	240 (51 to 393)	**0.009**

Rate of lesion positive patients (by MRI)

- At 2 days: 98% (48/49) in the filter group versus 98% (44/45) in the control group
- At 7 days : 98% (44/45) in the filter group versus 95% (41/43) in the control group

Neurological outcomes

- At 2 and 7 days, in the intention-to-treat analysis, the number of patients with neurological symptoms indicative of stroke was 5 in each group; all were minor and nondisabling in nature.
- None of the patients had a TIA.

Safety

The filter and control groups did not differ with regard to the incidence of any complications.

30-day mortality

-Filter: 0% (0/50)

-Control: 2% (1/50)

1 patient in the control group died from diastolic heart failure.

Life-threatening haemorrhage

-Filter: 2% (1/50)

-Control: 2% (1/50)

Major vascular complications

-Filter: 10% (5/50)

-Control: 12% (6/50)

Acute kidney injury

-Filter: 2% (1/50)

-Control: 10% (5/50)

Thoracotomy

-Filter: 6% (3/50)

-Control: 0% (0/50)

p=0.24

None of the thoracotomies appeared to be related to the cerebral protection device. All 3 patients recovered and were alive at 30 days.

Abbreviations used: CI, confidence interval; DWMRI: diffusion-weighted MRI; IQR interquartile range; NA, not applicable; SAVR, surgical aortic valve replacement; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack.

Study 5 Lansky A J (2015) – The DEFLECT III study

Details

Study type	**RCT**
Country	Europe and Israel (13 centres)
Recruitment period	2014-15
Study population and number	n=**85 (46 TriGuard compared with 39 control)** patients having TAVI
Age and sex	Mean 82 years; 54% (46/85) female
Patient selection criteria	Inclusion criteria: adults presenting with severe symptomatic aortic stenosis referred for TAVI due to high or extreme surgical risk. Exclusion criteria: recent acute myocardial infarction, recent stroke or transient ischaemic attack, cardiogenic shock, impaired renal function, past or pending organ transplant, active peptic ulcer or recent gastrointestinal bleeding, and history of bleeding diathesis or coagulopathy or contraindications to antiplatelet or anticoagulant therapy. TAVI procedure via the subclavian or direct aortic route, known hypersensitivity to device component materials or contrast that could not be adequately premedicated, severe peripheral artery disease that precluded vascular access, a heavily calcified or severely atheromatous aortic arch or aortic arch anatomy that could prevent positioning and stability of the device, contraindications to cerebral MRI, another intervention planned during or within 2 weeks before TAVI or treatment with any other investigational device or procedure planned at any time during the study period.
Technique	TAVI using primarily the SAPIEN transcatheter heart valve (Edwards Lifesciences) or the CoreValve transcatheter aortic valve replacement platform (Medtronic) according to standard institutional procedures via the transfemoral or transapical approach under local or general anaesthesia, with or without a cerebral protection device using the TriGuard HDH embolic deflection device (Keystone Heart Ltd).
Follow-up	**30 days**
Conflict of interest/source of funding	This study was supported by Keystone Heart, Ltd. and the National Institute of Health Research Bristol Cardiovascular Biomedical Research Unit.

Analysis
Follow-up issues:

- Patients had neurologic and cognitive evaluations at baseline, pre-discharge and 30 days; cerebral diffusion-weighted MRI was done at 4±2 days post-procedure and at 30 days.
- 28% (13/46) of patients in the TriGuard group were considered lost to follow-up for MRI before being discharged from hospital. The reasons were: stroke in 1 patient, consent withdrawal in 2, refusal in 1 and permanent pacemaker in 9 patients. In the control group, 33% (13/39) were considered lost to follow-up for MRI (2 patients died, 1 had a stroke and a permanent pacemaker, 2 withdrew, 2 refused and 6 had a permanent pacemaker).
- At 30-day follow-up, 41% (19/46) of patients in the TriGuard group and 41% (16/39) of patients in the control group were considered lost to follow-up for MRI. 42 patients (91%) in the TriGuard group and 32 patients (82%) in the Control group were assessed for safety at 30 days.

Study design issues:

- The primary safety endpoint was in-hospital procedural safety, defined as a composite of the following Major Adverse Cardiovascular and Cerebrovascular Events (MACCE): all-cause mortality, all stroke (disabling and non-disabling), life-threatening (or disabling) bleeding, acute kidney injury (stage 2 or 3), and major vascular complications.
- All endpoints were defined according to Valve Academic Research Consortium-2 (VARC-2) recommendations.
- All adverse events were adjudicated by an independent Clinical Events Committee (Yale Cardiovascular Research Group, New Haven, CT, USA), which included a cardiac surgeon, an interventional cardiologist, and a vascular neurologist.
- The primary analysis of all endpoints was conducted in the intention-to-treat (ITT) population. For efficacy measures, a per treatment (PT) analysis population was included, defined as patients in whom complete three-vessel cerebral coverage was maintained throughout the TAVI procedure.
- A total of 85 valves were implanted in 83 patients (two patients withdrew consent before valve implantation, and 2 had valve-in-prosthetic-valve implantation).
- This study was an exploratory trial that was not powered to detect statistically significant effects on major safety or efficacy endpoints.

Study population issues: 28 % of patients had atrial fibrillation on admission.
Other issues: This study was included in both of the systematic reviews and meta-analyses included in Table 2.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **85 (46 TriGuard compared with 39 control)**

Procedure outcomes

-45 TriGuard devices were used in 44 patients; 2 randomised patients withdrew consent before device introduction, and 1 patient received 2 TriGuard devices over the course of a valve-in-valve procedure.

- The device was successfully positioned and maintained in position throughout prosthetic-valve deployment, implantation, and retrieval in 89% (40/45, 95% CI [75% to 96%]) of patients.

-There were no device failures.

Freedom from new ischaemic brain lesions (% of patients)

- ITT population: 21% versus 11.5%
- PT population: 27% of patients versus 11.5%

Median single lesion volume per patient

- ITT population: 30.9 mm^3 versus 34.8 mm^3
- PT population: 19.6 mm^3 versus 34.8 mm^3

% of patients with new ischaemic lesions at 30 days: 11.5% (3/26) versus 9% (2/22)

Neurological and cognitive outcomes

% of patients with worsening National Institutes of Health Stroke Scale scores from baseline

- At discharge: 3.1% versus 15.4% (ITT); p=0.16
- At 30 days: 3.8% versus 4.5% (ITT)

% of patients with worsening Montreal Cognitive Assessment scores from baseline

- At discharge: 27.5% versus 37.1% (ITT)
- At 30 days: 27.3% versus 33.3% (ITT)

Safety

Safety outcomes

Endpoint or event	TriGuard (n= 46)	Control (n=39)	Relative risk [95% CI]	p value
Hierarchical composite in-hospital MACCE	22%	31%	0.71 [0.34 to 1.46]	0.34
All-cause death	2% (1)	5% (2)	0.42 [0.04 to 4.50]	0.46
All stroke	2% (1)	5% (2)	0.42 [0.04 to 4.5]	0.46
Life-threatening bleeding	2% (1)	5% (2)	0.42 [0.04 to 4.5]	0.46
AKI (Stage 2/3)	2% (1)	0% (0)	2.55 [0.11 to 60.9]	0.91
Major vascular complications	15% (7)	15% (6)	0.99 [0.36 to 2.7]	0.85
30 Day MACE (K–M estimates)	26% (12)	31% (12)	0.83 [0.37 to 1.84]	0.62
All-cause death	2% (1 pneumonia)	5% (2 aortic ring ruptures)	0.40 [0.04 to 4.44]	0.44
All stroke	4% (2)	6% (2)	0.81 [0.11 to 5.76]	0.83
Disabling	2% (1)	0% (0)	-	0.38
Non-disabling	2% (1)	6% (2)	0.41 [0.04 to 4.50]	0.45
Life-threatening bleeding	4% (2)	8% (3)	0.54 [0.09 to 3.24]	0.49
AKI (Stage 2/3)	2% (1)	0% (0)	-	0.38
Coronary obstruction with intervention	2% (1)	0% (0)	-	0.36
Major vascular complications	17% (8)	21% (8)	0.83 [0.31 to 2.21]	0.69
Valve-related dysfunction	0% (0)	0% (0)	-	-

Abbreviations used: AKI, acute kidney injury; CI, confidence interval; ITT, intention-to-treat; K–M, Kaplan–Meier; MACCE, major adverse cardiac and cerebrovascular event; PT, per treatment; TAVI, transcatheter aortic valve implantation

Study 6 Van Mieghem N M (2016) – The MISTRAL-C trial

Details

Study type	**Double-blinded RCT**
Country	Netherlands (4 centres)
Recruitment period	2013-15
Study population and number	n=**65 (32 Sentinel compared with 33 Control)** patients having transfemoral TAVI
Age and sex	Median 82 years; 48% (31/65) female
Patient selection criteria	Inclusion criteria: Patients at high risk for surgical aortic valve replacement and selected for transfemoral TAVI. Aortic arch anatomy had to fit the sizing requirements for the Sentinel CPS. Exclusion criteria: presence of a permanent pacemaker or automated internal cardiac defibrillator at baseline, a history of prior stroke with sequelae and dementia.
Technique	Transfemoral TAVI with or without the Sentinel CPS.
Follow-up	**30 days**
Conflict of interest/source of funding	The Erasmus Medical Centre received a research grant from Claret Medical that partially covered study-related costs. P. de Jaegere is a proctor for Boston Scientific. N. Van Mieghem has received research grants from Boston Scientific, Medtronic and Edwards Lifesciences. The other authors have no conflicts of interest to declare. The Guest Editor declares low-level consultancy work for Medtronic.

Analysis

Follow-up issues:

- Patients had DW-MRI and extensive neurological examination, including neurocognitive testing 1 day before and 5 to 7 days after TAVI. Follow-up DW-MRI was completed in 57% (37/65) of patients. Patients did not have a follow-up MRI for the following reasons: implantation of a non-MRI-compatible pacemaker (n=10), patient refusal (n=6), unstable clinical condition or deceased (n=5), logistical challenges (n=4) and delirium (n=3). The MRI exam was done with a 3.0 Tesla scanner.
- Neurocognitive testing was completed in 77% (50/65) of patients. Patients did not have a follow-up neurocognitive testing for the following reasons: logistical issues (n=11), delirium (n=2) and clinically unstable condition (n=2).

Study design issues: Power analysis was based on the primary endpoint of new cerebral lesions by DW-MRI 5 to 7 days after TAVI. To reach a reduction from 80% to 40% in volume of new ischaemic lesions by DW-MRI (standard deviation 50%) with the Sentinel CPS and based on the continuity-corrected chi-square test, it was estimated that 54 patients (27 in each treatment arm) would be needed with an 80% power and a two-sided alpha of 0.05. To balance a potential 20% drop-out in MRI follow-up, 65 patients would be needed to obtain 54 patients with MRI before and after TAVI.

Study population issues:

- The median (IQR) STS predicted risk of mortality at baseline was lower in the Sentinel cohort than in the control cohort (4.6 [3.4-6.3] versus 5.8 [3.5-9.8]).
- 54% of patients had an Edwards Sapien 3 valve, 25% a Medtronic CoreValve, 15% an Edwards Sapien XT valve, 5% a balloon dilatation valve and 1% a Portico valve.

Other issues: This study was included in both of the systematic reviews and meta-analyses included in Table 2.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **65 (32 Sentinel compared with 33 Control)**

Procedural outcomes

Successful deployment of the device: 94% (30/32)

Clinical endpoints at 30-day follow-up. VARC definitions were applied.

	Sentinel (n=32)	Control (n=33)	Relative risk (95% CI)	p-value
Dead after 5 days	3% (1)	0%	NA	NA
Dead after 30 days	3% (1)	10% (3)	0.36 [0.04-3.43]	0.371
Dead after 6 months	5% (1)	17% (4)	0.27 [0.30-2.44]	0.245
Non-disabling stroke	0%	0%	NA	NA
Disabling stroke	0%	7% (2)	NA	NA
Stroke causing delirium	3% (1)	15% (5)	0.21 [0.02-1.77]	0.150
New permanent pacemaker	23% (7)	16% (5)	1.45 [0.46-4.55]	0.529

Brain MRI (Overall, 78% of patients with follow-up MRI had new brain lesions).

Patients without any new brain lesions overall on MRI at 5 to 7 days:
27% (6/22) versus 13% (2/15); p=0.31

Patients without any new brain lesions in protected lobes on MRI at 5 to 7 days:
55% (12/22) versus 20% (3/15); **p=0.04**

Patients without any new brain lesions in unprotected lobes on MRI at 5 to 7 days:
32% (7/22) versus 33% (5/15); p=0.92

Patients with 10 or more new brain lesions on MRI at 5 to 7 days:
0% (0/22) versus 20% (3/15); **p=0.03**

Total lesion volume: 95 mm^3 [IQR 10-257] versus 197 mm^3 [95-525]; p=0.171

Total lesion volume in patients with self-expanding TAVI vs. balloon-expandable TAVI: 693 mm^3 [IQR 459-744] vs. 266 mm^3 [IQR 155-358], p=0.067

Neurocognitive deterioration (MMSE worsening) at 5 to 7 days: 4% (1/28) versus 27% (6/22); **p=0.017**

The MMSE score increased by 0.25±1.6 in patients with Sentinel CPS and decreased by 0.77±2.5 in the control group (p=0.086).

The filters captured debris in all patients with Sentinel CPS protection.

Safety

There were no device-related injuries.

Clinical endpoints at 30-day follow-up. VARC definitions were applied.

	Sentinel (n=32)	Control (n=33)	Relative risk (95% CI)	p-value
Coronary obstruction	0 (0%)	3% (1)	NA	NA
Valve embolisation	0 (0%)	0 (0%)	NA	NA
Cardiac tamponade	0 (0%)	6% (2)	NA	NA
Myocardial infarction	0 (0%)	6% (2)	NA	NA
Acute kidney injury	0 (0%)	3% (1)	NA	NA
Any bleeding within 1 day	32% (10)	44% (14)	0.74 [0.33-1.66]	0.462
Life-threatening bleeding within 1 day	0%	16% (5)	NA	NA
Any bleeding after 1 day	29% (9)	41% (13)	0.72 [0.31-1.67]	0.438
Life-threatening bleeding after 1 day	3% (1)	0%	NA	NA
Any vascular complication	39% (12)	59% (19)	0.65 [0.32-1.34]	0.246
Major vascular complication	0%	19% (6)	NA	NA

Abbreviations used: CI, confidence interval; IQR, interquartile range; MMSE, mini-mental state examination; NA, not applicable; STS PROM, Society of Thoracic Surgeons predicted risk of mortality; TAVI, transcatheter aortic valve implantation; VARC, Valve Academic Research Consortium.

Study 7 Seeger J (2017)

Details

Study type	**Prospective non-randomised comparative study**
Country	Germany
Recruitment period	2014-16
Study population and number	n=**802 (280 Sentinel compared with 522 control)** consecutive patients having transfemoral TAVI **Propensity-matched population: n=560 (280 Sentinel compared with 280 control)**
Age and sex	Propensity-matched population: Mean 81 years;55% (306/560) female
Patient selection criteria	Inclusion criteria: Consecutive patients having transfemoral TAVI. Since 2016 the protection device was used consecutively in all patients except if there was no vascular access or there were rare anatomic situations clearly not allowing the positioning of both filters. Exclusion criteria: Patients with valve-in-valve procedures.
Technique	Transfemoral TAVI with or without the Sentinel device.
Follow-up	**7 days**
Conflict of interest/source of funding	The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Analysis

Follow-up issues: Neurological follow-up was done within 7 days of the procedure.

Study design issues:

- The primary endpoint was a composite of all-cause mortality or all-stroke according to Valve Academic Research Consortium-2 criteria within 7 days.
- Propensity score matching was done to account for possible confounders. Matching was done for STS score, atrial fibrillation, aortic cusp calcification, left ventricular outflow tract calcification, valve type, carotid artery stenosis, peripheral vascular disease, sex, diabetes mellitus, and renal insufficiency.

Study population issues: In the propensity-matched population, there were statistically significant differences between groups for the valve size, the valve type and the pre-dilatation.

Other issues: This study was included in one of the systematic reviews and meta-analyses included in Table 2 (Mohananey 2018).

Key efficacy and safety findings

Efficacy

Number of patients analysed: **560 (280 Sentinel versus 280 control)**

Efficacy outcomes at 7 days

	Cerebral Embolic Protection	No Cerebral Embolic Protection	OR (95% CI)	p Value
Mortality or stroke	2% (6/280)	7% (19/280)	0.30 (0.12 to 0.77)	**0.01**
Disabling and non-disabling stroke	1% (4/280)	5% (13/280)	0.29 (0.10 to 0.93)	**0.03**
Disabling	<1% (1/280)	3% (9/280)	0.11 (0.01 to 0.86)	**0.01**
Non-disabling	1% (3/280)	1% (4/280)	0.75 (0.17 to 3.38)	0.70
Mortality	<1% (2/280)	3% (8/280)	0.25 (0.05 to 1.20)	0.06
SENTINEL endpoint*	2% (7/280)	8% (22/280)	0.32 (0.14 to 0.77)	**0.01**

* Sentinel endpoint: all-cause mortality, all stroke, acute kidney injury stage 3.

- In multivariable analysis, only STS score for mortality (p= 0.02) and TAVI procedure without cerebral embolic protection (p= 0.02) were independent predictors for the occurrence of death or stroke.
- Procedure without use of a cerebral embolic protection device was the only independent predictor (p=0.04) for the occurrence of stroke within 7 days.

The stroke rate was statistically significantly lower with use of the protection device compared with unprotected procedures within 48 h (3.6% vs. 1.1%; p= 0.03; OR: 0.29; 95% CI: 0.10 to 0.93; NNT 31).

Safety

Safety outcomes at 7 days

	Cerebral Embolic Protection	No Cerebral Embolic Protection	OR (95% CI)	p Value
Acute kidney injury stage 2/3	1% (3/280)	1% (4/280)	0.64 (0.15 to 2.71)	0.54
Major vascular complications	2% (5/280)	4% (10/280)		0.19
Major bleeding	1% (4/280)	4% (12/280)		**0.05**

Abbreviations used: CI, confidence interval; OR, odds ratio; STS, Society of Thoracic Surgeons; TAVI, transcatheter aortic valve implantation

Study 8 Naber C K (2012)

Details

Study type	**Prospective case series (first-in-human study)**
Country	Germany (2 centres) and Brazil (1 centre)
Recruitment period	2010-11
Study population and number	n=**40** patients having TAVI
Age and sex	Mean 81 years; 60% (24/40) female
Patient selection criteria	Inclusion criteria: Patients scheduled for elective TAVI, compatible left carotid artery (>3 mm) and brachiocephalic artery (>9 mm) diameters, female subjects of childbearing potential with a negative pregnancy test 48 hours before the study procedure, written informed consent. Exclusion criteria: Emergency procedure, carotid artery stenosis >70% in either carotid artery, significant stenosis, ectasia, dissection or aneurysm at the ostium or within 3 cm of the ostium of the brachiocephalic or left carotid artery, bleeding diatheses or coagulopathy or refusal of blood transfusion, renal insufficiency, defined as a creatinine level >2.5 mg/dl at the time of treatment, unless subject is on chronic haemodialysis, hyperthyroidism, recent stroke with permanent deficit or recent significant gastrointestinal bleed, participation in another clinical study or other medical illnesses that may cause the patient to be non-compliant with the protocol or confound the data interpretation, history of intolerance, allergic reaction or contraindication to any of the study medications or to materials from which the device is constructed.
Technique	- The Claret CE Pro (Claret Medical, Inc) cerebral protection device was placed via the right radial/ brachial artery before TAVI and was removed after the procedure. Two generations of the device were used in the study, with the first generation system delivered to the aortic arch without a guidewire under direct fluoroscopic visualisation in the first 7 patients. The second-generation device included the addition of a 0.014" guidewire lumen and a modified curve shape that included a "counter-bend" tip. - A non-proprietary second distal filter (SpiderFX™, Covidien or FilterWire™, Boston Scientific) was used with the Claret system and delivered to the left common artery. - TAVI was done with the third generation Medtronic CoreValve (CoreValve Revalving Technology, Medtronic) in 38 patients and with the Edwards SAPIEN valve prosthesis (Edwards Lifesciences) in 2 patients.
Follow-up	**30 days**
Conflict of interest/source of funding	None

Analysis

Study design issues:

- The primary endpoint was technical success rate.

Study population issues: The severity of comorbidities in the patient cohort was reflected by a mean logistic EuroSCORE of 27.9±18.7, with 5 patients (12.5%) having a history of cerebrovascular events.

Other issues: This study was included in 1 of the systematic reviews and meta-analyses included in Table 2 (Bagur 2017).

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 40

Primary technical outcome
The access site was radial in 5 (12.5 %) and brachial in 35 (87.5 %) patients.
Technical success
<table>
<tr><th>First-generation device</th><th>Rate of success</th><th>Comments</th></tr>
<tr><td>Device delivered to the aortic arch</td><td>71% (5/7)</td><td>One spasm and one dissection of the radial artery led to device placement failure.</td></tr>
<tr><td>Proximal and distal filter deployed</td><td>60% (3/5)</td><td>-</td></tr>
<tr><td>Proximal filter deployed only</td><td>40% (2/5)</td><td>Left carotid could not be accessed in both patients.</td></tr>
<tr><th>Second-generation device</th><th>Rate of success</th><th>Comments</th></tr>
<tr><td>Device delivered to the aortic arch</td><td>91% (30/33)</td><td>In 3 patients, the brachiocephalic artery was judged to be too tortuous.</td></tr>
<tr><td>Proximal and distal filter deployed</td><td>87% (26/30)</td><td>-</td></tr>
<tr><td>Proximal filter deployed only</td><td>13% (4/30)</td><td>In 2 patients, the distal filter could not be deployed due to suboptimal SpiderFX compatibility with the Claret catheter. In 1 patient, operator failure prevented the placement of the distal filter. In 1 patient, the left carotid could not be accessed.</td></tr>
</table>
Technical success improved statistically significantly with the use of the second-generation device (60% vs. 87%; p<0.05).

No procedural transient ischaemic attacks, minor strokes or major strokes occurred.
</td><td>
Device-related procedural complications: 10% (4/40)
-Dissection of the radial artery: 1/40. This was caused by the manipulation of the (first-generation) device and it had to be treated surgically.
-Rupture of a minor branch of the radial artery: 1/40. This also happened with a 1st generation device that lacked a guidewire. This led to a minor haematoma that was treated with manual compression without any clinical consequence for the patient during the follow-up period.

No device-specific procedural complications occurred with the second-generation system.

Procedural complications
-Brachial pseudo-aneurysm: 2/40. They developed after removal of the vascular sheath and following mechanical compression of the puncture site. Both were treated surgically.

Thirty-day follow-up showed 1 minor stroke occurring 30 days after the procedure and 2 major strokes at 4 hours and 27 days after the procedure.
</td></tr>
<tr><td colspan="2">Abbreviations used: TAVI, transcatheter aortic valve implantation</td></tr>
</table>

Study 9 Seeger J (2018)

Details

Study type	**Patient-level pooled analysis from the SENTINEL US IDE, the CLEAN-TAVI and the SENTINEL-Ulm studies**
Country	US and Germany
Recruitment period	Not reported
Study population and number	**n=1,306 (717 CEP versus 589 control)** patients having TAVR **Propensity-matched population: n=1,066 (533 CEP versus 533 control)**
Age and sex	Propensity-matched population: Mean 81 years; 53% (564/1066) female
Patient selection criteria	Patients with symptomatic severe aortic stenosis undergoing TAVR from the following studies: SENTINEL US IDE RCT: n=363 (244 CEP versus 119 control). CLEAN-TAVI RCT: n=100 (50 CEP versus 50 control) SENTINEL-Ulm registry (single centre): n=843 patients (423 sequential patients with CEP versus 420 control)
Technique	The Sentinel device (Claret Medical, dual-filter) was used in the CEP group. In SENTINEL-Ulm, TAVR was done under conscious sedation in all patients.
Follow-up	**72 hours**
Conflict of interest/source of funding	The SENTINEL trial was sponsored by Claret Medical, Inc. The SENTINEL-Ulm study was an independent research. The CLEAN TAVI trial was sponsored by Claret Medical, Inc. and Medtronic.

Analysis

Study design issues:

- The primary endpoint was procedural stroke within 72 hours post-TAVR according to Valve Academic Research Consortium-2 criteria.
- The secondary endpoint was the combination of all-cause mortality or all-stroke within 72 hours after TAVR.
- To account for differences between patients with and without CEP from the randomized SENTINEL US IDE study, the CLEAN-TAVI trial, and the SENTINEL-Ulm registry study, the authors did a propensity score analysis based on an optimal matching attempt. Matching was done for valve type, STS score, atrial fibrillation (AF), diabetes mellitus, gender, coronary artery disease (CAD), and peripheral vascular disease.
- The number of non-randomised patients was numerically much higher than randomised patients.
- All-stroke at 72 hours was not the primary endpoint of the SENTINEL and CLEAN-TAVI studies.
- Patients included in the SENTINEL trial randomised to the unprotected group and about half of patients randomised to the protected group, received cerebral MRI for assessment of both new lesions and lesion volume. In CLEAN-TAVI, all patients underwent cerebral MRI. In contrast, patients included from the SENTINEL-Ulm group received cerebral MRI only if there was a clinical suspicion of stroke following assessment by a neurologist.

Study population issues:

- Mean aortic valve gradient was statistically significantly higher in patients with use of CEP (p=0.02).

- For the total study group of 1,066 matched patients, non-general anaesthesia was used statistically significantly more in patients without CEP compared with patients with CEP (p=0.002).

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **1,066 (533 CEP versus 533 control)** **All-stroke rate within 72 hours:** 1.88% (10/533) versus 5.44% (29/533), odds ratio 0.35, 95% CI 0.17 to 0.72, relative risk reduction 65%, absolute risk reduction 3.54%; p = **0.0028** • **Disabling stroke rate:** 0.38% (2/533) versus 2.44% (13/533), odds ratio 0.14, 95% CI 0.03 to 0.66, **p=0.0045** • **Non-disabling stroke rate:** 1.50% (8/533) versus 3.00% (16/533), odds ratio 0.53, 95% CI 0.23 to 1.24, p=0.13 **All-cause mortality or stroke rate within 72 hours:** 2.06% (11/533) versus 6.00% (32/533), odds ratio 0.34, 95% CI 0.17 to 0.68, relative risk reduction 66%, absolute risk reduction 3.94%, p = **0.0013** **Subgroup analyses** • Use of general (n= 200) or local anaesthesia (n= 860) In patients with general anaesthesia, the rate of all-stroke was not statistically significantly different between both groups (2.50% versus 5.00%, p = 0.36). In patients having TAVR with non-general anaesthesia, the primary endpoint of all-stroke was also lower with CEP vs. without CEP (1.70% versus 5.58%, p = 0.0045) • Use of different valve types The primary endpoint was lower with use of CEP in the subgroup of patients treated with a balloon-expandable valve (n= 672), mechanically implantable valve (n= 170), and self-expandable valve (n= 224). Rates for all-stroke were for patients with versus without protection 0.89% vs. 3.57%, 2.35% vs. 7.06%, and 4.46% vs. 9.82%, respectively (p= 0.80).	There was no stroke-related death within 72 hours after the procedure in both groups.
Abbreviations used: CEP, cerebral embolic protection; CI, confidence interval; STS, Society of Thoracic Surgeons; TAVR, transcatheter aortic valve replacement.	

Validity and generalisability of the studies

- The cerebral protection devices used in the studies differ in mechanism of action. They work either by filtration or diversion of debris.
- The valves used for the TAVI procedure also differ and might have an impact on the efficacy outcomes of the cerebral protection.
- The device Embol-X was used in 1 of the studies included in the systematic review and meta-analysis by Bagur[2]. This device is inserted through a different procedure (trans-aortic) and therefore is out of remit.
- The studies evaluating the device Embol-X were not selected for the purpose of this review.
- Two systematic reviews and meta-analyses[1,2] were included in Table 2. Other systematic reviews and meta-analyses were included in the Appendix. Study 1 is the most recent and does not include any study on the Embol-X device, and study 2 includes the greatest number of studies. There were some patient overlaps between both systematic reviews.
- Only a few studies reported peri-procedural strokes or transient ischaemic attacks.
- Studies 3 to 8 were included in the systematic reviews and meta-analyses.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure.

Interventional procedures

- Transcatheter aortic valve implantation for aortic stenosis. NICE Interventional procedures guidance 586 (2017). Available from http://www.nice.org.uk/guidance/ipg586
- Transcervical extracorporeal reverse flow neuroprotection for reducing the risk of stroke during carotid artery stenting. NICE Interventional procedures guidance 561 (2016). Available from http://www.nice.org.uk/guidance/ipg561
- Transapical transcatheter mitral valve-in-valve implantation for a failed surgically implanted mitral valve bioprosthesis. NICE Interventional procedures guidance 541 (2015). Available from http://www.nice.org.uk/guidance/ipg541
- Transcatheter valve-in-valve implantation for aortic bioprosthetic valve dysfunction. NICE Interventional procedures guidance 504 (2014). Available from http://www.nice.org.uk/guidance/ipg504

NICE guidelines

- Stroke and transient ischaemic attack in over 16s: diagnosis and initial management. NICE clinical guideline 68 (2017). Available from http://www.nice.org.uk/guidance/cg68

Additional information considered by IPAC

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Three Specialist Advisor Questionnaires for percutaneous insertion of a cerebral protection device to prevent cerebral embolism during transcatheter aortic valve implantation were submitted and can be found on the NICE website.

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Company engagement

A structured information request was sent to 4 companies who manufacture a potentially relevant device for use in this procedure. NICE received 3 completed submission. This was considered by the IP team and any relevant points have been taken into consideration when preparing this overview.

Issues for consideration by IPAC

Ongoing trials:

- NCT02895737 PROTECT TAVI - Prospective Randomized Outcome Study in TAVI Patients Undergoing Periprocedural Embolic Cerebral Protection With the Claret Sentinel™ Device (PROTECT). Germany. Estimated enrolment: 328 patients. RCT. Estimated primary completion date: September 2019.

- NCT02536196 The REFLECT Trial: Cerebral Protection to Reduce Cerebral Embolic Lesions After Transcatheter Aortic Valve Implantation. Germany, Italy, Netherlands, United States. Estimated enrolment: 285 patients. RCT. Estimated study completion date: December 2017.

- NCT03325283 The PROTEMBO SF Trial. Ireland, Latvia. Estimated enrolment: 10 patients. Prospective case series. Estimated study completion date: December 2018.

- NCT03130491 European study evaluating the Emblok embolic protection system during TAVR. Italy. Estimated enrolment: 30 patients. Case series. Estimated study completion date: February 2019.

- The TRiGUARD 3 – First in man study (n=10 patients).

- TriGUARD 3 EU Post-Market Study (multicentre registry, n=500 patients). Upcoming.

References

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2. Bagur R, Solo K, Alghofaili S et al. (2017) Cerebral Embolic Protection Devices During Transcatheter Aortic Valve Implantation: Systematic Review and Meta-Analysis. Stroke 48(5), 1306-1315
3. Kapadia S R, Kodali S, Makkar R et al. (2017) Protection Against Cerebral Embolism During Transcatheter Aortic Valve Replacement. Journal of the American College of Cardiology 69(4), 367-377
4. Haussig S, Mangner N, Dwyer M G 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
5. Lansky A J, Schofer J, Tchetche D et al. (2015) A prospective randomized evaluation of the TriGuardTM HDH embolic DEFLECTion device during transcatheter aortic valve implantation: results from the DEFLECT III trial. European heart journal 36(31), 2070-2078
6. Van Mieghem N M, van Gils L, Ahmad H et al. (2016) Filter-based cerebral embolic protection with transcatheter aortic valve implantation: the randomised MISTRAL-C trial. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 12(4), 499-507
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9. Seeger J, Kapadia SR, Kodali S et al. (2018) Rate of Peri-procedural Stroke Observed with Cerebral Embolic Protection During Transcatheter Aortic Valve Replacement: A Patient-level Propensity-matched Analysis. European Heart Journal doi: 10.1093/eurheartj/ehy847. [Epub ahead of print]

Literature search strategy

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	16/01/2019	Issue 1 of 12, January 2019
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	16/01/2019	Issue 1 of 12, January 2019
HTA database (CRD website)	16/01/2019	n/a
MEDLINE (Ovid)	16/01/2019	1946 to January 15, 2019
MEDLINE In-Process (Ovid) & Medline ePub ahead (Ovid)	16/01/2019	January 15, 2019
EMBASE (Ovid)	16/01/2019	1974 to 2019 January 15

Trial sources searched 24th July 2018

- Clinicaltrials.gov
- ISRCTN
- WHO International Clinical Trials Registry

Websites searched 24th – 25th July 2018

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- EuroScan
- General internet search

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1 Transcatheter Aortic Valve Replacement/
2 ((percutan* or transcath*) adj4 (heart* or aortic*) adj4 valve*).tw.
3 ((percutan* or transcath*) adj4 valve*).tw.
4 (PAVR or TAVR or TAVI).tw.
5 ((transap* or transventric* or percutan* or transcath*) adj4 (deliver* or access* or approach* or minimal*)).tw.
6 or/1-5
7 Embolic Protection Devices/
8 ((cerebr* or emboli* or distal*) adj4 (deflect* or protect* or barrier* or filter* or double-filter* or dual-filter*)).tw.
9 (transcatheter adj4 cerebral adj4 embolic adj4 protect*).tw.
10 TCEP.tw.
11 or/7-10
12 6 and 11
13 (Embrella* or TriGUARD* or Emblok* or protembo*).tw.
14 ((claret or sentinel or sentineltm) adj2 device*).tw.
15 or/13-14
16 12 or 15
17 animals/ not humans/
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Appendix

The following table outlines the studies that are considered potentially relevant to the IP overview but were not included in the main data extraction table (table 2). It is by no means an exhaustive list of potentially relevant studies.

Article	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Almeida J G, Ferreira S, Caeiro D et al. (2017) Transcatheter Aortic Valve Implantation with Embolic Protection System in a Patient with Left Ventricle Apical Thrombus. Arquivos brasileiros de cardiologia 109(5), 495-496	Single case report FU=1 year	The procedure went without complications and the patient showed remarkable clinical and haemodynamic improvement, being discharged 11 days after TAVI.	Larger studies are already included in table 2.
Baumbach A, Mullen M, Brickman A M et al. (2015) Safety and performance of a novel embolic deflection device in patients undergoing transcatheter aortic valve replacement: results from the DEFLECT I study. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 11(1), 75-84	Prospective case series n=37 FU=30 days	Use of the first-generation TriGuard Embolic deflection device (EDD) during TAVR is safe, and device performance was successful in 80% of cases during the highest embolic-risk portions of the TAVR procedure. The potential of the TriGuard EDD to reduce total cerebral ischaemic burden merits further randomised investigation.	Larger studies are already included in table 2.
Campelo-Parada F, Regueiro A, Dumont E et al. (2016) Embolic protection in patients undergoing transaortic transcatheter aortic valve replacement: initial experience with the TriGuard HDH embolic deflection device. Journal of cardiac surgery 31(10), 617-622	Case series n=10 FU=30 days	This study shows the safety and feasibility of using the TriGuard HDH embolic protection device in transaortic TAVR. Further studies are warranted to determine the efficacy of embolic protection in this population.	Larger studies are already included in table 2.
Giustino G, Mehran R, Veltkamp R et al. (2016) Neurological Outcomes With Embolic Protection Devices in Patients Undergoing Transcatheter Aortic Valve Replacement: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. JACC. Cardiovascular interventions 9(20), 2124-2133	Systematic review and meta-analysis n=252 patients from 4 RCTs Search up until 31/12/2015	Use of embolic protection (EP) was associated: • with lower total lesion volume (standardized mean difference -0.65; 95% confidence interval [CI]: -1.06 to -0.25; p = 0.002) and • smaller number of new ischemic lesions (standardized mean difference -1.27; 95% CI: -2.45 to -0.09; p = 0.03). • EP was associated with a trend toward lower risk for	2 systematic reviews and meta-analyses that are more recent and that include more patients are already included in Table 2.

		deterioration in National Institutes of Health Stroke Scale score at discharge (risk ratio: 0.55; 95% CI: 0.27 to 1.09; p = 0.09) and • higher Montreal Cognitive Assessment score (standardized mean difference 0.40; 95% CI: 0.04 to 0.76; p = 0.03). • Risk for overt stroke and all-cause mortality were non-significantly lower in the EP group.	
Grover P M, O'Neill B P, Velazquez O et al. (2013) Cerebral protection against left ventricular thrombus during transcatheter aortic valve replacement in a patient with critical aortic stenosis. Texas Heart Institute journal 40(4), 477-80	Single case report FU=30 days	Successful TAVI under cerebral protection. With the use of cerebral protection, TAVI might still be feasible in inoperable patients who have a persistent left ventricular thrombus and critical aortic stenosis.	Larger studies are already included in table 2.
Nietlispach F, Wijesinghe N, Gurvitch R et al. (2010) An embolic deflection device for aortic valve interventions. JACC. Cardiovascular interventions 3(11), 1133-8	Case series n=3 FU=not reported	Embolic protection during transcatheter aortic valve intervention seems feasible and might have the potential to reduce the risk of cerebral embolism and stroke.	Larger studies are already included in table 2.
Onsea K, Agostoni P, Samim M et al. (2012) First-in-man experience with a new embolic deflection device in transcatheter aortic valve interventions. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 8(1), 51-6	Case series n=15 FU=4 days	In this first-in-man experience, the feasibility of a new embolic deflection device is demonstrated. Larger randomised, prospective studies are required to confirm these findings and prove safety and efficacy by reducing the incidence of cerebral embolism and stroke after TAVI.	Larger studies are already included in table 2.
Pagnesi M, Martino E A, Chiarito M et al. (2016) Silent cerebral injury after transcatheter aortic valve implantation and the preventive role of embolic protection devices: A systematic review and meta-analysis. International journal of cardiology 221, 97-106	Systematic review and meta-analysis n=384 patients from 4 published papers and 2 conference abstracts Search up until 24/12/2015	Silent cerebral injury occurs in the majority of patients undergoing TAVI and DW-MRI allows a precise characterisation of new ischemic brain lesions. CPDs reduce the total and single volume of such lesions detected after the procedure, although the number of new lesions per patient and the number of patients with new lesions are not significantly reduced by such devices.	2 systematic reviews and meta-analyses that are more recent and that include more patients are already included in Table 2.
Paradis J-M, Nazif T M, and Rodes-Cabau J (2018) First-in-man use of the new generation	Single case report	The patients had no neurological deficits or vascular complications	Studies with more patients are

TRIGUARD 3 cerebral embolic protection device during transcatheter aortic valve implantation. Eurointervention 18, 18	Follow-up=6 days	during or after the procedure. He was discharged home on day six. The design features of the new-generation TriGUARD 3 device are expected to improve generalisability and ease of use, and enhance embolic protection properties. Future trials will determine the efficacy of this device for preventing cerebral embolism during TAVI procedures.	included in Table 2.
Rodes-Cabau J, Kahlert P, Neumann F-J et al. (2014) Feasibility and exploratory efficacy evaluation of the Embrella Embolic Deflector system for the prevention of cerebral emboli in patients undergoing transcatheter aortic valve replacement: the PROTAVI-C pilot study. JACC. Cardiovascular interventions 7(10), 1146-55	Non-randomised comparative study n=52 (41 Embrella versus 11 without Embrella) FU=30 days	This study showed the feasibility and safety of using the EED system in TAVR procedures. The EED system did not prevent the occurrence of cerebral microemboli during TAVR or new transient ischemic lesions as evaluated by DW-MRI, but it was associated with a reduction in lesion volume. Further studies are warranted to determine the efficacy of using the EED system during TAVR procedures.	Larger studies are already included in table 2.
Samim M, van der Worp B, Agostoni P et al. (2017) TriGuard™ HDH embolic deflection device for cerebral protection during transcatheter aortic valve replacement. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 89(3), 470-477	Prospective case series n=14 FU=90 days	This study showed the feasibility and safety of using the TriGuard™HDH for cerebral protection during TAVR. This device did not decrease the number of post-procedural new cerebral DWI lesions, however its use showed decreased lesion volume as compared to unprotected TAVR.	Larger studies are already included in table 2.
Samim M, Agostoni P, Hendrikse J et al. (2015) Embrella embolic deflection device for cerebral protection during transcatheter aortic valve replacement. The Journal of thoracic and cardiovascular surgery 149(3), 799-2	Case series and retrospective comparative study n=52 (15 cerebral protection versus 37 TAVI only) FU=4 days	The use of the Embrella device during TAVR increased the number of cerebral ischemic lesions on postprocedural brain imaging. This increase in number was however accompanied by a significant reduction in single-lesion volume and the absence of large total infarct volumes.	Larger studies are already included in table 2.
Showkathali R, Dwarakowski R, Byrne J et al. (2017) The use of embolic deflector device in Transcatheter Aortic Valve Implantation (TAVI). IHJ Cardiovascular Case Reports (CVCR) 1(1), 17-18	Single case report FU=2 days	The Embrella device was removed at the end of the procedure. The patient was discharged after 2 days and doing well.	Larger studies are already included in table 2.
Sinning J-M, Hammerstingl C, Vasa-Nicotera M et al. (2012)	Single case report	After retrieval of the cerebral protection device, debris and	Larger studies are

Transcatheter aortic valve implantation and closure of the left atrial appendage under cerebral protection. EuroIntervention : journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 8(5), 640-1	FU=6 days	embolic material were found captured within the filters. The patient was discharged uneventfully after 6 days.	already included in table 2.
Testa L, Latib A, Casenghi M et al. (2018) Cerebral Protection During Transcatheter Aortic Valve Implantation: An Updated Systematic Review and Meta-Analysis. Journal of the American Heart Association 7(10),	Systematic review and meta-analysis n=1285 patients from 8 studies (including 5 RCTs) Search up until December 2017	• The CPD delivery success rate was reported in all studies and was achieved in 94.5% of patients. • The use of CPD was not associated with significant differences in terms of 30-day mortality (odds ratio 0.43 [0.18-1.05], P=0.3) but • it was associated with a lower rate of 30-day stroke (odds ratio 0.55 [0.31-0.98], P=0.04), although this result is driven by a single nonrandomized study. • No differences were detected with respect to the number of new lesions (standardized mean difference -0.19 [-0.71 to 0.34], P=0.49). • The use of CPD was associated with a significantly smaller ischemic volume per lesion (standardized mean difference, -0.52 [-0.85 to -0.20], P=0.002) and smaller total volume of lesions (standardized mean difference, -0.23 [-0.42 to -0.03], P=0.02).	2 systematic reviews and meta-analyses are already included in Table 2. This meta-analysis includes the same studies that are included in Study 1 (Mohananey 2018) but also includes an RCT which assesses the Embol-X device which is out of the remit of this review.
Van Gils L, Kroon H, Daemen J et al. (2018) Complete filter-based cerebral embolic protection with transcatheter aortic valve replacement. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions 91(4), 790-797	Case series n=11 FU=8 days	The left vertebral artery is an important entry route for embolic material to the brain during TAVR. Selective filter protection of the left vertebral artery revealed embolic debris in all patients. The clinical value of complete filter-based TCEP during TAVR warrants further research.	Larger studies are already included in table 2.
Van Mieghem N M, El Faquir, N, Rahhab Z et al. (2015) Incidence and predictors of debris embolizing to the brain during transcatheter aortic valve implantation. JACC.	Case series n=81 FU=6 weeks	Debris is captured with filter-based embolic protection in the vast majority of patients undergoing TAVR. Tissue-derived material is found in 63% of cases and is more frequent with the use	Larger studies are already included in table 2.

Cardiovascular interventions 8(5), 718-24		of balloon-expandable systems and more oversizing.	
Wang N, and Phan K (2018) Cerebral protection devices in transcatheter aortic valve replacement: a clinical meta-analysis of randomized controlled trials. Journal of thoracic disease 10(3), 1927-1935	Systematic review and meta-analysis of RCTs n=643 patients from 5 RCTs Search up until May 2017	• The primary composite endpoint of all-cause mortality and stroke at 30 days was lower in patients having cerebral protection compared to those patients with TAVI alone (OR, 0.54; 95% CI, 0.30 to 0.98). • Use of embolic protection was also associated with lower new total lesion volume (standardised mean difference, -0.49; 95% CI, -0.96 to -0.03). • There was a non-significant reduction in the risk of secondary clinical endpoints of all-cause mortality, stroke, life-threatening bleed, acute kidney injury and major vascular complications in patients randomised to cerebral protection.	2 systematic reviews and meta-analyses are already included in Table 2. This meta-analysis includes the same studies that are included in Study 1 (Mohananey 2018) but also includes an RCT which assesses the Embol-X device which is out of the remit of this review.