Clinically relevant perioperative neurological events during transcatheter aortic valve implantation compared to high-risk open aortic valve replacement: results from prospective randomised data

Abstract

Introduction: Transcatheter aortic valve implantation (TAVI) has emerged as a minimally invasive surgical option for patients with severe aortic stenosis who are deemed high risk for open aortic valve replacement (AVR). Complication rates for TAVI should be less than or equal to those of traditional AVR in order to justify its use.

Methods: This study was part of a clinical trial studying patients that suffer from aortic stenosis whose surgical mortality risk was deemed to be greater than 15%. The purpose of this study was to determine the perioperative neurological event rates seen in TAVI when compared to traditional open AVR. Patients exhibiting signs of neurological changes were examined by a neurologist and assigned a score on the NIH Stroke Scale (NIHSS). Patients with a NIHSS change of at least 2 and/or neurological changes from baseline within 30 days of operation were identified and compared across both cohorts and within each randomised group. In this study, cohort A refers to patients who were deemed to be of moderate surgical risk of mortality (≥15%), while cohort B refers to patients deemed to be at a high risk of surgical mortality (≥50%).

Results: Incidence of neurological events was compared based on cohort designation and procedure type. The overall perioperative neurological event rate for all patients in the trial was 5.30% (8/151), with no events coming from cohort B (0/36). Eight out of 115 patients (6.96%) in cohort A demonstrated neurological events. Two of 25 patients (8.00%) who underwent open AVR demonstrated neurological changes. Of 50 patients undergoing transfemoral TAVI, five (10%) exhibited neurological changes. Of 40 patients undergoing transapical TAVI, one (2.5%) showed neurological changes. Relevant cross comparisons were made, none of which demonstrated significance.

Discussion: No statistically significant difference was shown between patient groups receiving different interventions, suggesting that TAVI does not pose an increased risk of perioperative neurological changes when compared to open AVR. Diffusion-weighted MRI should be considered to detect clinically silent neurological events for a more correct assessment of risk.

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Introduction

Aortic stenosis (AS) is a common valvular heart disease. It mainly affects individuals in the seventh and eighth decades of life and is usually caused by senile calcification of the valve leaflets.[1] Less commonly, AS is caused by rheumatic heart disease or congenital bicuspid valves. In severe cases, AS patients exhibit symptoms of heart failure, angina and syncope. After the onset of symptoms, patients usually survive for no more than two to three years and thus require urgent

treatment.[2] Traditionally, first-line therapy has been open heart aortic valve replacement (AVR). This method has long shown success in improving life expectancy. However, those considered unfit for such surgery usually only receive medical therapy to manage their symptoms, including the administration of diuretics, nitrovasodilators, beta-blockers and ACE inhibitors. One drawback to the traditional approach to treatment is that many octogenarians who suffer from AS also suffer from several crippling comorbidities, making them unfit for open heart surgery. Transcatheter aortic valve implantation (TAVI) is an alternative intervention in such situations, and is quickly proving to be safe and effective for those patients who may have previously been consigned to symptomatic medical therapy.[3] TAVI is less invasive than open heart surgery and is thus less physically stressful. Open heart surgery is usually a four- to six-hour procedure with patients needing months to recover, whereas TAVI can take as little as 90 minutes and patients usually recover within days.[4] TAVI involves the replacement of a calcified aortic valve with a catheter-mounted bioprosthetic valve (the Edwards SAPIEN device) by either transfemoral (access via the femoral artery) or transapical (access via a small thoracotomy at the apex of the left ventricle) routes. Similar to stenting of coronary arteries, TAVI involves the placement of a new valve within the opening of the original valve and the inflation of a balloon until the new valve functionally replaces the original valve. Within the device are prosthetic leaflets surrounded by a wire mesh similar to a coronary artery stent. Under fluoroscopy guidance, a surgical team can implant the device quickly before removing the catheter and suturing the small access sites. Overall, it is a minimally invasive procedure and, importantly, can be done without the need for cardiopulmonary bypass. These low-impact features allow TAVI to cure severe AS in previously inoperable patients.

While still undergoing clinical trials in the United States (PARTNER Trial), TAVI has shown dramatic success in patients at high risk for open AVR and even those previously deemed inoperable. In Europe, thousands of TAVI procedures have been conducted and it has been recognised as safe and effective.[5] With more success, TAVI could potentially be the future of AVR. However, there are some complications associated with the procedure, and before it can completely replace traditional open heart surgery, TAVI must demonstrate complication rates less than or equal to those of current surgical methods. The most concerning outcome of TAVI clinical trials worldwide is the claim that there is an increased incidence of perioperative stroke in TAVI patients compared to those receiving open AVR.[5] Furthermore, research demonstrating the superiority of one approach – that is, transapical or transfemoral – could inform best practice guidelines. The focus of this investigation is to determine the difference, if any, in the incidence of neurological events between the two new surgical methods (transfemoral and transapical) and traditional open AVR. A second objective is to quantify the severity of calcification and atheromatous disease within the aortic arch and study how this might contribute to stroke risk in any one of the surgical procedures.

Methods

Records on all 178 patients currently enrolled in the PARTNER Trial at the University of Pennsylvania were gathered. Patients were first designated to either cohort A (risk of operative mortality ≥15%) or cohort B (risk of operative mortality ≥50%), who are traditionally considered inoperable. Patients in cohort A were then randomised to receive transfemoral TAVI, transapical TAVI or open heart AVR, while those in cohort B were randomised to receive either transfemoral TAVI or best medical management (BMM) (**Figure 1**). Patients who had suffered clinically evident neurological changes in the 30-day postoperative period were identified (**Figure 2**). These

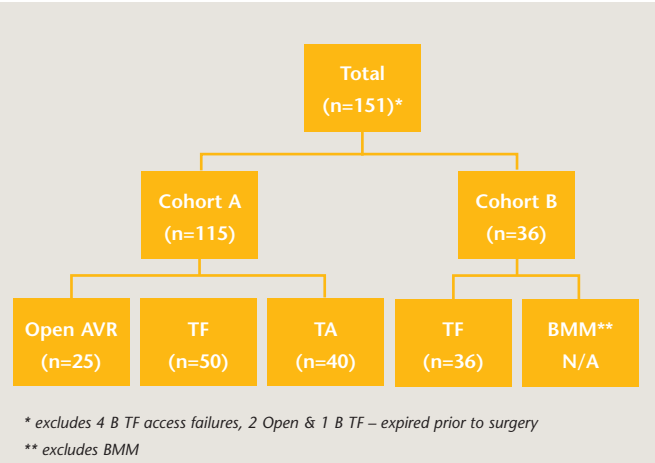

FIGURE 1: Study participants used for perioperative neurological events analysis.
TA = transapical; TF = transfemoral; AVR = aortic valve replacement; BMM = best medical management.
Cohort A: moderate risk of surgical mortality (≥15%); cohort B: high risk of surgical mortality (≥50%).

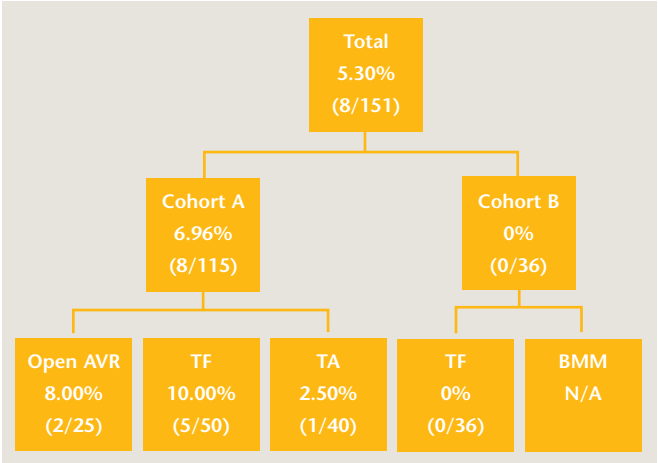

FIGURE 2: Incidence of clinically evident neurological events in the perioperative period (within 30 days of intervention).
TA = transapical; TF = transfemoral; AVR = aortic valve replacement; BMM = best medical management.
Cohort A: moderate risk of surgical mortality (≥15%); cohort B: high risk of surgical mortality (≥50%).

Table 1: Patients who suffered clinically evident neurological changes in the perioperative period (n=8).

Event	Intervention	Type of stroke suffered
1	Cohort A – transfemoral	Embolic – new minor stroke
2	Cohort A – transfemoral	Embolic – new minor stroke
3	Cohort A – Open AVR	Embolic – new minor stroke
4	Cohort A – Open AVR	Embolic – major stroke
5	Cohort A – transfemoral	Embolic stroke and hypoperfusion
6	Cohort A – transfemoral	Embolic stroke due to heparin-induced thrombocytopaenia
7	Cohort A – transfemoral	Embolic – major stroke
8	Cohort A – transapical	Embolic stroke and hypoperfusion

Table 2: Grading scale for calcification of the aortic arch, reflecting the most severe circumferential calcification as assessed by CT chest.

Score	Calcification
0	No calcification visible
1	<25% of circumference
2	25-50% of circumference
3	>50% of circumference
4	Circumferential (porcelain aorta)

Table 3: Modified CT grading scale for aortic atheroma.[9]

Grade	Description
I	Smooth and continuous aortic intimal surface
II	Intimal thickening 3 to 5mm
III	Atheroma protruding <5mm into aortic lumen
IV	Atheroma protruding >5mm into aortic lumen and ulcerated or pedunculated

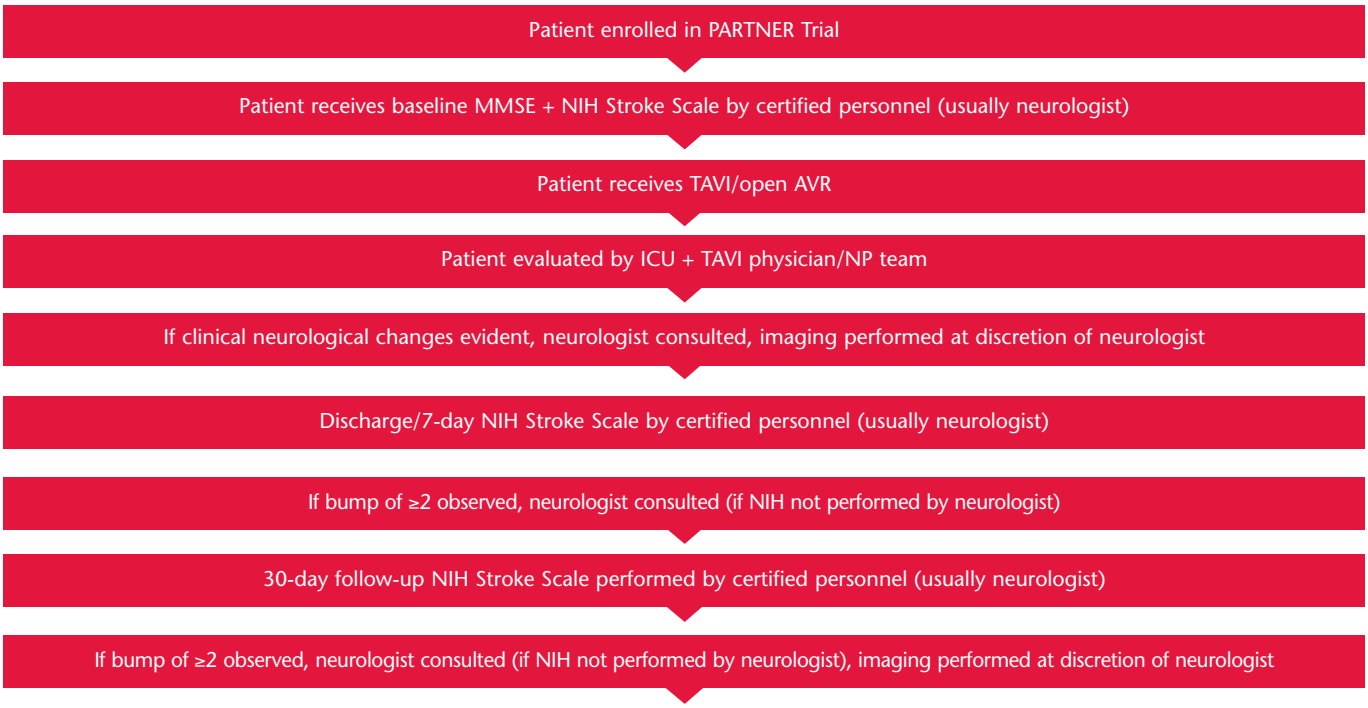

FIGURE 3: PARTNER Trial protocol regarding the neurological assessment of patients.

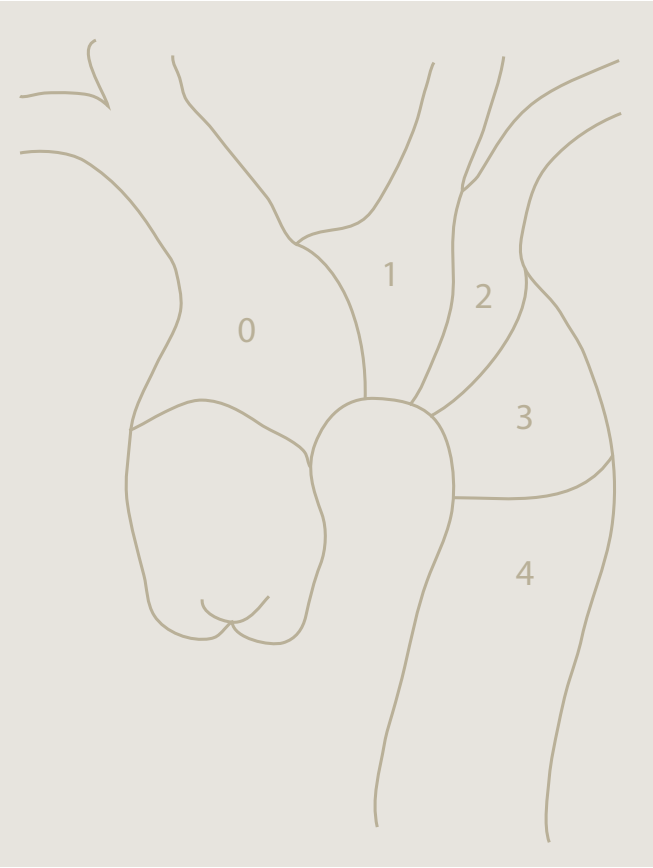

FIGURE 4: The zones of the aortic arch.[7]

patients were classified by the cause of their stroke (embolic vs. hypoperfusive) and the type of procedure they had undergone (transfemoral TAVI, transapical TAVI or open heart AVR) (**Table 1**). Neurological status was measured preoperatively using the Mini Mental State Examination (MMSE) and the National Institute of Health Stroke Scale (NIHSS).[6] Only the NIHSS was repeated postoperatively. The MMSE quantifies cognitive function testing for orientation, attention, calculation, recall, language and motor skills. Patients are scored on a scale of 30 points.[7] The NIHSS is a quantitative evaluation of cerebral infarction consisting of 15 items. A score of greater than 25 indicates a large stroke, while scores less than four may suggest a small stroke.[8] In this trial, if a patient's NIHSS increased by at least two points from pre- to postoperative assessment, it was considered sufficient to warrant a neurology consultation and possibly imaging (**Figure 3**).

The second objective of the study was to assess the role atherosclerosis plays in causing embolic strokes in TAVI patients. Because transfemoral TAVI is performed by passing a catheter across the aortic arch, the risk of dislodging atheromatous or calcific emboli into the carotid arteries needs to be appraised. Using 3D-CT imaging software, each of the 178 patients' preoperative CT angiograms were examined and each aortic arch was graded for calcification in three zones and for atheroma in one zone (**Figure 4; Table 2**). To study the association between atherosclerotic disease and neurological events in TAVI patients, the severity of atheroma and calcification in patients who suffered strokes was compared to those who did not.

Using 3D-CT imaging, three zones of each patient's aorta were graded: zone 1, zone 3 and an axial view of zone 1 at the base of the head vessels (**Figure 4**). The grading scheme used for calcification (**Table 2**), designed by Joseph Bavaria, reflects the most severe circumferential calcification observed on CT of the chest. The grading scheme used to assess zone 3 atheromata (**Table 3**) quantifies the severity of atheromatous disease in the aortic arch. Gutsche previously demonstrated the useful applications of this scale, finding that "high grade aortic atheroma of the aortic arch predicted a high probability for cerebral embolisation and can be used to identify patients at high risk for stroke".[9] For this reason, the same scale was adopted for use in this study.

Table 4: Comparisons of incidence of neurological events between patient groups.

Comparison	Results	p-value
Cohort A TA vs. open AVR	2.50% (1/40) vs. 8.00% (2/25)	p = 0.55
Cohort A TF vs. open AVR	10.00% (5/50) vs. 8.00% (2/25)	p = 1.00
Cohort A TF vs. cohort A TA	10.00% (5/50) vs. 2.50% (1/40)	p = 0.22
Cohort A TF + B TF vs. open AVR	5.81% (5/86) vs. 8.00% (2/25)	p = 0.65
Cohort A TF + B TF vs. cohort A TA	5.81% (5/86) vs. 2.70% (1/40)	p = 0.66

TA = transapical; TF = transfemoral; AVR = aortic valve replacement Cohort A: moderate risk of surgical mortality (≥15%); cohort B: high risk of surgical mortality (≥50%).

Results

Patients were assigned to cohorts based on surgical mortality risk and randomised to receive TAVI, open AVR or BMM as treatment for AS. Clinically evident neurological events were documented and radiological evidence of atheromatous

build-up and calcification was collected for all patients.
Figure 1 demonstrates how study participants were randomised (n=151). Cohort A patients (n=115) were randomised to receive open AVR (n=25), transfemoral TAVI (n=50) or transapical TAVI (n=40). Cohort B patients (n=36) were randomised to receive either transfemoral TAVI (n=36) or BMM.
Data regarding the incidence of neurological events, specifically stroke, in each patient group is shown in **Figure 2**. Overall, neurological events occurred in 5.3% of patients (n=8). Cohort A had a neurological event incidence of 6.96% (n=8). Of these, 8% of patients in the open AVR group (n=2) and 10% of patients in the transfemoral TAVI group (n=5) experienced neurological events. Only 2.5% of patients in the transapical TAVI group (n=1) suffered an embolic event after intervention. In cohort B, no patients experienced perioperative neurological events. The BMM group did not have reportable results as these patients were lost to follow-up.
Next, the type of neurological event each patient experienced in the perioperative period was investigated (**Table 1**). All eight patients suffered strokes due to emboli. However, two patients were also diagnosed with hypoperfusive ischaemia.
The relative risks between the types of intervention – open AVR, transfemoral TAVI and transapical TAVI – were computed (**Table 4**). The differences between all patient groups were found to be statistically insignificant.
Table 5.1 displays the average calcification and atheroma scores for all patients who had CT scans available to grade. **Tables 5.2** and **5.3** present the scores of patients who did not suffer neurological adverse events and those who did, respectively. The original hypothesis was that the scores of those who suffered clinically evident neurological events would be higher due to the risk of atheromatous or calcified plaques becoming dislodged and embolising to the brain. However, the data indicate otherwise; those that suffered clinically evident neurological events in the perioperative period actually had a lower average score than those who did not.

Discussion

TAVI has been associated with a risk of developing new perioperative cerebral ischaemic lesions.[8] The aim of this study was to identify the relative risk of stroke in patients receiving transfemoral TAVI, transapical TAVI, open AVR and BMM. Comparisons of the incidence of neurological events in the perioperative period between these treatment groups indicate

Table 5.1: Average calcification and atheroma scores for all patients (n=175).

Zone 1 calcification circumferential	Distal arch calcification grade	Distal arch atheromatous grade (Gutsche Scale)	Zone 1 calcification – axial @ head vessels
1.72	1.66	1.36	1.57

Table 5.2: Average calcification and atheroma scores for patients who did not suffer from clinically evident perioperative neurological events (n=167).

Zone 1 calcification circumferential	Distal arch calcification grade	Distal arch atheromatous grade (Gutsche Scale) [n=131*]	Zone 1 calcification – axial @ head vessels
1.73	1.67	1.38	1.58

**CTs for 36 patients were either non-contrast or of too poor quality to assign an atheroma score.*

Table 5.3: Average calcification and atheroma scores for patients who suffered from clinically evident perioperative neurological events (n=8).

Zone 1 calcification circumferential	Distal arch calcification grade	Distal arch atheromatous grade (Gutsche Scale)	Zone 1 calcification – axial @ head vessels
1.5	1.38	1	1.38

that TAVI offers no increased risk of perioperative neurological changes compared to open AVR.

Another aim of the study was to identify any increased risk of neurological events that may be associated with atherosclerotic or calcific disease of the aortic arch. It was expected that the arch scores of patients who experienced a stroke in the perioperative period would be higher than those who did not, but the data indicate that there is no association between vessel disease and embolic stroke. Rodés-Cabau *et al.* demonstrated that TAVI patients have an increased incidence of stroke compared to those who receive open AVR.[10] The data in this study show no significant difference in neurological sequelae among intervention types. The second objective of this study complements research conducted by Gutsche – that is, examining the severity of atherosclerotic disease and calcification of the aorta in relation to embolic strokes to the brain in procedures that involve manipulation of devices within the aorta.[8] However, this study is unique in that it is the first to attempt to identify atherosclerotic risk factors specific to TAVI procedures.

There is some controversy regarding the superiority of transapical to transfemoral approaches to TAVI. One theory proposed that transfemoral access is riskier than the transapical approach due to the catheterisation of the aortic arch and crossing of the aortic valve.[3] However, Rodés-Cabau *et al.* found no difference in safety between transfemoral and transapical approaches, a finding that is supported by data collected in this trial.

The size of this study is small, which results in a low statistical power. An unexpected result was that patients in cohort B, who were clinically less well than their counterparts in cohort A, had no clinically evident neurological events. The primary investigators were puzzled to find that cohort B transfemoral TAVI patients suffered no strokes, while their counterparts in cohort A experienced a stroke incidence of 10%. This surprising finding may be attributed to the low power of this study. This study is ongoing, and further data will be collected in the coming year. With a larger sample size, the stroke rate in high-risk patients undergoing transapical TAVI may match or exceed that in lower risk patients undergoing the same procedure.

Moreover, more data may reveal an association between larger vessel disease and neurological events in perioperative TAVI patients, given that Rodés-Cabau *et al.* performed diffusion-weighted MRIs on all of their patients and noticed that a significant percentage of their patients suffered from perioperative cerebral ischaemic lesions.[10] These lesions were silent – that is, the patients did not exhibit any symptoms – and therefore would go undetected by a neurological scale, such as the NIHSS or MMSE used in this study. Further studies should be conducted to investigate the efficacy of deflector 'umbrella' devices and their role in the prevention of embolisation during and after TAVI procedures. These devices are currently under clinical assessment, but show great promise in sequestering emboli that would otherwise travel to the brain.[5]

Traditionally, open AVR has been the treatment of choice for valve replacement in aortic valve disease. However, TAVI is now providing a new option for high-risk patients who are deemed unfit for open heart surgery. In the future, TAVI may replace open AVR as the primary method of treatment for AS patients of all ages and risk levels.

Acknowledgements

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