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Silent Cerebral Infarction and Cognitive Function following TAVI: a comparison of the 1st generation CoreValve and 2nd generation Lotus valve

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Short title: Silent cerebral injury: CoreValve Vs. Lotus

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ABSTRACT

Objective: To compare the incidence of silent cerebral infarction and impact upon cognitive function following Transcatheter Aortic Valve Implantation (TAVI) with the first-generation CoreValve (Medtronic, Minneapolis, Minnesota) and second-generation Lotus valve (Boston Scientific, Natick Massachusetts).

Design: A prospective observational study comprising a 1.5 T cerebral MRI scan, performed preoperatively and immediately following TAVI, and neurocognitive assessments performed at baseline, 30 days and 1-year follow-up.

Setting: University hospitals of Leeds and Leicester, UK.

Patients: 66 (80.6±8.0 years, 47% male) high-risk severe symptomatic aortic stenosis patients recruited between April 2012 to May 2015.

Main outcome measures: Incidence of new cerebral micro0infarctionm and objective decline in neurocognitive performance.

Results: All underwent cerebral MRI at baseline and immediately following TAVI, and 49 (25 Lotus, 24 CoreValve) completed neurocognitive assessments at baseline, 30 days and 1 year. There was a significantly greater incidence in new cerebral micro-infarction observed following the Lotus TAVI (23(79%) vs 22(59%), p=0.025) with a greater number of new infarcts per patient (median 3.5 (IQR 7.0) vs. 2.0 (IQR 3.0), p=0.002). The mean volume of infarcted cerebral tissue per patient was equivalent following the two prostheses (p=0.166). More patients suffered new anterior (14(48%) vs. 2(5%), p=0.001) and vertebrobasilar (15(52%) vs. 7(19%), p=0.005) lesions following Lotus. Lotus was associated with a decline in verbal memory and psychomotor speed at 30 days. However, performance longitudinally at one year was preserved in all neurocognitive domains.

Conclusions: There was a higher incidence of silent cerebral micro-infarction and a greater number of lesions per patient following Lotus compared to CoreValve. However, there was no objective decline in neurocognitive function discernible at 1-year following TAVI with either prosthesis.

Article Summary

Before the use of Transcatheter Aortic Valve Implantation can be extended to younger clinical groups, the association with silent cerebral infraction and impact upon neurocognitive function must be further understood. We sought to define the profiles of cerebral injury following TAVI with the novel Boston Lotus iteration and the first-generation Medtronic CoreValve.

Strengths and Limitations of this Study

- Contemporary study comprising both a novel TAVI design technology and an established device.
- A two-centre study combining both DW-MRI and cognitive assessments to comprehensively assess cerebral injury following TAVI.
- Mid-term follow-up to 1 year

- Not randomised.
- Higher field strength MRI available for more sensitive detection of cerebral embolic infarction.

KEYWORDS: Transcatheter Aortic Valve Implantation, Medtronic CoreValve, Boston Lotus Valve, Cerebral MRI, Neurocognitive function

Abbreviations list

BAV:	balloon aortic valvuloplasty
CABG:	coronary artery bypass grafting
DSST:	digit symbol substitution test
DW-MRI:	diffusion weighted magnetic resonance imaging
eGFR	estimated glomerular filtration rate
GPBT:	grooved pegboard test
HVLT:	Hopkins verbal learning test
IQ:	intelligent quotient
LNS:	letter number sequencing
MDCT:	multi detector computed tomography
MI:	myocardial infarction
MMSE:	mini mental state examination
PCI:	percutaneous coronary intervention

SD:	standard deviation
STS:	Society of Thoracic Surgeons
TAVI:	transcatheter aortic valve implantation
TMT:	trail making test
VARC:	valve academic research consortium

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is advocated by both European[1] and US[2] guidance in patients with symptomatic aortic stenosis deemed inoperable or with too high a predicted postoperative mortality. TAVI is cost-effective[3], significantly improves quality of life[4], and recent trial data suggest non-inferior to surgery in intermediate-risk patients[5], potentially expanding its application to a broader population.

However, since the landmark PARTNER trial in 2010[6], the inherent risk of disabling stroke associated with TAVI has been well recognised. Despite 10 years of refinement in transcatheter technology and delivery technique, stroke rates remain similar[7]. Importantly, TAVI is also associated with a high incidence (up to 84%) of silent cerebral embolism as detected by diffusion-weighted MRI (DW-MRI) [8-10]; more frequent than that following aortic valve surgery[11].

The association of new DW-MRI lesions post-TAVI with cognitive decline is an issue currently under intense scrutiny, as it has long been recognised that silent cerebral infarcts can more than double the risk of dementia[12]. Indeed the concept of post-operative cognitive dysfunction and its relationship with DW-MRI has been described following valvular surgery, bypass grafting and left heart catheterization[13].

The Boston Scientific Lotus valve is a novel TAVI iteration that incorporates a number of features specifically designed to improve upon first-generation devices[14]. As such it exhibits superior deployment success rates when compared to the older Medtronic CoreValve[15]. However, the key concern of silent cerebral injury following implantation and cognitive decline remains unanswered. We sought to characterise the extent of new silent cerebral infarction using DW-MRI, and investigate

longitudinally cognitive function following TAVI with the first generation self-expanding Medtronic CoreValve and the second-generation mechanically-expanded Boston Scientific Lotus valve.

METHODS

Patient selection

This study prospectively recruited 74 patients with severe degenerative AS from two large UK tertiary cardiothoracic centres (Leeds and Leicester) who were referred for TAVI between April 2012 and May 2015. Severe AS was classified by echocardiography as an aortic valve area of ≤1.0cm^2 or peak velocity >4m/s. The decision for TAVI in all cases was taken by a multidisciplinary heart team in accordance with international guidance[16]. Exclusion criteria included any contraindication to MRI or pre-existing severe cognitive impairment (a mini-mental state examination (MMSE) score<10). Any patient deemed to exhibit new focal neurological dysfunction consistent with clinical stroke post-TAVI was also excluded. The study was approved by the National Research Ethics Service (08/H1307/106), complied with the Declaration of Helsinki and all patients provided written informed consent.

Transcatheter Aortic Valve Implantation

TAVI was performed using either a first-generation CoreValve system (Medtronic, Minneapolis, Minnesota, USA) or the Lotus™ Aortic Valve system (Boston Scientific Corporation, Natick, MA, USA) employing standard techniques as previously described for both vendors[17,18]. Multidetector computed tomography (MDCT) was employed to assist annular sizing and assess aortic calcification prior to TAVI. Percutaneous femoral artery access was the default approach. Balloon valvuloplasty, rapid ventricular pacing and post-dilatation (in the case of CoreValve)

were employed at the discretion of the operator. All patients received weight-adjusted unfractionated heparin to maintain an activated clotting time >200s and were treated with dual antiplatelet therapy (aspirin 75mg and clopidogrel 75mg) for a minimum of 3 months. None of the TAVI cases involved the use of a cerebral protection device.

Neurocognitive assessment

The neurocognitive test battery was performed by trained assessors (medical/nursing) in a quiet comfortable environment at three Valve Academic Research Consortium (VARC) recommended time points (baseline, 30d and 12m)[19]. Training of assessors and performance validation was undertaken by an experienced neuropsychologist (CL). Follow-up assessment was conducted at the patient home or the hospital. Total assessment time ranged between 60-90min with appropriate rest periods. Baseline characteristics, patient handedness and years of education were recorded. The national adult reading test (NART) was used to calculate the full scale intelligent quotient (FSIQ=123.2-(1.029 x NART error score)). A broad battery of previously validated neurocognitive assessments were undertaken at the designated time points[20] and included evaluation of: *cognitive reasoning*: using the mini mental state examination (MMSE), *verbal memory*: using the Hopkins Verbal Learning Tests (HVLT), *executive function*: using the Letter Number Sequencing task (LNS), *psycho-motor speed*: using the Trail Making Test (TMT) A and B, *perceptual and visual memory*: using the Digit-Symbol Substitution Test (DSST), and *fine motor co-ordination and speed:* using the Grooved Pegboard Test (GPBT - Model 32025, Lafayette Instruments Co, IN, USA). Cognitive decline was defined as a reduction of the score by 1 SD of the baseline score for all tests[21-23].

Cerebral MRI

Cerebral MRI was conducted pre- and post-procedure (within 7d) using identical imaging protocols. MRI was performed on the same 1.5T system for all serial scans for any individual patient (Intera, Phillips Healthcare, Best, The Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany). The imaging protocol consisted of T2 weighted fast field echo, T2 turbo field echo and diffusion weighted imaging (DWI) (22 slices, 5mm thick, 1mm gap, FOV 350, RFOV 100). Each scan was independently assessed by two experienced Neuroradiologists (AG, MI), blinded to all clinical/procedural details. Cerebral embolism or micro-infarction was defined as a new restricted diffusion lesion on DWI. New cerebral micro-infarcts were localised to one hemisphere and vascular territory. Infarct diameter was used to categorise patients into small or large lesion sub-groups (<5mm or >5mm; in the case of multiple lesions the largest lesion was used to determine status). The total infarct volume (ml) was measured off-line using standard post-processing software (QMass 7.2, Medis, The Netherlands) as previously published[10,11].

Statistical Analysis Data was tested for normality using the Shapiro-Wilks test. Continuous variables were expressed as mean±SD or median (Q2-Q3 or IQR) and were tested for differences by means of a 2-sided, unpaired Student t test (for comparison between groups) or a 2-sided, paired Student t test (for intra-group comparison). Non-parametric testing (Mann–Whitney test) was performed where indicated. Categorical variables were given as frequencies and percentages and compared by $\chi 2$ statistics or Fisher exact test. All statistical analyses were performed using the PASW software package (V.21.0 SPSS, IBM, Chicago, Illinois, USA) with a two-sided significance level of $p<0.05$ was considered statistically significant. Sample size to detect cognitive decline (reduction in score by 1SD) was estimated using *IBM*

SPSS Sample power version 3, and using normative data for the test to have 80% power (alpha 0.05), a minimum of 17 patients were required in each group.

RESULTS

Patient population

A total of 66 patients (37 Medtronic CoreValve and 29 Boston Lotus) underwent both the pre-operative (median 1 day pre-procedure, IQR 14 days) and immediate post-TAVI MRI scans (median 4 days, IQR 4 days). The baseline characteristics of these groups are shown in Table 1. Forty-nine of these (24 CoreValve and 25 Lotus) completed serial neurocognitive assessments out to 12 months. Reasons for non-completion were varied reflecting an elderly frail population (Figure 1).

Patient Involvement

Patients were not involved with the study design, recruitment, conduct or interpretation of results obtained. Outcome measures were objectively measured and not based on patient experience.

Procedural data

TAVI was successful in all cases. Catheterization data for the TAVI implant procedures is summarised in Table 2. Of the 29 Lotus implants, 7(24%) involved device repositioning. Of the CoreValve implants, there were three instances of embolization and the requirement of a second valve in three cases (two of whom were due to embolization).

Cerebral MRI

Typical cerebral DWI images at baseline and immediately after TAVI are depicted in Figures 2A and 2B respectively.

Baseline: At baseline, 5(17%) of the Lotus patients and 10(27%) of the CoreValve patients had evidence of pre-existing established stroke (p=0.346) with equivalent lesion volume (p=0.529). There was also evidence of recent micro-infarction on

cerebral DWI in 2(7%) Lotus and 4(11%) CoreValve patients (p=0.583). A greater proportion of patients undergoing Lotus TAVI had evidence of periventricular ischaemia compared to those undergoing CoreValve (19(66%) vs. 14(38%), p=0.026).

Post-procedure: Table 3 summarises the findings of DWI imaging following TAVI. There was a significantly greater incidence in new micro-infarction observed following Lotus TAVI with a greater number of new infarcts per patient. These were predominantly of small size, with a comparable mean infarcted cerebral tissue volume per patient with both TAVI designs. More patients suffered new anterior and vertebro-basilar lesions following Lotus than CoreValve. The number of new lesions following Lotus repositioning (n=7) and non-repositioning (n=22) did not differ (1.0 (IQR 8.0) vs. 3.0 (IQR 3.75), p=0.438) and Lotus repositioning did not correlate with number of new lesions (p=0.435). For the CoreValve group, the three patients in whom embolization occurred had significantly greater frequency of new lesions post-procedure (4.0 (IQR 0.0) vs. 1.0 (IQR 2.0), p=0.011), but no difference was seen in the three requiring a second valve (4.0 (IQR 0.0) vs. 1.0 (IQR 2.0), p=0.148). Typical findings of new cerebral infarction detected by DW-MRI post-TAVI are exemplified in Figure 2.

Baseline education and intelligence

The vast majority of patients were right handed (CoreValve: 21(88%) vs. Lotus: 24(96%), p=0.234) with equivalent reporting of disability on Modified Rankin Scale (CoreValve: 1.9±1.1 vs. Lotus: 2.0±0.7, p=0.929). The CoreValve and Lotus patients were similar in respect of years in education (10.9±1.9 vs. 11.6±2.5yrs, p=0.279), and full scale IQ (106±12 vs. 102±15, p=0.313). Global cognition measured using the MMSE was also equivalent (28.8±1.8 vs. 28.6±1.6, p=0.279) with only 1 patient from

the Lotus group indicating cognitive impairment (defined as an MMSE of less than 24[24]).

Effect of TAVI design on absolute neurocognitive function scores

Neurocognitive performance, prior to and following Lotus and CoreValve TAVI, are shown in Table 4. For the vast majority of domains, including global cognition, psychomotor speed, executive function and fine motor co-ordination, no change in test scores were observed at 30 days or 12 months following TAVI, with either the Lotus or CoreValve prostheses.

The HVLT was utilised to test mnemonic function and verbal memory, and total learning scores remained unchanged over time for both CoreValve and Lotus. However, delayed recall scores and discrimination index were significantly lower at 30 days following Lotus (Table 4), with 12 month scores returning to baseline level (delayed recall: 7.6±3.0 vs. 9.0±6.7, p=0.320, discrimination index: 10.2±1.5 vs. 10.1±2.4, p=0.867), with no change observed following CoreValve.

The TMT assesses executive function and psychomotor speed, with TMT A preceding the more challenging TMT B. The TMT B scores were significantly lower at 30 days following Lotus (Table 4), with 12 month scores again returning to baseline level (170.9±86.5 vs. 152.3±87.5, p=0.215), with no change observed following CoreValve at any time point.

Presence or absence of DW-MRI lesions

At one-year follow-up, for each TAVI prosthesis we sought to compare individuals with and without DW-MRI lesions in respect of neurocognitive performance (Table 5). Of the 25 Lotus patients that completed 12 month assessments, 19(76%) exhibited new DW-MRI lesions post-TAVI, and of the 24 CoreValve patients, 13(54%) were DW-MRI positive (p=0.140). Lotus patients with DW-MRI lesions

exhibited an overall decline in global cognition (MMSE) at 12 months compared to those without (Figure 3A and B). CoreValve patients with DW-MRI lesions had a significantly lower HVLT discrimination index at 12 months compared to those without (Figure 3C and D). For all of the remaining neurocognitive domains, no difference in performance at 1 year was noted between patients with and without DW-MRI lesions for either TAVI prosthesis.

DISCUSSION

This two-centre study is the first to use DW-MRI and cognitive assessments to comprehensively compare two first- and second-generation TAVI devices. This study provides several new insights: 1) there was a high occurrence of silent cerebral embolism during TAVI affecting both first- and second-generation prosthesis designs (with 66% of the total study population exhibiting new DW-MRI lesions post-TAVI); 2) the Lotus valve exhibited a significantly higher incidence of new DW-MRI micro-infarcts, with more than twice the number of lesions per patient than observed following CoreValve; 3) DW-MRI lesions are of similar size, but more frequently observed in the anterior cerebral and vertebro-basilar territories following Lotus compared with CoreValve; 4) despite a higher DW-MRI burden and an initial deterioration in verbal memory following Lotus, TAVI does not appear detrimental to mid-term neurocognitive function, with 12 month scores in all domains being equivalent to baseline following both Lotus and CoreValve; 5) for the majority of domains, including executive function, psycho-motor speed, perceptual and visual memory and fine motor co-ordination and speed, the presence of DW-MRI lesions did not influence neurocognitive function at 1 year for either valve. This latter point is consistent with previous work that demonstrated preserved 2-year cognitive performance in an unselected TAVI population, irrespective of DW-MRI status[22].

Cognitive decline after cardiac surgery is associated with increased morbidity and mortality [25] and has significant social and economic implications[22]. TAVI has revolutionised the management of high risk patients with symptomatic aortic stenosis worldwide. However, determining whether the high incidence of silent DW-MRI lesions seen post-TAVI predisposes to cognitive decline, and whether TAVI design has any impact upon this, remains a crucial pre-requisite to its more widespread use. Despite its advanced design, our study suggests that the use of the second-generation Lotus valve carries a higher risk of silent cerebral infarction, but without an objectively discernible decline in neurocognitive function at one year, comparable to the CoreValve prosthesis.

The multiple and diffusely distributed silent cerebral lesions detected by DW-MRI post-TAVI are in keeping with an embolic aetiology. We have previously shown severity of aortic arch atheroma is an independent risk factor for the development of new cerebral infarcts following TAVI[10]. Transcranial Doppler studies, performed during TAVI, have indicated balloon valvuloplasty, prosthesis positioning and implantation as particular moments for cerebral embolization[26], suggesting that manipulation of the native aortic valve is also an important source.

Oversizing has been associated with tissue embolization on histopathological analysis [27] and is recommended to a degree with first-generation designs in order to prevent paravalvular regurgitation. The higher cover index and greater displacement forces upon degenerate native leaflets might consequently be expected to precipitate a greater degree of tissue dehiscence and embolization. Balloon post-dilatation has also been demonstrated to significantly predict acute neurological events[7]. Despite the larger valve size, greater frequency of valve embolization and use of post-dilatation, new DW-MRI lesions were less frequently seen following CoreValve. The

Lotus valve is fully repositionable, reflecting the longer fluoroscopy times observed with this prosthesis. However, our data suggests that repositioning per se was not a significant contributor to the frequency of new DW-MRI lesions observed. The Lotus delivery system typically requires 20F sheaths or wider, and thus greater endothelial disruption during manipulation around the aortic arch may underlie the higher incidence of cerebral micro-infarction seen after Lotus TAVI. Future studies are required to determine whether these findings may translate into variation in the incidence of clinical stroke.

We and others have previously demonstrated the majority of DW-MRI lesions immediately post-TAVI appear to resolve by 6 months[11]. However, this resolution does not necessarily indicate tissue normalisation. The insensitivity of lower field strength imaging has been suggested as one explanation[13]. Furthermore, rat models of cerebral ischaemic insult confirm histological neuronal damage despite DW-MRI resolution, cautioning the use of imaging alone to assess ischaemic injury[28]. We therefore sought to compliment cerebral MR imaging with a battery of well validated neurocognitive assessment tools.

There is a large body of evidence to indicate silent cerebral injury heralds adverse cognitive consequences. They are associated with an increased risk of mild cognitive impairment[29], and may double the risk of dementia (most commonly Alzheimer's disease), with a steeper rate of cognitive decline observed the greater the number of infarctions[12]. It is feasible that the decline in verbal memory seen at 30 days following Lotus, which was not observed following CoreValve, is a reflection of the associated higher burden of DW-MRI lesions.

To date, few studies have combined DW-MRI and cognitive assessment following TAVI with CoreValve or Edwards-Sapien. The largest involved 111 subjects [22] with

the other three averaging 40 patients[8,21,30]. No decline in any cognitive domain was observed despite the occurrence of diffuse micro-infarcts affecting both cerebral hemispheres[21]; and patients with and without DW-MRI lesions performed equally well[22]. These findings are consistent with our study. Our observed high incidence of new DW-MRI lesions post-TAVI appeared to lack clinical sequelae when cognition was objectively assessed at 12 months, and this was the case following both first and second-generation devices.

This study is noteworthy in the context of contemporary TAVI trials. Results from the PARTNER 2 trial have suggested transfemoral TAVI results in a lower rate of death or disabling stroke in intermediate-risk patients, with an average age similar to this study of 81.5 years, when compared with surgery[31]. Younger patients would expectedly exhibit lower burdens of aortic atheroma and thus fewer silent DW-MRI lesions, irrespective of TAVI design. In the recent CLEAN-TAVI[32] and SENTINEL[33] trials, cerebral protection reduced new ischaemic cerebral lesions. However, Lotus patients were notably absent from both studies. Whilst pre-existing lesion volume predicted future cerebral lesion volume[33], the baseline and post-TAVR volume of established DWI lesions in our study of both CoreValve and Lotus were equivalent. Our work suggests devices to reduce lesion frequency maybe a particularly pertinent adjunct to Lotus TAVI and potentially offset the decline in verbal memory and psychomotor speed we observed at 30 days.

Whilst our work indicates DW-MRI, our lesions does not seem to affect mid-term neurocognitive function caution is required not to dismiss DW-MRI lesions as entirely innocuous, particularly given even small lesions tripled the risk of stroke-related death in healthy subjects aged 50 – 73 years over 14 years of follow-up[34]. Longer

follow-up is required to clinically appreciate the natural history of cerebral injury incurred during TAVI.

Limitations

Patients were not randomised to CoreValve or Lotus and hence the study is vulnerable to selection bias. Furthermore, we have not directly compared cognitive performance from our two TAVI groups with that of healthy octogenarians, or patients managed conservatively.

There was attrition in patients completing the study protocol, with 5 patients failing to complete post-intervention imaging and 17 patients with imaging data failing to complete 12 month neurocognitive assessments. There is hence an inherent risk of bias as potentially those with most marked decline in cognitive function might have been excluded.

The CoreValve has been clinically in use for much longer than the Lotus valve. Therefore, the greater degree of new DWI lesion seen in the Lotus group may partly reflect an operator “learning curve” during which experience and fluency in use of Lotus delivery equipment was refined.

Presently, there is no internationally accepted definition of cognitive decline following cardiac procedures, with the potential for variation between studies. We have utilised a comprehensive battery of validated tests that cover a wide variety of important higher neurocognitive faculties, but potentially these may be insensitive to change and lack validation in the context of TAVI.

Our work employed 1.5 Tesla field strength imaging, which is the case for the majority of similar published studies. However, the use of higher-field strengths may have increased detection of micro-infarction and characterise more accurately the

burden associated with different TAVI devices.

CONCLUSION

There was a higher incidence of silent micro-infarction with a greater number of lesions per patient following second-generation Lotus compared to the first-generation CoreValve implantation. However, there was no objective decline in neurocognitive function discernible 1-year following TAVI with either prosthesis.

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COMPETING INTERESTS

DB and CJM are consultants and proctors for both Medtronic and Boston Scientific.

JPG and SP have received an educational research grant from Philips Healthcare.

Author's Contribution

JPG conceived and designed the study. TAM drafted the manuscript. CL compiled the comprehensive battery of neurocognitive tests and instructed on their correct implementation. FR, TAM, AU, LED and AS performed the recruitment of patients and their neurocognitive assessment. GPM supervised and AS oversaw the University of Leicester contribution. MI and AJPG performed MRI image analysis. DJB and CM carried out TAVI implantation. TAM and AU analysed data and interpreted the results. PPS and PG gave input into data interpretation. PPS, PG,

JRJF, GJF, SP and GPM were involved in critical and intellectual revision of the article. All authors edited and revised the manuscript. All authors read and approved the final manuscript.

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TABLES

Table 1 – Patient characteristics in those with 6 month follow up.

	Lotus (n=29)	**CoreValve (n=37)**	p Value*
Age (years)	79.8±8.9	81.2±7.2	0.459
Male, n (%)	14 (48)	17 (46)	0.851
EuroSCORE II	4.13±3.30	5.55±3.79	0.115
STS score (%)	4.04±2.59	5.28±3.41	0.109
BMI (kg/m^2)	28.5±5.2	27.2±5.4	0.323
Hypertension, n (%)	11 (38)	20 (54)	0.157
Diabetes, n (%)	5 (17)	4 (11)	0.450
Hyperlipidaemia, n (%)	17 (59)	18 (49)	0.488
Atrial Fibrillation, n (%)	5 (17)	9 (24)	0.449
Previous MI, n (%)	7 (24)	2 (5)	**0.026**
Previous PCI, n (%)	9 (31)	10 (27)	0.774
Previous CABG, n (%)	5 (17)	8 (22)	0.618
Previous Stroke, n (%)	7 (24)	6 (16)	0.454
Peripheral Vascular Disease, n (%)	4 (14)	5 (14)	0.991
eGFR ($ml/min/1.73m^2$)	69±19	64±17	0.342

Values are mean±SD or n (%). *p Value for comparison between procedure types.

STS, Society of Thoracic Surgeons score; BMI, body mass index; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction.

Table 2 – Catheterization data for TAVI implant procedures

	Lotus (n=29)	**CoreValve (n=37)**	**p Value***
TAVI size (n(%))	23mm (7 (24%)) 25mm (8 (28%)) 27mm (14 (48%))	23mm (4 (11%)) 26mm (8 (22%)) 29mm (18 (49%)) 31mm (7 (19%))	-
Femoral route, n (%)	29 (100)	27 (73)	0.081
Sheath size (French)	18 (28%) 20 (52%) 22 (20%)	18 (100%)	
Pullback PG (mmHg)	56±27	43±19	**0.023**
Fluoroscopy time (min)	29±8	18±11	**0.001**
Procedure time (min)	159±42	143±50	0.194
Contrast (ml)	120±43	134±43	0.212
Pre-dilatation BAV, n (%)	25 (86)	28 (77)	0.286
Post-dilatation, n (%)	0 (0)	5 (14)	**0.039**
TAVI repositioned, n (%)	7 (24)	0 (0)	**0.002**
TAVI embolization, n (%)	0 (0)	3 (8)	0.117
Need for second TAVI, n (%)	0 (0)	3 (8)	0.117

*Independent samples t-test

Table 3 – Comparison of MRI DWI imaging following Boston Lotus and Medtronic CoreValve

	Lotus (n=29)	CoreValve (n=37)	p Value
Incidence of new micro-infarction (n(%))	23(79)	22(59)	**0.025**
Number of new micro-infarcts per patient	3.5 (IQR 7.0)	2.0 (IQR 3.0)	**0.002**
Mean micro-infarct volume per patient (ml)	0.36 (IQR 0.57)	0.17 (IQR 0.21)	0.166
Number of new small lesions (<5mm) (n(%))	124(78)	41(72)	**0.005**
Number of new large lesions (≥5mm) (n(%))	34(22)	16(28)	**0.036**
Number of patients with new ACA lesions (n(%))	14(48)	2(5)	**0.001**
Number of patients with new MCA lesions (n(%))	20(69)	19(51)	0.149
Number of patients with new PCA lesions (n(%))	10(34)	6(16)	0.086
Number of patients with new VBA lesions (n(%))	15(52)	7(19)	**0.005**

ACA: anterior cerebral artery, MCA: middle cerebral artery, PCA: posterior cerebral artery, VBA: vertebrobasilar artery.

Table 4 – Summary of neurocognitive test scores at baseline, 30d and 12m.

	TAVI	Baseline	30 days	p Value*	12 months	p Value**
MMSE	Lotus	28.6±1.6	28.8±1.8	0.468	28.7±2.0	0.743
	CoreValve	28.8±1.8	28.4±2.0	0.251	27.9±2.8	0.277
HVLT						
Total learning	Lotus	21.4±7.2	21.5±4.1	0.913	23.3±6.1	0.104
	CoreValve	17.7±6.3	18.6±6.1	0.512	18.3±7.8	0.764
Delayed Recall	Lotus	7.6±3.0	6.3±3.4	**0.038**	9.0±6.7	**0.028**
	CoreValve	5.8±2.8	5.3±3.8	0.296	4.3±4.4	0.419
Discrimination Index	Lotus	10.2±1.5	8.6±2.9	**0.015**	10.1±2.4	**0.010**
	CoreValve	9.6±2.1	9.1±3.4	0.373	7.9±4.5	0.147
Trail Making Tests						
A	Lotus	47.0±15.0	56.0±27.6	0.112	50.5±19.7	0.354
	CoreValve	56.9±27.8	61.1±40.0	0.566	66.1±49.8	0.431
B	Lotus	170.9±86.5	140.7±62.8	**0.006**	152.3±87.5	0.273
	CoreValve	171.1±121.4	155.2±79.0	0.548	143.3±64.4	0.969
DSST	Lotus	43.2±15.8	45.5±16.0	0.254	44.2±13.5	0.253
	CoreValve	33.9±14.1	34.6±13.3	0.704	34.4±15.7	0.633
LNS	Lotus	7.6±4.5	8.6±3.5	0.387	8.6±2.6	0.876
	CoreValve	8.3±5.1	8.8±4.2	0.662	7.9±4.8	0.291
Grooved Pegboard						
Dominant score	Lotus	163.1±102.4	136.9±75.7	0.336	142.7±38.0	0.670
	CoreValve	157.3±57.2	132.1±81.3	0.162	169.0±60.4	0.110
Non-dominant score	Lotus	158.0±37.7	148.5±53.4	0.373	159.6±47.0	0.658
	CoreValve	180.9±58.2	173.9±104.2	0.654	215.9±124.4	**0.004**

Mean±SD.
* comparing values at baseline and 30d, same TAVI design, paired samples t-test
** comparing values at 30d and 12 months, same TAVI design, paired samples t-test

Table 5 – Within group comparison of mean change in cognitive domain over 12 months in patients with and without DW-MRI lesions.

	Boston Lotus (n=25)			Medtronic CoreValve (n=24)		
	DWI -ve (n=6)	**DWI +ve (n=19)**	**p Value**	**DWI –ve (n=11)**	**DWI+ve (n=13)**	**p Value**
MMSE	1.2±0.8	-0.4±1.9	**0.025**	-0.9±2.5	-0.7±2.6	0.840
HVLT Learning	4.2±5.2	1.2±7.3	0.454	1.1±3.9	1.0±9.1	0.691
HVLT Delayed	6.3±12.9	-0.1±3.3	0.177	-0.2±2.5	-1.1±3.1	0.456
HVLT Discrimination	0.0±1.5	-0.1±2.6	0.733	0.8±2.3	-2.3±3.5	**0.019**
TMT A	15.5±20.8	-0.1±15.3	0.059	18.9±64.9	5.0±14.7	0.562
TMT B	-13.0±88.9	-18.3±61.4	0.870	19.6±61.6	-1.4±64.4	0.454
DSST	4.0±10.0	-0.4±9.8	0.346	-0.1±6.7	5.0±13.7	0.370
LNS	2.4±3.0	0.7±5.1	0.534	-0.5±5.0	0.8±3.6	0.474
GPBT Dominant	-8.2±31.5	-24.5±108.0	0.721	0.5±37.6	22.6±37.7	0.186
GPBT Non-Dominant	-26.0±83.7	-3.2±51.3	0.914	43.0±81.3	20.8±66.8	0.235

Mean±SD.

Figure 1: Study Profile

Figure 2: Diffusion weighted MRI of the brain examining silent injury with TAVI.

Cerebral images, including the brainstem and cerebellum before (A) and after (B) TAVI procedure. Multiple new cerebral infarctions were seen, some of which are highlighted by the red arrows.

Figure 3: Line graph depicting change in MMSE (A and B) and HVLT Discrimination Index (C and D) over time following Lotus and CoreValve.

(Red lines indicate patients with DW-MRI micro-infarcts, blue lines those without).

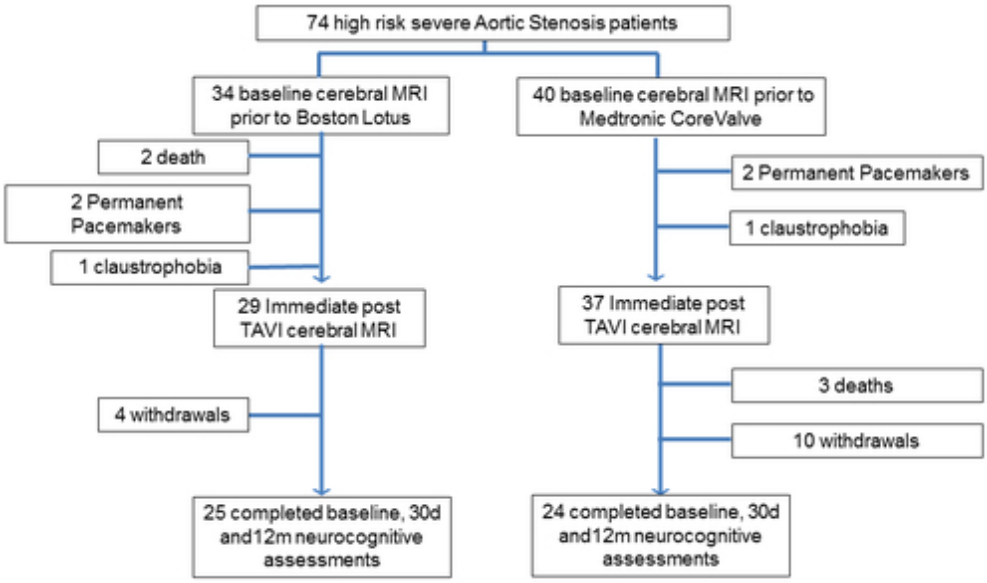


Figure 1: Study Profile

42x25mm (300 x 300 DPI)

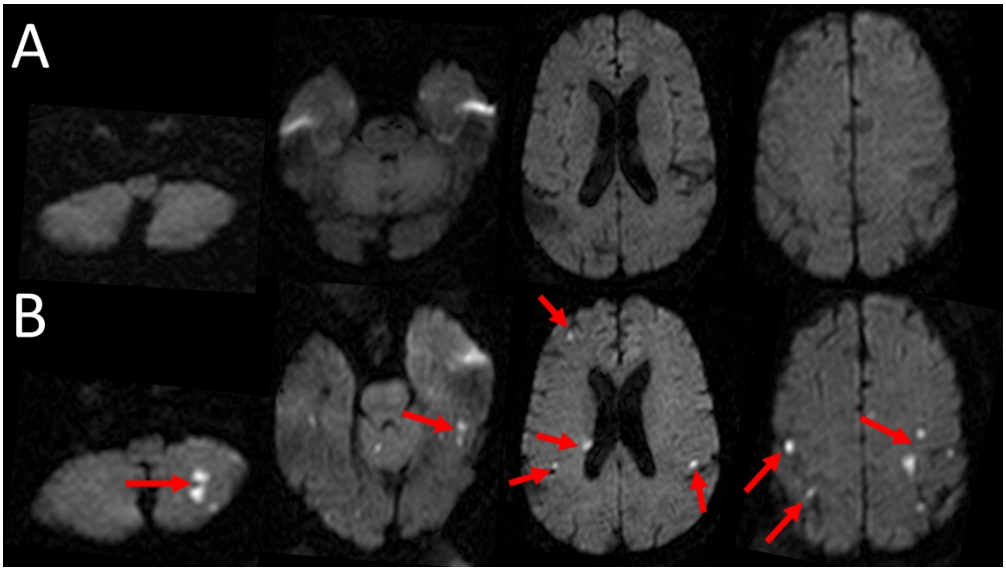


Figure 2: Diffusion weighted MRI of the brain examining silent injury with TAVI.
Cerebral images, including the brainstem and cerebellum before (A) and after (B) TAVI procedure. Multiple new cerebral infarctions were seen, some of which are highlighted by the red arrows.

338x190mm (300 x 300 DPI)

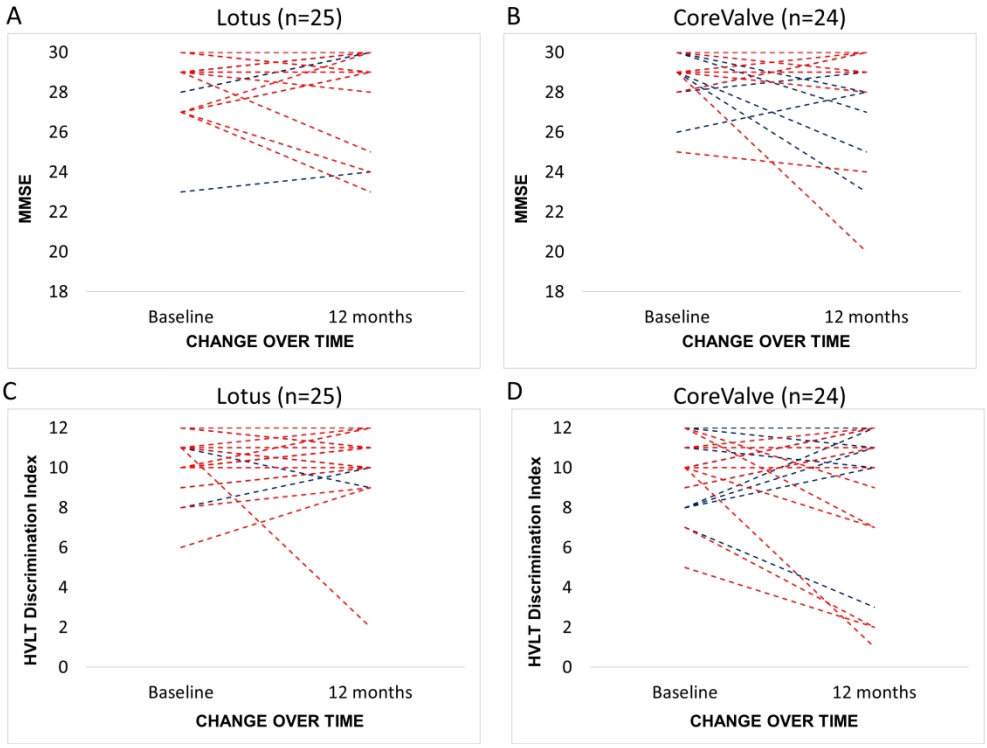
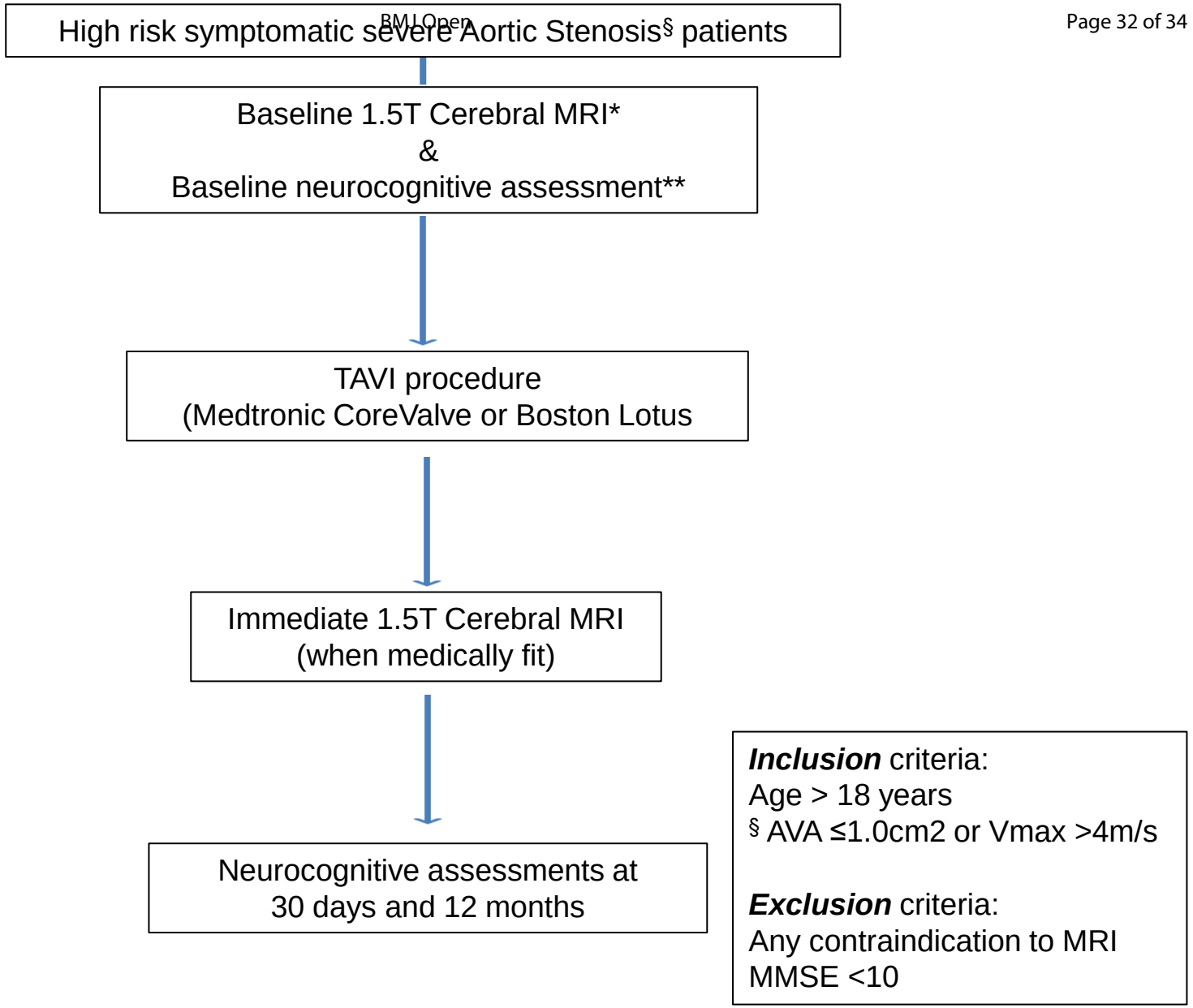


Figure 3: Line graph depicting change in MMSE (A and B) and HVLT Discrimination Index (C and D) over time following Lotus and CoreValve.
(Red lines indicate patients with DW-MRI micro-infarcts, blue lines those without).

254x190mm (300 x 300 DPI)



* Comprising T2 weighted Turbo Spin Echo sequence, T2 weighted Fast Field Echo, Diffusion weighted spin echo sequence

** Comprising NART, mini mental state examination, Hopkins Verbal Learning Tests, Letter Number Sequencing task, Trail Making Tests A and B, Digit-Symbol Substitution Test and the Grooved Pegboard Test

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (pages 1 and 3)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (page 3)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (page 6-7)
Objectives	3	State specific objectives, including any prespecified hypotheses (pages 3, 7)
Methods		
Study design	4	Present key elements of study design early in the paper (pages 3, 7)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (page 3, 7)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (pages 8, 9)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (pages 8, 9)
Bias	9	Describe any efforts to address potential sources of bias (pages 9, 16)
Study size	10	Explain how the study size was arrived at (page 10)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (page 9)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (page 9)
		(*b*) Describe any methods used to examine subgroups and interactions (page 9)
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Page 10, Figure 1)
		(b) Give reasons for non-participation at each stage (Figure 1)
		(c) Consider use of a flow diagram (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Table 1 on page 23)
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives (page 13)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (page 17)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (pages 14-16)
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (page 18)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Silent Cerebral Infarction and Cognitive Function following TAVI:
An observational two-centre UK comparison of the 1st generation CoreValve and 2nd generation Lotus valve

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Silent Cerebral Infarction and Cognitive Function following TAVI: An observational two-centre UK comparison of the 1st generation CoreValve and 2nd generation Lotus valve

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ABSTRACT

Objective: To compare the incidence of silent cerebral infarction and impact upon cognitive function following Transcatheter Aortic Valve Implantation (TAVI) with the first-generation CoreValve (Medtronic, Minneapolis, Minnesota) and second-generation Lotus valve (Boston Scientific, Natick Massachusetts).

Design: A prospective observational study comprising a 1.5 T cerebral MRI scan, performed preoperatively and immediately following TAVI, and neurocognitive assessments performed at baseline, 30 days and 1-year follow-up.

Setting: University hospitals of Leeds and Leicester, UK.

Patients: 66 (80.6±8.0 years, 47% male) high-risk severe symptomatic aortic stenosis patients recruited between April 2012 to May 2015.

Main outcome measures: Incidence of new cerebral micro0infarctionm and objective decline in neurocognitive performance.

Results: All underwent cerebral MRI at baseline and immediately following TAVI, and 49 (25 Lotus, 24 CoreValve) completed neurocognitive assessments at baseline, 30 days and 1 year. There was a significantly greater incidence in new cerebral micro-infarction observed following the Lotus TAVI (23(79%) vs 22(59%), p=0.025) with a greater number of new infarcts per patient (median 3.5 (IQR 7.0) vs. 2.0 (IQR 3.0), p=0.002). The mean volume of infarcted cerebral tissue per patient was equivalent following the two prostheses (p=0.166). More patients suffered new anterior (14(48%) vs. 2(5%), p=0.001) and vertebrobasilar (15(52%) vs. 7(19%), p=0.005) lesions following Lotus. Lotus was associated with a decline in verbal memory and psychomotor speed at 30 days. However, performance longitudinally at one year was preserved in all neurocognitive domains.

Conclusions: There was a higher incidence of silent cerebral micro-infarction and a greater number of lesions per patient following Lotus compared to CoreValve. However, there was no objective decline in neurocognitive function discernible at 1-year following TAVI with either prosthesis.

Strengths and Limitations of this Study

• Contemporary study comprising both a novel TAVI design technology and an established device.

• A two-centre study combining both DW-MRI and cognitive assessments to comprehensively assess cerebral injury following TAVI.

• Mid-term follow-up to 1 year

• Not randomised.

• Higher field strength MRI available for more sensitive detection of cerebral embolic infarction.

KEYWORDS: Transcatheter Aortic Valve Implantation, Medtronic CoreValve, Boston Lotus Valve, Cerebral MRI, Neurocognitive function

Abbreviations list

BAV:	balloon aortic valvuloplasty
CABG:	coronary artery bypass grafting
DSST:	digit symbol substitution test
DW-MRI:	diffusion weighted magnetic resonance imaging
eGFR	estimated glomerular filtration rate
GPBT:	grooved pegboard test
HVLT:	Hopkins verbal learning test
IQ:	intelligent quotient
LNS:	letter number sequencing
MDCT:	multi detector computed tomography
MI:	myocardial infarction
MMSE:	mini mental state examination
PCI:	percutaneous coronary intervention
SD:	standard deviation
STS:	Society of Thoracic Surgeons
TAVI:	transcatheter aortic valve implantation
TMT:	trail making test
VARC:	valve academic research consortium

INTRODUCTION

Transcatheter aortic valve implantation (TAVI) is advocated by both European[1] and US[2] guidance in patients with symptomatic aortic stenosis deemed inoperable or with too high a predicted postoperative mortality. TAVI is cost-effective[3], significantly improves quality of life[4], and recent trial data suggest non-inferior to surgery in intermediate-risk patients[5], potentially expanding its application to a broader population.

However, since the landmark PARTNER trial in 2010[6], the inherent risk of disabling stroke associated with TAVI has been well recognised. Despite 10 years of refinement in transcatheter technology and delivery technique, stroke rates remain similar[7]. Importantly, TAVI is also associated with a high incidence (up to 84%) of silent cerebral embolism as detected by diffusion-weighted MRI (DW-MRI) [8-10]; more frequent than that following aortic valve surgery[11].

The association of new DW-MRI lesions post-TAVI with cognitive decline is an issue currently under intense scrutiny, as it has long been recognised that silent cerebral infarcts can more than double the risk of dementia[12]. Indeed the concept of post-operative cognitive dysfunction and its relationship with DW-MRI has been described following valvular surgery, bypass grafting and left heart catheterization[13].

The Boston Scientific Lotus valve is a novel TAVI iteration that incorporates a number of features specifically designed to improve upon first-generation devices[14]. As such it exhibits superior deployment success rates when compared to the older Medtronic CoreValve[15,16]. However, the key concern of silent cerebral injury following implantation and cognitive decline remains unanswered. We sought to characterise the extent of new silent cerebral infarction using DW-MRI, and investigate

longitudinally cognitive function following TAVI with the first generation self-expanding Medtronic CoreValve and the second-generation mechanically-expanded Boston Scientific Lotus valve.

METHODS

Patient selection

This study prospectively recruited 74 patients with severe degenerative AS from two large UK tertiary cardiothoracic centres (Leeds and Leicester) who were referred for TAVI between April 2012 and May 2015. Severe AS was classified by echocardiography as an aortic valve area of ≤1.0cm^2 or peak velocity >4m/s. The decision for TAVI in all cases was taken by a multidisciplinary heart team in accordance with international guidance[17]. Exclusion criteria included any contraindication to MRI or pre-existing severe cognitive impairment (a mini-mental state examination (MMSE) score<10). Any patient deemed to exhibit new focal neurological dysfunction consistent with clinical stroke post-TAVI was also excluded. The study was approved by the National Research Ethics Service (08/H1307/106), complied with the Declaration of Helsinki and all patients provided written informed consent.

Transcatheter Aortic Valve Implantation

TAVI was performed using either a first-generation CoreValve system (Medtronic, Minneapolis, Minnesota, USA) or the Lotus™ Aortic Valve system (Boston Scientific Corporation, Natick, MA, USA) employing standard techniques as previously described for both vendors[18,19]. Multidetector computed tomography (MDCT) was employed to assist annular sizing and assess aortic calcification prior to TAVI. Percutaneous femoral artery access was the default approach. Balloon valvuloplasty, rapid ventricular pacing and post-dilatation (in the case of CoreValve)

were employed at the discretion of the operator. All patients received weight-adjusted unfractionated heparin to maintain an activated clotting time >200s and were treated with dual antiplatelet therapy (aspirin 75mg and clopidogrel 75mg) for a minimum of 3 months. None of the TAVI cases involved the use of a cerebral protection device.

Neurocognitive assessment

The neurocognitive test battery was performed by trained assessors (medical/nursing) in a quiet comfortable environment at three Valve Academic Research Consortium (VARC) recommended time points (baseline, 30d and 12m)[20]. Training of assessors and performance validation was undertaken by an experienced neuropsychologist (CL). Follow-up assessment was conducted at the patient home or the hospital. Total assessment time ranged between 60-90min with appropriate rest periods. Baseline characteristics, patient handedness and years of education were recorded. The national adult reading test (NART) was used to calculate the full scale intelligent quotient (FSIQ=123.2-(1.029 x NART error score)). A broad battery of previously validated neurocognitive assessments were undertaken at the designated time points[21] and included evaluation of: *cognitive reasoning*: using the mini mental state examination (MMSE), *verbal memory*: using the Hopkins Verbal Learning Tests (HVLT), *executive function*: using the Letter Number Sequencing task (LNS), *psycho-motor speed*: using the Trail Making Test (TMT) A and B, *perceptual and visual memory*: using the Digit-Symbol Substitution Test (DSST), and *fine motor co-ordination and speed:* using the Grooved Pegboard Test (GPBT - Model 32025, Lafayette Instruments Co, IN, USA). Cognitive decline was defined as a reduction of the score by 1 SD of the baseline score for all tests[22-24].

Cerebral MRI

Cerebral MRI was conducted pre- and post-procedure (within 7d) using identical imaging protocols. MRI was performed on the same 1.5T system for all serial scans for any individual patient (Intera, Phillips Healthcare, Best, The Netherlands or Avanto, Siemens Medical Systems, Erlangen, Germany). The imaging protocol consisted of T2 weighted fast field echo, T2 turbo field echo and diffusion weighted imaging (DWI) (22 slices, 5mm thick, 1mm gap, FOV 350, RFOV 100). Each scan was independently assessed by two experienced Neuroradiologists (AG, MI), blinded to all clinical/procedural details. Cerebral embolism or micro-infarction was defined as a new restricted diffusion lesion on DWI. New cerebral micro-infarcts were localised to one hemisphere and vascular territory. Infarct diameter was used to categorise patients into small or large lesion sub-groups (<5mm or >5mm; in the case of multiple lesions the largest lesion was used to determine status). The total infarct volume (ml) was measured off-line using standard post-processing software (QMass 7.2, Medis, The Netherlands) as previously published[10,11].

Statistical Analysis Data was tested for normality using the Shapiro-Wilks test. Continuous variables were expressed as mean±SD or median (Q2-Q3 or IQR) and were tested for differences by means of a 2-sided, unpaired Student t test (for comparison between groups) or a 2-sided, paired Student t test (for intra-group comparison). Non-parametric testing (Mann–Whitney test) was performed where indicated. Categorical variables were given as frequencies and percentages and compared by $\chi 2$ statistics or Fisher exact test. All statistical analyses were performed using the PASW software package (V.21.0 SPSS, IBM, Chicago, Illinois, USA) with a two-sided significance level of $p<0.05$ was considered statistically significant. Sample size to detect cognitive decline (reduction in score by 1SD) was estimated using *IBM*

SPSS Sample power version 3, and using normative data for the test to have 80% power (alpha 0.05), a minimum of 17 patients were required in each group.

RESULTS

Patient population

A total of 66 patients (37 Medtronic CoreValve and 29 Boston Lotus) underwent both the pre-operative (median 1 day pre-procedure, IQR 14 days) and immediate post-TAVI MRI scans (median 4 days, IQR 4 days). The baseline characteristics of these groups are shown in Table 1. Forty-nine of these (24 CoreValve and 25 Lotus) completed serial neurocognitive assessments out to 12 months. Reasons for non-completion were varied reflecting an elderly frail population (Figure 1).

Patient Involvement

Patients were not involved with the study design, recruitment, conduct or interpretation of results obtained. Outcome measures were objectively measured and not based on patient experience.

Procedural data

TAVI was successful in all cases. Catheterization data for the TAVI implant procedures is summarised in Table 2. Of the 29 Lotus implants, 7(24%) involved device repositioning. Of the CoreValve implants, there were three instances of embolization and the requirement of a second valve in three cases (two of whom were due to embolization).

Cerebral MRI

Typical cerebral DWI images at baseline and immediately after TAVI are depicted in Figures 2A and 2B respectively.

Baseline: At baseline, 5(17%) of the Lotus patients and 10(27%) of the CoreValve patients had evidence of pre-existing established stroke (p=0.346) with equivalent lesion volume (p=0.529). There was also evidence of recent micro-infarction on

cerebral DWI in 2(7%) Lotus and 4(11%) CoreValve patients (p=0.583). A greater proportion of patients undergoing Lotus TAVI had evidence of periventricular ischaemia compared to those undergoing CoreValve (19(66%) vs. 14(38%), p=0.026).

Post-procedure: Table 3 summarises the findings of DWI imaging following TAVI. There was a significantly greater incidence in new micro-infarction observed following Lotus TAVI with a greater number of new infarcts per patient. These were predominantly of small size, with a comparable mean infarcted cerebral tissue volume per patient with both TAVI designs. More patients suffered new anterior and vertebro-basilar lesions following Lotus than CoreValve. The number of new lesions following Lotus repositioning (n=7) and non-repositioning (n=22) did not differ (1.0 (IQR 8.0) vs. 3.0 (IQR 3.75), p=0.438) and Lotus repositioning did not correlate with number of new lesions (p=0.435). For the CoreValve group, the three patients in whom embolization occurred had significantly greater frequency of new lesions post-procedure (4.0 (IQR 0.0) vs. 1.0 (IQR 2.0), p=0.011), but no difference was seen in the three requiring a second valve (4.0 (IQR 0.0) vs. 1.0 (IQR 2.0), p=0.148). Typical findings of new cerebral infarction detected by DW-MRI post-TAVI are exemplified in Figure 2.

Baseline education and intelligence

The vast majority of patients were right handed (CoreValve: 21(88%) vs. Lotus: 24(96%), p=0.234) with equivalent reporting of disability on Modified Rankin Scale (CoreValve: 1.9±1.1 vs. Lotus: 2.0±0.7, p=0.929). The CoreValve and Lotus patients were similar in respect of years in education (10.9±1.9 vs. 11.6±2.5yrs, p=0.279), and full scale IQ (106±12 vs. 102±15, p=0.313). Global cognition measured using the MMSE was also equivalent (28.8±1.8 vs. 28.6±1.6, p=0.279) with only 1 patient from

the Lotus group indicating cognitive impairment (defined as an MMSE of less than 24[25]).

Effect of TAVI design on absolute neurocognitive function scores

Neurocognitive performance, prior to and following Lotus and CoreValve TAVI, are shown in Table 4. For the vast majority of domains, including global cognition, psychomotor speed, executive function and fine motor co-ordination, no change in test scores were observed at 30 days or 12 months following TAVI, with either the Lotus or CoreValve prostheses.

The HVLT was utilised to test mnemonic function and verbal memory, and total learning scores remained unchanged over time for both CoreValve and Lotus. However, delayed recall scores and discrimination index were significantly lower at 30 days following Lotus (Table 4), with 12 month scores returning to baseline level (delayed recall: 7.6±3.0 vs. 9.0±6.7, p=0.320, discrimination index: 10.2±1.5 vs. 10.1±2.4, p=0.867), with no change observed following CoreValve.

The TMT assesses executive function and psychomotor speed, with TMT A preceding the more challenging TMT B. The TMT B scores were significantly lower at 30 days following Lotus (Table 4), with 12 month scores again returning to baseline level (170.9±86.5 vs. 152.3±87.5, p=0.215), with no change observed following CoreValve at any time point.

Presence or absence of DW-MRI lesions

At one-year follow-up, for each TAVI prosthesis we sought to compare individuals with and without DW-MRI lesions in respect of neurocognitive performance (Table 5). Of the 25 Lotus patients that completed 12 month assessments, 19(76%) exhibited new DW-MRI lesions post-TAVI, and of the 24 CoreValve patients, 13(54%) were DW-MRI positive (p=0.140). Lotus patients with DW-MRI lesions

exhibited an overall decline in global cognition (MMSE) at 12 months compared to those without (Figure 3A and B). CoreValve patients with DW-MRI lesions had a significantly lower HVLT discrimination index at 12 months compared to those without (Figure 3C and D). For all of the remaining neurocognitive domains, no difference in performance at 1 year was noted between patients with and without DW-MRI lesions for either TAVI prosthesis.

DISCUSSION

This two-centre study is the first to use DW-MRI and cognitive assessments to comprehensively compare two first- and second-generation TAVI devices. This study provides several new insights: 1) there was a high occurrence of silent cerebral embolism during TAVI affecting both first- and second-generation prosthesis designs (with 66% of the total study population exhibiting new DW-MRI lesions post-TAVI); 2) the Lotus valve exhibited a significantly higher incidence of new DW-MRI micro-infarcts, with more than twice the number of lesions per patient than observed following CoreValve; 3) DW-MRI lesions are of similar size, but more frequently observed in the anterior cerebral and vertebro-basilar territories following Lotus compared with CoreValve; 4) despite a higher DW-MRI burden and an initial deterioration in verbal memory following Lotus, TAVI does not appear detrimental to mid-term neurocognitive function, with 12 month scores in all domains being equivalent to baseline following both Lotus and CoreValve; 5) for the majority of domains, including executive function, psycho-motor speed, perceptual and visual memory and fine motor co-ordination and speed, the presence of DW-MRI lesions did not influence neurocognitive function at 1 year for either valve. This latter point is consistent with previous work that demonstrated preserved 2-year cognitive performance in an unselected TAVI population, irrespective of DW-MRI status[23].

Cognitive decline after cardiac surgery is associated with increased morbidity and mortality [26] and has significant social and economic implications[23]. TAVI has revolutionised the management of high risk patients with symptomatic aortic stenosis worldwide. However, determining whether the high incidence of silent DW-MRI lesions seen post-TAVI predisposes to cognitive decline, and whether TAVI design has any impact upon this, remains a crucial pre-requisite to its more widespread use. Despite its advanced design, our study suggests that the use of the second-generation Lotus valve carries a higher risk of silent cerebral infarction, but without an objectively discernible decline in neurocognitive function at one year, comparable to the CoreValve prosthesis.

The multiple and diffusely distributed silent cerebral lesions detected by DW-MRI post-TAVI are in keeping with an embolic aetiology. We have previously shown severity of aortic arch atheroma is an independent risk factor for the development of new cerebral infarcts following TAVI[10]. Transcranial Doppler studies, performed during TAVI, have indicated balloon valvuloplasty, prosthesis positioning and implantation as particular moments for cerebral embolization[27], suggesting that manipulation of the native aortic valve is also an important source.

Oversizing has been associated with tissue embolization on histopathological analysis [28] and is recommended to a degree with first-generation designs in order to prevent paravalvular regurgitation. The higher cover index and greater displacement forces upon degenerate native leaflets might consequently be expected to precipitate a greater degree of tissue dehiscence and embolization. Balloon post-dilatation has also been demonstrated to significantly predict acute neurological events[7]. Despite the larger valve size, greater frequency of valve embolization and use of post-dilatation, new DW-MRI lesions were less frequently seen following CoreValve. The

Lotus valve is fully repositionable, reflecting the longer fluoroscopy times observed with this prosthesis. However, our data suggests that repositioning per se was not a significant contributor to the frequency of new DW-MRI lesions observed. The Lotus delivery system typically requires 20F sheaths or wider, and thus greater endothelial disruption during manipulation around the aortic arch may underlie the higher incidence of cerebral micro-infarction seen after Lotus TAVI. Future studies are required to determine whether these findings may translate into variation in the incidence of clinical stroke.

We and others have previously demonstrated the majority of DW-MRI lesions immediately post-TAVI appear to resolve by 6 months[11]. However, this resolution does not necessarily indicate tissue normalisation. The insensitivity of lower field strength imaging has been suggested as one explanation[13]. Furthermore, rat models of cerebral ischaemic insult confirm histological neuronal damage despite DW-MRI resolution, cautioning the use of imaging alone to assess ischaemic injury[29]. We therefore sought to compliment cerebral MR imaging with a battery of well validated neurocognitive assessment tools.

There is a large body of evidence to indicate silent cerebral injury heralds adverse cognitive consequences. They are associated with an increased risk of mild cognitive impairment[30], and may double the risk of dementia (most commonly Alzheimer's disease), with a steeper rate of cognitive decline observed the greater the number of infarctions[12]. It is feasible that the decline in verbal memory seen at 30 days following Lotus, which was not observed following CoreValve, is a reflection of the associated higher burden of DW-MRI lesions.

To date, few studies have combined DW-MRI and cognitive assessment following TAVI with CoreValve or Edwards-Sapien. The largest involved 111 subjects [23] with

the other three averaging 40 patients[8,22,31]. No decline in any cognitive domain was observed despite the occurrence of diffuse micro-infarcts affecting both cerebral hemispheres[22]; and patients with and without DW-MRI lesions performed equally well[23]. These findings are consistent with our study. Our observed high incidence of new DW-MRI lesions post-TAVI appeared to lack clinical sequelae when cognition was objectively assessed at 12 months, and this was the case following both first and second-generation devices.

This study is noteworthy in the context of contemporary TAVI trials. Results from the PARTNER 2 trial have suggested transfemoral TAVI results in a lower rate of death or disabling stroke in intermediate-risk patients, with an average age similar to this study of 81.5 years, when compared with surgery[32]. Younger patients would expectedly exhibit lower burdens of aortic atheroma and thus fewer silent DW-MRI lesions, irrespective of TAVI design. In the recent CLEAN-TAVI[33] and SENTINEL[34] trials, cerebral protection reduced new ischaemic cerebral lesions. However, Lotus patients were notably absent from both studies. Whilst pre-existing lesion volume predicted future cerebral lesion volume[34], the baseline and post-TAVR volume of established DWI lesions in our study of both CoreValve and Lotus were equivalent. Our work suggests devices to reduce lesion frequency maybe a particularly pertinent adjunct to Lotus TAVI and potentially offset the decline in verbal memory and psychomotor speed we observed at 30 days.

Whilst our work indicates DW-MRI, our lesions does not seem to affect mid-term neurocognitive function caution is required not to dismiss DW-MRI lesions as entirely innocuous, particularly given even small lesions tripled the risk of stroke-related death in healthy subjects aged 50 – 73 years over 14 years of follow-up[35]. Longer

follow-up is required to clinically appreciate the natural history of cerebral injury incurred during TAVI.

Limitations

Patients were not randomised to CoreValve or Lotus and hence the study is vulnerable to selection bias. Furthermore, we have not directly compared cognitive performance from our two TAVI groups with that of healthy octogenarians, or patients managed conservatively.

There was attrition in patients completing the study protocol, with 5 patients failing to complete post-intervention imaging and 17 patients with imaging data failing to complete 12 month neurocognitive assessments. Fourteen patients (19%) withdrew from the study and this was often due to deteriorating health or transfer into long-term nursing care There is hence an inherent risk of bias as potentially those with most marked decline in cognitive function might have been excluded. Furthermore, our final analysed patient group sizes confer limited power to report 'no difference' in baseline variables raising the possibility of Type 1 and Type 2 errors, and transfer bias influencing our final group comparisons.

The CoreValve has been clinically in use for much longer than the Lotus valve. Therefore, the greater degree of new DWI lesion seen in the Lotus group may partly reflect an operator "learning curve" during which experience and fluency in use of Lotus delivery equipment was refined.

Presently, there is no internationally accepted definition of cognitive decline following cardiac procedures, with the potential for variation between studies. We have utilised a comprehensive battery of validated tests that cover a wide variety of important higher neurocognitive faculties, but potentially these may be insensitive to change

and lack validation in the context of TAVI.

Patients in atrial fibrillation on formal anticoagulation had their warfarin withheld prior to, with full dose heparin during the TAVI implant and recommencement of warfarin on the evening of the procedure. However, it is not possible to exclude cardiac thrombus associated with atrial fibrillation as a potential contributor to micro-infarction.

Our work employed 1.5 Tesla field strength imaging, which is the case for the majority of similar published studies. However, the use of higher-field strengths may have increased detection of micro-infarction and characterise more accurately the burden associated with different TAVI devices.

CONCLUSION

There was a higher incidence of silent micro-infarction with a greater number of lesions per patient following second-generation Lotus compared to the first-generation CoreValve implantation. However, there was no objective decline in neurocognitive function discernible 1-year following TAVI with either prosthesis.

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COMPETING INTERESTS

DB and CJM are consultants and proctors for both Medtronic and Boston Scientific.

JG and SP have received an educational research grant from Philips Healthcare.

AUTHOR'S CONTRIBUTION

JG conceived and designed the study. TAM drafted the manuscript. CL compiled the comprehensive battery of neurocognitive tests and instructed on their correct implementation. FR, TAM, AU, LED and AS performed the recruitment of patients and their neurocognitive assessment. GPM supervised and AS oversaw the University of Leicester contribution. MI and AJPG performed MRI image analysis. DJB and CM carried out TAVI implantation. TAM and AU analysed data and interpreted the results. PPS and PG gave input into data interpretation. PPS, PG, JRJF, GJF, SP and GPM were involved in critical and intellectual revision of the article. All authors edited and revised the manuscript. All authors read and approved the final manuscript.

DATA SHARING STATEMENT

All clinically important data from this observational study has been reported on in the manuscript.

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TABLES

Table 1 – Patient characteristics in those with 6 month follow up.

	Lotus (n=29)	**CoreValve (n=37)**	p Value*
Age (years)	79.8±8.9	81.2±7.2	0.459
Male, n (%)	14 (48)	17 (46)	0.851
EuroSCORE II	4.13±3.30	5.55±3.79	0.115
STS score (%)	4.04±2.59	5.28±3.41	0.109
BMI (kg/m^2)	28.5±5.2	27.2±5.4	0.323
Hypertension, n (%)	11 (38)	20 (54)	0.157
Diabetes, n (%)	5 (17)	4 (11)	0.450
Hyperlipidaemia, n (%)	17 (59)	18 (49)	0.488
Atrial Fibrillation, n (%)	5 (17)	9 (24)	0.449
Previous MI, n (%)	7 (24)	2 (5)	**0.026**
Previous PCI, n (%)	9 (31)	10 (27)	0.774
Previous CABG, n (%)	5 (17)	8 (22)	0.618
Previous Stroke, n (%)	7 (24)	6 (16)	0.454
Peripheral Vascular Disease, n (%)	4 (14)	5 (14)	0.991
eGFR (ml/min/1.73m^2)	69±19	64±17	0.342

Values are mean±SD or n (%). *p Value for comparison between procedure types.

STS, Society of Thoracic Surgeons score; BMI, body mass index; eGFR, estimated glomerular filtration rate; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; MI, myocardial infarction.

Table 2 – Catheterization data for TAVI implant procedures

	Lotus (n=29)	**CoreValve (n=37)**	**p Value***
TAVI size (n(%))	23mm (7 (24%)) 25mm (8 (28%)) 27mm (14 (48%))	23mm (4 (11%)) 26mm (8 (22%)) 29mm (18 (49%)) 31mm (7 (19%))	-
Femoral route, n (%)	29 (100)	27 (73)	0.081
Sheath size (French)	18 (28%) 20 (52%) 22 (20%)	18 (100%)	
Pullback PG (mmHg)	56±27	43±19	**0.023**
Fluoroscopy time (min)	29±8	18±11	**0.001**
Procedure time (min)	159±42	143±50	0.194
Contrast (ml)	120±43	134±43	0.212
Pre-dilatation BAV, n (%)	25 (86)	28 (77)	0.286
Post-dilatation, n (%)	0 (0)	5 (14)	**0.039**
TAVI repositioned, n (%)	7 (24)	0 (0)	**0.002**
TAVI embolization, n (%)	0 (0)	3 (8)	0.117
Need for second TAVI, n (%)	0 (0)	3 (8)	0.117

*Independent samples t-test

Table 3 – Comparison of MRI DWI imaging following Boston Lotus and Medtronic CoreValve

	Lotus (n=29)	CoreValve (n=37)	p Value
Incidence of new micro-infarction (n(%))	23(79)	22(59)	**0.025**
Number of new micro-infarcts per patient	3.5 (IQR 7.0)	2.0 (IQR 3.0)	**0.002**
Mean micro-infarct volume per patient (ml)	0.36 (IQR 0.57)	0.17 (IQR 0.21)	0.166
Number of new small lesions (<5mm) (n(%))	124(78)	41(72)	**0.005**
Number of new large lesions (≥5mm) (n(%))	34(22)	16(28)	**0.036**
Number of patients with new ACA lesions (n(%))	14(48)	2(5)	**0.001**
Number of patients with new MCA lesions (n(%))	20(69)	19(51)	0.149
Number of patients with new PCA lesions (n(%))	10(34)	6(16)	0.086
Number of patients with new VBA lesions (n(%))	15(52)	7(19)	**0.005**

ACA: anterior cerebral artery, MCA: middle cerebral artery, PCA: posterior cerebral artery, VBA: vertebrobasilar artery.

Table 4 – Summary of neurocognitive test scores at baseline, 30d and 12m.

	TAVI	Baseline	30 days	p Value*	12 months	p Value**
MMSE	Lotus	28.6±1.6	28.8±1.8	0.468	28.7±2.0	0.743
	CoreValve	28.8±1.8	28.4±2.0	0.251	27.9±2.8	0.277
HVLT						
Total learning	Lotus	21.4±7.2	21.5±4.1	0.913	23.3±6.1	0.104
	CoreValve	17.7±6.3	18.6±6.1	0.512	18.3±7.8	0.764
Delayed Recall	Lotus	7.6±3.0	6.3±3.4	**0.038**	9.0±6.7	**0.028**
	CoreValve	5.8±2.8	5.3±3.8	0.296	4.3±4.4	0.419
Discrimination Index	Lotus	10.2±1.5	8.6±2.9	**0.015**	10.1±2.4	**0.010**
	CoreValve	9.6±2.1	9.1±3.4	0.373	7.9±4.5	0.147
Trail Making Tests						
A	Lotus	47.0±15.0	56.0±27.6	0.112	50.5±19.7	0.354
	CoreValve	56.9±27.8	61.1±40.0	0.566	66.1±49.8	0.431
B	Lotus	170.9±86.5	140.7±62.8	**0.006**	152.3±87.5	0.273
	CoreValve	171.1±121.4	155.2±79.0	0.548	143.3±64.4	0.969
DSST	Lotus	43.2±15.8	45.5±16.0	0.254	44.2±13.5	0.253
	CoreValve	33.9±14.1	34.6±13.3	0.704	34.4±15.7	0.633
LNS	Lotus	7.6±4.5	8.6±3.5	0.387	8.6±2.6	0.876
	CoreValve	8.3±5.1	8.8±4.2	0.662	7.9±4.8	0.291
Grooved Pegboard						
Dominant score	Lotus	163.1±102.4	136.9±75.7	0.336	142.7±38.0	0.670
	CoreValve	157.3±57.2	132.1±81.3	0.162	169.0±60.4	0.110
Non-dominant score	Lotus	158.0±37.7	148.5±53.4	0.373	159.6±47.0	0.658
	CoreValve	180.9±58.2	173.9±104.2	0.654	215.9±124.4	**0.004**

Mean±SD.
* comparing values at baseline and 30d, same TAVI design, paired samples t-test
** comparing values at 30d and 12 months, same TAVI design, paired samples t-test

Table 5 – Within group comparison of mean change in cognitive domain over 12 months in patients with and without DW-MRI lesions.

	Boston Lotus (n=25)			Medtronic CoreValve (n=24)		
	DWI -ve (n=6)	**DWI +ve (n=19)**	**p Value**	**DWI –ve (n=11)**	**DWI+ve (n=13)**	**p Value**
MMSE	1.2±0.8	-0.4±1.9	**0.025**	-0.9±2.5	-0.7±2.6	0.840
HVLT Learning	4.2±5.2	1.2±7.3	0.454	1.1±3.9	1.0±9.1	0.691
HVLT Delayed	6.3±12.9	-0.1±3.3	0.177	-0.2±2.5	-1.1±3.1	0.456
HVLT Discrimination	0.0±1.5	-0.1±2.6	0.733	0.8±2.3	-2.3±3.5	**0.019**
TMT A	15.5±20.8	-0.1±15.3	0.059	18.9±64.9	5.0±14.7	0.562
TMT B	-13.0±88.9	-18.3±61.4	0.870	19.6±61.6	-1.4±64.4	0.454
DSST	4.0±10.0	-0.4±9.8	0.346	-0.1±6.7	5.0±13.7	0.370
LNS	2.4±3.0	0.7±5.1	0.534	-0.5±5.0	0.8±3.6	0.474
GPBT Dominant	-8.2±31.5	-24.5±108.0	0.721	0.5±37.6	22.6±37.7	0.186
GPBT Non-Dominant	-26.0±83.7	-3.2±51.3	0.914	43.0±81.3	20.8±66.8	0.235

Mean±SD.

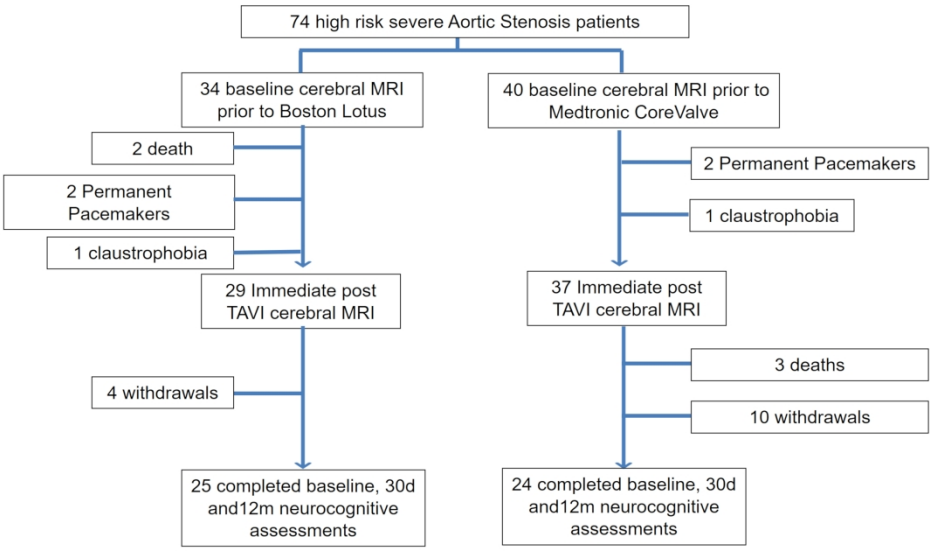
Figure 1: Study Profile

Figure 2: Diffusion weighted MRI of the brain examining silent injury with TAVI.

Cerebral images, including the brainstem and cerebellum before (A) and after (B) TAVI procedure. Multiple new cerebral infarctions were seen, some of which are highlighted by the red arrows.

Figure 3: Line graph depicting change in MMSE (A and B) and HVLT Discrimination Index (C and D) over time following Lotus and CoreValve.

(Red lines indicate patients with DW-MRI micro-infarcts, blue lines those without).



Study Profile

296x163mm (300 x 300 DPI)

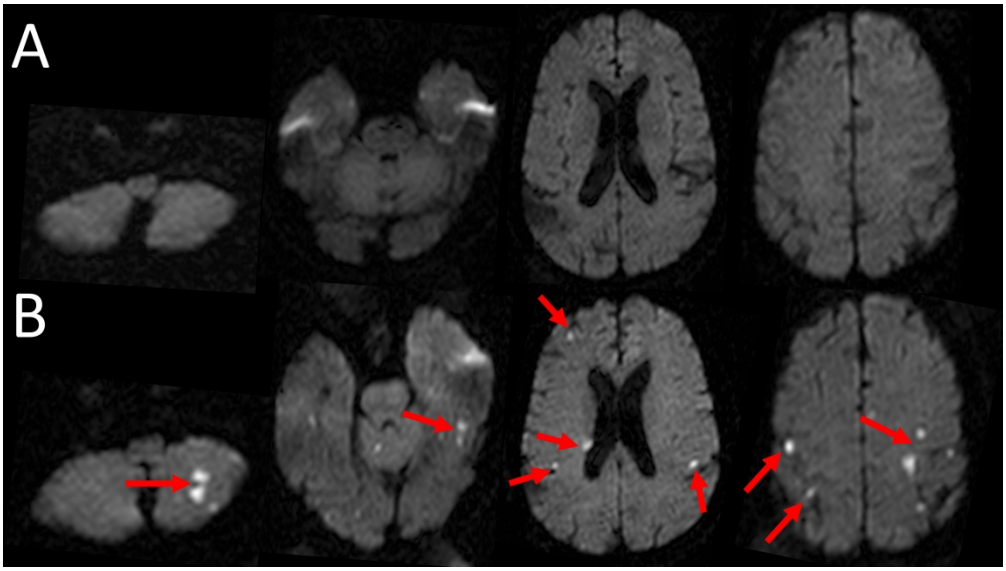


Figure 2: Diffusion weighted MRI of the brain examining silent injury with TAVI.
Cerebral images, including the brainstem and cerebellum before (A) and after (B) TAVI procedure. Multiple new cerebral infarctions were seen, some of which are highlighted by the red arrows.

338x190mm (300 x 300 DPI)

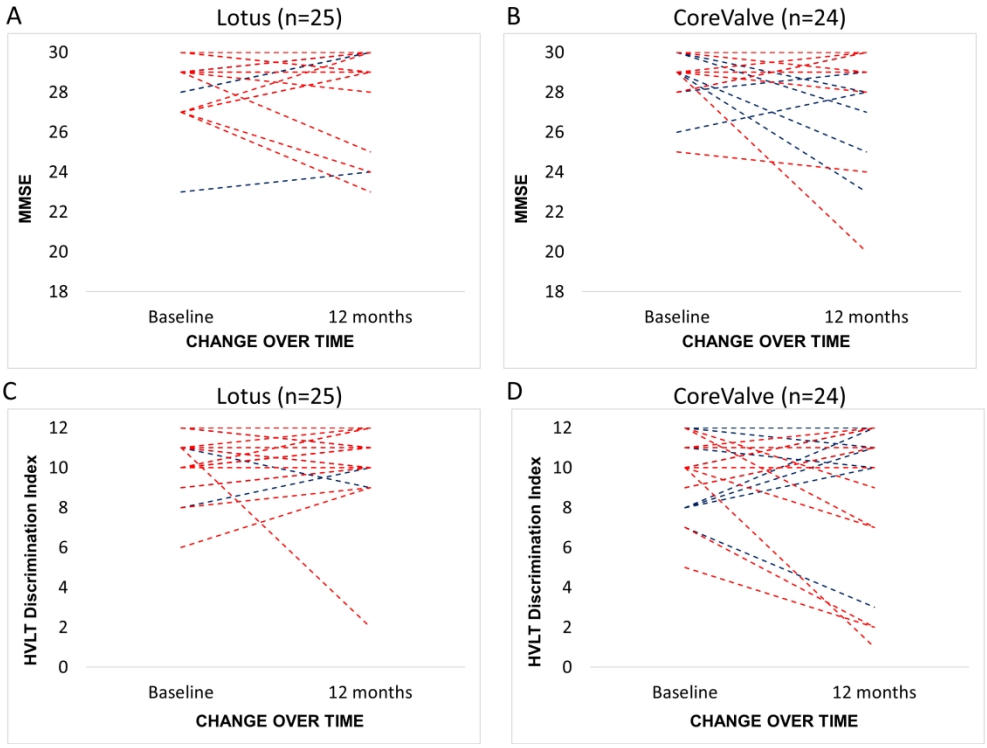


Figure 3: Line graph depicting change in MMSE (A and B) and HVLT Discrimination Index (C and D) over time following Lotus and CoreValve.
(Red lines indicate patients with DW-MRI micro-infarcts, blue lines those without).

254x190mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (pages 1 and 3)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found (page 3)
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported (page 6-7)
Objectives	3	State specific objectives, including any prespecified hypotheses (pages 3, 7)
Methods		
Study design	4	Present key elements of study design early in the paper (pages 3, 7)
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (page 3, 7)
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable (pages 8, 9)
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group (pages 8, 9)
Bias	9	Describe any efforts to address potential sources of bias (pages 9, 16)
Study size	10	Explain how the study size was arrived at (page 10)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why (page 9)
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (page 9)
		(*b*) Describe any methods used to examine subgroups and interactions (page 9)
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (Page 10, Figure 1)
		(b) Give reasons for non-participation at each stage (Figure 1)
		(c) Consider use of a flow diagram (Figure 1)
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (Table 1 on page 23)
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives (page 13)
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias (page 17)
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence (pages 14-16)
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based (page 18)

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.