PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Silent Cerebral Infarction and Cognitive Function following TAVI: An observational two-centre UK comparison of the 1st generation CoreValve and 2nd generation Lotus valve
AUTHORS	Musa, Tarique; Uddin, Akhlaque; Loveday, Catherine; Dobson, Laura; Igra, Mark; Richards, Fiona; Swoboda, Peter; Singh, Anvesha; Garg, Pankaj; Foley, James; Fent, Graham; Goddard, Anthony; Malkin, Christopher; Plein, Sven; Blackman, Daniel; McCann, G; Greenwood, John

VERSION 1 – REVIEW

REVIEWER	Chiara De Biase Clinique Pasteur, Toulouse, France
REVIEW RETURNED	23-Apr-2018

GENERAL COMMENTS	Dear authors, the article is well written and the aim is clear. Anyway I have the following comments: - Was the procedure timing similar for both groups? From the fluoroscopy time reported in table it seems that LOTUS procedures were longer. - The sizing iof your population is really poor (66 patients from 2 centers in 3 years) and indeed you aimed to compare two devices of two different generations, without any real connections. To be of interest, maybe it would be better to compare devices of the same manufacturing or rather of the same generation. -Did you use any cerebral protection device? It would be useful to have a MSCT description of the aortic root (Calcium score, aortic aneurism, etc...).

REVIEWER	Firas Zahr Oregon Health and Science University
REVIEW RETURNED	02-May-2018

GENERAL COMMENTS	This is an important paper reviewing the incidence of silent strikes on DW-MRI and the cognitive impairment associated with it as it relates to CoreValve in comparison to the Lotus valve. The authors should be congratulated for this nicely written manuscript and efforts. 1- it appears that it is highly selected population of overall intermediate risk patients undergoing TAVR (STS 4-5). On over 3 year period only 66 patients were enrolled in 2 busy centers. The

	authors should discuss the limitation of enrollment and how it might have impacted the study results 2. repositioning the Lotus device as expected was associated with more events, but not balloon valvuloplasty. The authors should further clarify the effect of that and redo the analysis excluding patients who had to reposition the valve as this might be related to the learning curve and had important implication especially that it was not compared to the second generation repositionable Evolut. 3. patients who had clinical strokes were excluded. Understanding that this study is designed to look at silent events, it is crucial to look at clinical events as it might skew the results completely, and has major clinical impact 4. pre TAVR MRI was performed up to 7 days pre TAVR. Was there any invasive procedure done in the interim (diagnostic angio, PCI?). 5. the authors should discuss the implication of peri-TAVR anticoagulation regimen especially in the Afib population (pre and post TAVR) as it might have an impact on cardioembolic events. Also the impact of larger percentage of prior MI in the lotus group on cardioembolic events. 6. what is the impact of larger proportion of alternative access in the CoreValve group? Assuming they were primarily subclavian access, could avoiding the Aortic arch result in less events?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Chiara De Biase
Institution and Country: Clinique Pasteur, Toulouse, France
Please state any competing interests: "none declared"

Please leave your comments for the authors below

Dear authors,

the article is well written and the aim is clear. Anyway I have the following comments:

- Was the procedure timing similar for both groups? From the fluoroscopy time reported in table it seems that LOTUS procedures were longer.

Response: Statistically, procedure times for the two valve groups were similar. However, a longer duration (on average 11 minutes per case) was spent using fluoroscopy during Boson Lotus implants. This in part reflects the Lotus design; being mechanically expanded, fully retrievable and repositionable allowing assessment of TAVI function and haemodynamics prior to final deployment.

- The sizing iof your population is really poor (66 patients from 2 centers in 3 years) and indeed you aimed to compare two devices of two different generations, without any real connections. To be of interest, maybe it would be better to compare devices of the same manufacturing or rather of the same generation.

Response: We thank the Reviewer for their comment and agree there is an attrition of patients as stated in the limitations section. Nonetheless, to our knowledge, this is one of the largest studies of its kind. This was an observational study to compare silent cerebral injury associated with the use of the

established CoreValve and novel Boston Lotus iterations which we feel is of crucial clinical importance. Our work is a noteworthy contribution particularly as the recent CLEAN-TAVI and SENTINEL trials did not include the Boston Lotus iteration. Furthermore, our line of enquiry is similar to previous randomised trials such as the CHOICE trial (comparing the Medtronic CoreValve with the Edwards Sapien XT, Abdel-Wahab et al, JAMA; 311(15):1503-14) and indeed we have recently published work contrasting CoreValve and Lotus in respect of aortic regurgitation and ventricular remodelling (Musa et al. J Interv Cardiol. 2018 Jun;31(3):391-399).

-Did you use any cerebral protection device? It would be useful to have a MSCT description of the aortic root (Calcium score, aortic aneurism, etc...).
Response: None of the patients studied involved the use of a cerebral protection device, as detailed in the methods section. All patients underwent multi-detector computed tomography contrast studies to assist annular sizing and device selection. However, non-contrast CT was not undertaken, and hence specific calcium scores were not measured.

Reviewer: 2
Reviewer Name: Firas Zahr
Institution and Country: Oregon Health and Science University

Please state any competing interests: N/A

Please leave your comments for the authors below

This is an important paper reviewing the incidence of silent strikes on DW-MRI and the cognitive impairment associated with it as it relates to CoreValve in comparison to the Lotus valve. The authors should be congratulated for this nicely written manuscript and efforts.

1- it appears that it is highly selected population of overall intermediate risk patients undergoing TAVR (STS 4-5). On over 3 year period only 66 patients were enrolled in 2 busy centers. The authors should discuss the limitation of enrollment and how it might have impacted the study results.

Response: We thank the Reviewer for their comment. There is an attrition over the study period with only 66 (89%) and 49 (66%) completing the imaging and 12 month neurocognitive assessments respectively. We have included this important acknowledgement in our limitations section. The main limitation is the attrition of patients who were unable to complete the CMR protocol at 6 months. Our study TAVI population, with an average age of 80 and associated co-morbidities are a very challenging group to study, particularly in respect of neurocognitive assessment. due to age, frailty and comorbidity. Fourteen patients (19%) withdrew from the study and this was often due to deteriorating health or transfer into long-term nursing care. This remains one of the largest studies of its kind. Nonetheless, the potential for bias cannot be excluded as the sickest patients who withdrew may have had worst outcomes. 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. We have expanded our limitations section in accordance with the Reviewer’s request.

2. repositioning the Lotus device as expected was associated with more events, but not balloon valvuloplasty. The authors should further clarify the effect of that and redo the analysis excluding patients who had to reposition the valve as this might be related to the learning curve and had important implication especially that it was not compared to the second generation repositionable Evolut.

Response: We acknowledge the Reviewer's comment and accept inevitably with novel device technology there will be an adjustment period and the workhorse 1st generation CoreValve studied is not repositionable. However, our data suggests that repositioning per se was not a significant contributor to the frequency of new DW-MRI lesions observed, as detailed in the Result section. On removing the 7 Lotus implants that involved repositioning, comparison with the CoreValve group still indicates a higher incidence of new micro-infarction (p=0.02) and number of new micro-infarcts per patient (p=0.001) following the Boston Lotus implant.

3. patients who had clinical strokes were excluded. Understanding that this study is designed to look at silent events, it is crucial to look at clinical events as it might skew the results completely, and has major clinical impact

Response: We thank the Reviewer for their comment. We agree that clinical stroke is a significant morbidity, the incidence of which is well recognised following TAVI from multiple clinical trials. None of our study population suffered a clinical stroke. The presence and consequence of silent cerebral injury is much less well recognised and before TAVI can be considered in younger patient groups; the impact of such injury must be understood. Our work thus affords crucial insight in this regard.

4. pre TAVR MRI was performed up to 7 days pre TAVR. Was there any invasive procedure done in the interim (diagnostic angio, PCI?).

Response: We can confirm no such invasive procedures were performed in any patient from either group.

5. the authors should discuss the implication of peri-TAVR anticoagulation regimen especially in the Afib population (pre and post TAVR) as it might have an impact on cardioembolic events. Also the impact of larger percentage of prior MI in the lotus group on cardioembolic events.

Response: We are grateful to the Reviewer for highlighting this important issue. All patients received dual antiplatelet therapy for three months following TAVI. Patients on formal anticoagulation as deemed clinically appropriate per their CHADS2VASc score had their warfarin withheld prior, with full dose heparin during the TAVI implant and recommencement of warfarin on the evening of the procedure. The number of patients with atrial fibrillation was similar among the two groups and whilst a greater percentage of Lotus patients had suffered previous myocardial infarction, the degree of coronary revascularisation with PCI or CABG were equivalent. In regression analysis, there was no association between the presence of AF or previous myocardial infarction at baseline with the incidence of new micro-infarction following TAVI; neither in the Lotus group alone (p= 0.592 and 0.985 respectively) nor when the group was analysed as a whole (p=0.751 and 0.444 respectively). This would support the occurrence of new cerebral infarction observed in the post-procedure scans being related to TAVI manipulation and deployment; rather than a consequence of atrial fibrillation per se. However, we acknowledge it is not possible to be completely certain cardiac thrombus did not contribute to micro-infarction particularly in AF patients. We have updated the limitations section in line with this important enquiry.

6. what is the impact of larger proportion of alternative access in the CoreValve group? Assuming they were primarily subclavian access, could avoiding the Aortic arch result in less events?

Response: We thank the Reviewer for this enquiry. We have previously shown severity of aortic arch atheroma is an independent risk factor for the development of new cerebral infarcts following TAVI (Fairbairn et al. 2012; Heart;98:18-23). Of the CoreValve group, 27(73%) were implanted via the femoral route, with only 6(16%) via a subclavian approach. Comparing patients based upon femoral

or subclavian route of access, there was no difference in the proportion of new patients with new lesions nor the average number of lesions per patient (p=0.843 and 0.551 respectively). We feel that the interpretation of this analysis is significantly limited by the small subclavian group size and further work is required to determine whether choice of route can optimise cerebral protection during TAVI.

VERSION 2 – REVIEW

REVIEWER	Chiara De Biase Clinique Pasteur Toulouse, Toulouse, France
REVIEW RETURNED	11-Sep-2018

GENERAL COMMENTS	Dear authors, The tonic of cerebral conplications after TAVI is of great interest. Anyway I did not fond out anything in your papers showing: -anti thrombotic therapy - calcium score and calcium distribution at aortic root level - use of any brain protection device These points are important to evaluate the real cause at thé bases of cerebral injury.