

# Retinal embolic events: frequency and impact following transcatheter aortic valve implantation (TAVI) for aortic stenosis

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**To cite:** Fusi-Rubiano WJ, Yang YC, Smallwood AF, *et al*. Retinal embolic events: frequency and impact following transcatheter aortic valve implantation (TAVI) for aortic stenosis. *BMJ Open Ophthalm* 2017;**1**:e000033. doi:10.1136/bmjophth-2016-000033

Received 13 August 2016  
Revised 06 May 2017  
Accepted 24 May 2017

## ABSTRACT

**Objectives** Transcatheter aortic valve implantation (TAVI) is an established treatment for patients with severe symptomatic aortic stenosis. It has a cerebrovascular accident rate of about 5% but the effect on retinal embolic events has not been previously reported. This study investigated the occurrence of retinal emboli following TAVI.

**Methods and analysis** In this prospective observational study, 20 patients underwent full ophthalmic examination to assess retinal embolic events prior to TAVI and at 48 hours and 1 month post-TAVI.

**Results** At 48 hours post-TAVI, one patient had a new cotton wool spot in the right eye. At 1 month, another two patients had new retinal emboli events in at least one eye and a fourth patient developed retinal splinter haemorrhages in the right eye.

**Conclusion** Retinal embolic events and new retinal abnormalities following TAVI occurred in 15% and 20% of our cohort, respectively, without any associated retinal damage or significant visual problems. Retinal evaluation may be a useful surrogate test for cerebral embolisation in future studies assessing the utility of new valve prostheses and embolic protection devices

## INTRODUCTION

Retinal arterial occlusive events caused by cholesterol, fibrinoplatelet or calcific emboli are known to occur in individuals with atheromatous vessels and aortic valves especially during or after interventional procedures such as cardiac catheterisation and coronary artery bypass graft procedures. Previous studies have shown the risk of retinal embolisation to be as high as 55% to 100% after coronary bypass surgery,<sup>1 2</sup> about 1.25% to 13.2% after carotid stenting<sup>3 4</sup> and about 6.3% after cardiac catheterisation.<sup>5</sup> For patients with severe symptomatic aortic stenosis (AS), valvular replacement has been increasingly performed via a femoral catheter technique called

## Key messages

What is already known about this subject?

- ▶ TAVI procedures for severe aortic stenosis are associated with a 5% risk of cerebrovascular accident but the risk of retinal arterial emboli have not been studied

What are the new findings?

- ▶ Retinal embolic events following TAVI occurred in approximately 15% of patients but were not associated with visual loss

How might these results change the focus of research or clinical practice?

- ▶ Retinal examination and detection of emboli in the early postoperative period may provide a useful tool for evaluation of the risk of arterial emboli with new cardiac prostheses and embolic protection devices in the future

transcatheter aortic valve implantation (TAVI).<sup>6 7</sup> While it is a significantly less invasive procedure than traditional surgical valve replacement, current studies suggest that TAVI carries a moderately high cerebrovascular accident rate of up to 5%.<sup>6 7</sup> Furthermore, sub-clinical cerebral emboli are seen on brain MRI scanning in over 75% of patients following TAVI,<sup>8</sup> with up to 72% showing 75 emboli or more.<sup>9</sup> It has been postulated that these emboli are likely to be caused by the dislodgement of atheromatous material from the aorta or debris from the native valve, especially when there has been multiple-device passage across the aortic arch and/or balloon aortic valvuloplasty (BAV) intraoperatively, just prior to device placement or deployment of prosthetic valves. Recent studies on the use of embolic deflection devices have shown promising results,<sup>10 11</sup> but there is a continuing challenge to reduce the risk of cerebral embolisation and stroke following



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TAVI. Although the majority of small retinal emboli are asymptomatic and often not associated with significant visual sequelae, their detection post-TAVI may serve as an easily measurable parameter for monitoring the outcomes and safety of TAVI and also be used to evaluate the efficacy of future emboli deflection devices.

Given the known association of TAVI with cerebral emboli, it is reasonable to hypothesise that small asymptomatic emboli could occur during or after TAVI but to our knowledge, the effect of the TAVI procedure on retinal embolic events has not been previously reported. This prospective study aims to investigate the presence and frequency of retinal emboli, the calibre of vessels affected and any associated visual changes following TAVI.

## MATERIALS AND METHODS

The study design was a single centre, prospective observational study. The trial protocol was approved by a local research ethics committee and the study was conducted in accordance with the Declaration of Helsinki. In a 26-month recruitment period between October 2012 and December 2014, patients undergoing a TAVI procedure at the Heart and Lung Centre of the Royal Wolverhampton Hospitals NHS Trust, UK, were invited to participate in the study and were given verbal and written study information in clinic when the plan for TAVI treatment was first offered. Informed consent was obtained. Screening and baseline evaluation were performed on admission to the hospital the day before their TAVI procedure.

After screening, patients were excluded if they had any of the following criteria: a diagnosis of diabetes mellitus (DM); any contraindication to pupillary dilation with tropicamide 1% drops (Minims, Bausch and Lomb); women of childbearing age; any eye condition that made fundus examination difficult or unreliable and comorbidities that precluded transport to the ophthalmology department. Patients with DM were excluded as diabetic retinal changes may have been miscategorised as emboli and led to an overestimate of the number of events. Although patients with systemic hypertension were not excluded, careful interpretation of the retinal images were done to minimise the confounding effects on diagnosis of new retinal emboli from hypertension retinopathy changes such as flame haemorrhages, cotton wool spots and exudates. For those ineligible, a screening event was logged and reason for screen failure documented.

Eligible patients underwent full baseline evaluation. Data collected on baseline characteristics included demographic data, comorbidities and concomitant medications. Cardiovascular data including blood pressure, New York Heart Association (NYHA) class, cardiac rhythm, indication for TAVI procedure, structural and physiological valve parameters were also evaluated.

Ophthalmic data including visual acuity (VA) using logMAR chart, visual fields by confrontation, slit lamp examination findings of the anterior segment, intraocular pressure (IOP) measurement and retinal examination findings using an in-direct ophthalmoscope and slit-lamp biomicroscopy. Bilateral retinal imaging was undertaken using standard seven-field colour photo of fundus using Canon CX1 (Canon USA, New York) 50° camera with additional 35° field for higher magnification if emboli were found.

Following baseline evaluations, TAVI procedures were undertaken as per routine clinical practice at our centre. All patients were pretreated with aspirin and loaded with clopidogrel post-procedure (300 mg stat) and maintained on clopidogrel 75 mg/day throughout the follow-up period.

Intraoperative data were documented including the anaesthetic type; access route; the use (or not) of BAV; the number of balloon and valve passages across the aortic arch; the number of TAVI prostheses deployed and any intraprocedural complications.

Following the TAVI procedure, first and second ophthalmological follow-up evaluations were performed at day 2 and 1 month, respectively. At day 2, patients received visual field testing and dilated fundus examination from the bedside using an indirect binocular ophthalmoscope. Any field defects and retinal emboli were recorded to determine VA and visual fields on confrontation. At 1 month, patients received the final evaluation comprising of full history, VA measurement using logMAR chart, visual field testing on confrontation, slit-lamp examination, dilated funduscopy on a slit lamp and retinal photography. Any field defects and new retinal emboli were documented. All adverse events were recorded and reported. Data analysis was performed to describe the TAVI procedures in detail and to determine the numbers of retinal emboli at each time point before and after TAVI.

## RESULTS

Out of a total of 135 consecutive patients undergoing TAVI who were screened for the study, 115 were excluded for the following reasons: presence of DM (n=48), patient declined study (n=16), late additions to TAVI list precluding effective consent (n=11), cardiac angiograms scheduled on same day as baseline examination (n=9), presence of other ocular abnormality (n=5), anticipated difficulty in attending follow-up visits and other miscellaneous reasons (n=26). The remaining 20 patients (13 males, 7 females, mean age 82 years, 68–93 years) who were eligible and willing to participate were recruited in the study. At baseline, all ophthalmic characteristics were normal except one patient who had a pre-existing retinal embolus in a second-order branch retinal arteriole in the left nasal quadrant. Baseline mean VA score in all patients was 71 letters in right eyes and 71 letters in left eyes and mean IOP was 15 mm Hg in right eyes and 14 mm Hg in left eyes.

**Table 1** Baseline characteristics of study participants

Baseline characteristics	Number
Mean age (year)	81.65
Age range (year)	68–93
Males	13
Females	7
<b>Risk factors</b>	
CKD	6
AF prior to procedure	5
Hypertension	15
Hyperlipidaemia	15
Current smoker	1
Ex-smoker	6
Never smoker	12
Previous MI	6
Previous CABG	10
Previous PCI	5
Previous TIA/CVA	2
<b>Clinical presentation</b>	
Native aortic stenosis	17
Valve-in-valve	3
NYHA 3	14
NYHA 2	6
Bicuspid valve	0

The mean logistic EuroSCORE was 22.45 (10.98–39.46) and the mean EuroSCORE II was 5.407% (2.36%–11.94%).

AF, atrial fibrillation; CABG, coronary artery bypass surgery; CKD, chronic kidney disease; CVA, cerebrovascular accident; MI, myocardial infarction; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TIA, transient ischaemic attack.

The systemic and cardiac baseline characteristics are summarised in [table 1](#).

All patients underwent the TAVI procedure for either AS (n=17) or prosthetic valve stenosis (n=3) under general (n=11) or local (n=9) anaesthesia. Two patients were treated with bicuspid valves and three with ‘valve-in-valve’ procedures for prosthetic valve stenosis. Fourteen (70%) patients were NYHA stage 3 and six (30%) were NYHA stage 2. Four different types of valves were used:

Medtronic CoreValve prostheses (n=15), Boston Scientific Lotus valves (n=3), Medtronic Engager valve (n=1) and Edwards Sapien XT valve (n=1).

The procedures were undertaken via four main approaches: transfemoral (n=15), subclavian (n=2), direct aortic (n=2) and transapical (n=1). Valve size ranged from 23 to 29 mm. Predilation, when used, was

performed using Nu-Med balloons of diameters 18–22 mm. All TAVI procedures were clinically successful with a mean length of stay in hospital of 9.4 days (3–24 days) and in-hospital mortality of 0%.

All 20 patients completed the 48 hours post-TAVI ophthalmic assessment. Only one patient did not have the final ophthalmic assessment at 1 month post-TAVI due to illness. The visual data analysis was performed using the full dataset from 19 patients and there was no significant difference in VA between baseline and final visits and all patients were visually asymptomatic throughout the study period.

At the 48-hour post-TAVI assessment, 1 patient out of 20 had a new cotton wool spot next to the right supratemporal arteriole indicating a new retinal embolic event. This had resolved at the final 1 month, follow-up visit.

At the 1-month follow-up visits, another 2 patients out of 19 were found to have new retinal embolic events in at least one eye. In the first patient, there was a cotton wool spot near the right supratemporal arteriole. In the second patient, there was a calcific embolus in the right parafoveal zone. For these two patients with new retinal embolic events, one had Medtronic CoreValve (transfemoral approach) and the other had Engager valve type (transapical approach)—both performed under general anaesthesia. Neither patient had BAV with a balloon passage across the arch nor had evidence of paroxysmal or sustained atrial fibrillation pre-TAVI or at subsequent follow-up. A fourth patient developed retinal splinter haemorrhages near the infratemporal arteriole in the right fundus at 1-month follow-up. A fifth patient sustained a clinical stroke with right haemiparesis 6 days following implantation of a CoreValve, but this patient did not have visual symptoms nor retinal emboli detected at any study visit and was able to complete 1-month follow-up with good recovery from the stroke. The embolus identified in one patient pre-TAVI was still present in the same location at the 1-month post-TAVI assessment.

## DISCUSSION

In this study, we found retinal abnormalities possibly resulting from unilateral retinal embolic events occurring in the early postoperative period in a total of 4 out of 20 patients (20%) undergoing elective TAVI procedures. Fortunately, none of the patients in the study had any visual consequences postoperatively but 1 in 20 had a clinical stroke on day 6 postoperatively. These findings highlight the recognised risk of embolic phenomenon associated with TAVI and the 20% rate found in our study is in keeping with the rate of cerebrovascular accidents reported in previous separate studies by Fairbairn *et al* and Ghanem *et al*.<sup>8 9</sup>

Although there are no other studies on retinal embolic events post-TAVI, there has been one study by Ascione *et al* in 2005 which investigated the occurrence

of retinal embolic events using supine intraoperative fluorescein fundus angiography during open chest, (cardiopulmonary bypass and 'off pump') coronary artery bypass graft operations.<sup>1</sup> They found that 5 out of 20 patients in the cardiopulmonary bypass group had angiographic signs of retinal microvascular damage. In another comprehensive, prospective study by Kojuri *et al* in 2011 looking at retinal and visual changes after diagnostic and therapeutic cardiac catheterisation procedures in 300 patients, 6.3% (n=19) of patients were found to have retinal emboli 17 to 96 hours following cardiac catheterisation.<sup>5</sup> This study included patients with diabetes which accounted for one third of their study population but only used the direct ophthalmoscope examination and unfortunately did not report on the breakdown of the exact subtypes of retinal lesions that were diagnosed as embolic in nature.

The independent risk factors for development of retinal emboli reported in a large epidemiological study by Klein *et al* and Baker *et al* included age, hypertension, smoking, diabetes and cardiovascular disease.<sup>12 13</sup> In our study, we excluded patients with diabetes due to the difficulties in differentiating the origin of retinal embolic signs such as cotton wool spots and flame haemorrhages which can also occur due to the microangiopathy in diabetic retinopathy. However, over one third of all patients screened for our study were excluded because of diabetes and it may be warranted to include those patients with diabetes but without any retinopathy for future studies to evaluate the risk of embolic phenomenon in this important subgroup.

Our study employed assessment of central VA and visual field testing on confrontation and found no significant impact on visual function following TAVI. This is also in keeping with the negative visual assessments reported by Kojuri *et al* following cardiac catheterisation.<sup>5</sup>

A potential limitation of our study is the timing of the first retinal assessment at 48 hours using direct and indirect ophthalmoscopy but without retinal imaging. This design was necessary due to the difficulties and risks of transferring patients in the early postoperative period from the cardiac ward to the eye department. This delay may have missed some transient fibrinoplatelet emboli in the first two postoperative days as it is likely that the emboli occur intraoperatively from the passage of the instruments in the aortic arch or the deployment of the prosthetic valve or when the prosthetic valve is functioning without full antiplatelet cover in the early post-TAVI period. Both ischaemic and bleeding events post-TAVI remain a significant issue and so far there is no definitive consensus on best practice for antithrombotic therapy post-TAVI. General recommendations for post-TAVI therapy are aspirin 75 mg in addition to a second antiplatelet such as the P2Y12 inhibitor clopidogrel.<sup>14 15</sup> Although these are

recommended, it is not known whether this regime improves thrombotic events post-TAVI and may worsen bleeding. Further trials including the POPular-TAVI trial are currently seeking to answer this.<sup>15</sup> Given that all high volume centres encounter ischaemic complications in patients treated with dual antiplatelet therapy, there is almost certainly a need for further therapeutic advances to limit this complication.

Lack of comparative radiological methods assessing cerebral emboli limits the conclusive correlation to retinal emboli in practice and further studies should aim to include this. Another potential limitation of our study is the limited numbers within the study and thus results should be interpreted with caution, however despite this, the results of this study has shown that visualisation of retinal emboli may provide clinically useful marker of perioperative arterial emboli associated with the TAVI procedure. However, as patients undergoing TAVI are usually frail and elderly, perioperative intravenous fluorescein angiography to evaluate the retinal circulation may not be feasible in many patients. The recent emergence of optical coherence tomography angiography with capability of wider field scanning may provide a non-invasive way for evaluating the occurrence of retinal emboli in TAVI in future studies.

## CONCLUSION

In conclusion, retinal embolic events following TAVI occurred in 15% of our cohort with new retinal abnormalities seen in 20%. These events appear not to cause severe retinal damage or significant visual problems however. Due to the ability to detect retinal emboli in the early postoperative period using non-invasive retinal imaging techniques, a retinal examination for emboli may provide a meaningful outcome for evaluating embolic protection devices and newer valve prostheses in future studies.

**Contributors** WF-R: involved in analysis of all data and manuscript preparation of the study. YCY: involved in design, submission, ocular assessment and manuscript preparation during the study. AFS: involved in participant recruitment, design, data collection, analysis and final manuscript review during the study. RCC: involved in design, planning, ocular assessment and final manuscript review during the study. SK: involved in study recruitment, cardiac assessment, conducting TAVI procedures and final manuscript review during the study. NN: involved in planning, ocular assessment and final manuscript review during the study. JMC: involved in design, submission, recruitment, cardiac assessment, lead for the study, conducting TAVI procedures and manuscript preparation during the study.

**Competing interests** SK is a proctor and trainer for both Boston scientific and Medtronic Ltd, and received travel support and speaker fees. JMC has received travel support from Medtronic Ltd and Speaker fees from Boston Scientific.

**Patient consent** Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

**Ethics approval** NRES Committee West Midlands - The Black Country.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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