Neurological and Cognitive Outcomes of Transcatheter Aortic Valve Implantation

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I, Suneil Kumar Aggarwal, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract

Transcatheter aortic valve implantation (TAVI) is a recent development in the treatment of severe aortic stenosis, whereby a new valve is inserted without the need for open heart surgery. It has been associated with a high stroke risk in early studies and the risk is thought to be primarily embolic.

I used Transcranial Doppler (TCD) to assess the effects of embolization on the brain. Initially a pilot study was performed with TCD to establish a suitable protocol, prior to moving to a full study of TCD. This showed embolization was present in all TAVI procedures at each stage, but most frequent during valve deployment. The same TCD protocol along with MRI scans was used in a multi-centre study called DEFLECT-1, looking at a novel embolic deflection device named the TriGuard device. This showed cerebral infarct volume, but not embolic number, was reduced using the device compared with historical controls. I also used the data collected from TCD in a study showing that balloon aortic valvuloplasty (BAV) was an unnecessary part of the TAVI procedure when using balloon-expandable valves.

Highly calcified valve tissue is displaced during the TAVI procedure, a likely embolic source. I assessed aortic valve calcification from CT scans and showed that the degree of calcification correlated with the number of emboli released during valve deployment.

Finally I looked at the effects of TAVI on cognitive function. The rationale for a new battery of cognitive tests using a fully computerised system of cognitive testing (CANTAB Eclipse) is given. This battery of tests was then used to assess cognitive function pre-TAVI and post-TAVI at various time intervals. I showed that there was improvement in certain domains and overall there was no evidence of declining cognition in any domain.

Impact Statement

Several important insights have been gained from this work, which could impact both future research and clinical practice.

Academic impact

Research methodologies have been developed during this research. The most important has been the development of a test battery for cognitive assessment using the CANTAB Eclipse system. This has been shown to be practical in an elderly age group and also suitable in assessing patients undergoing cardiac procedures, neither of which had been done before using this system. This will be useful in future, larger-scale studies of cognitive function changes after cardiac intervention.

Clinical impact

A few important aspects relating to the transcatheter aortic valve implantation (TAVI) procedure have been shown to have clinical relevance. Firstly, I have shown that there is no requirement for the use of balloon valvuloplasty prior to valve deployment, when using balloon-expandable TAVI valves. This is now standard practice worldwide. Secondly, I have shown that calcification of the valve correlates with cerebral embolization. This could impact on the use of neuroprotective devices in future. Finally, I have shown that there is no cognitive detriment of the TAVI procedure. This is important in the elderly age group we treat and reassures us that we can continue to do so without being concerned about cognitive decline. Clearly there is more work to be done in this field, but this work is a good starting point for many avenues of future research in the field of neurological and cognitive impact of TAVI and other cardiac interventional procedures.

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1. Introduction

1.1 History of Aortic Stenosis (AS), Natural History of the Disease, Surgical Aortic Valve Replacement (SAVR) and Transcatheter Aortic Valve Implantation (TAVI)

Aortic stenosis (AS) is a narrowing of the aortic valve and was first described by French physician Lazare Rivière in 1663.[1] It has a prevalence of 2-4% in those over age 65 years and is the most common valvular pathology in the developed world.[2] The most common cause of AS is degenerative, with over 50% of cases due to progressive calcification of the valve and presenting at a mean age of 65 to 70 years. In 30-40% of patients it is due to a congenital bicuspid aortic valve and in these patients it typically presents earlier, in the 4th or 5th decades of life. Rheumatic heart disease secondary to acute rheumatic fever in childhood accounts for less than 10% of cases. There are other rare causes such as systemic lupus erythematosus, Paget's disease, infection, Fabry's disease and hyperuricaemia.

Pathophysiology

In both degenerative and bicuspid aortic valve-related disease, the fundamental pathophysiology is similar to atherosclerosis. The initiation of the pathology is through endothelial damage secondary to shear stress, with subsequent inflammation with macrophage infiltration and the deposition LDL cholesterol and Lipoprotein (a) into the aortic valve. Over time, calcium deposits within the valve and this leads to a hardened, less pliable valve. The stiffness of the valve may also lead to a failure of adequate coaptation of the leaflets, resulting in aortic regurgitation as well as stenosis.

Due to the narrowing of the valve orifice, the left ventricle needs to generate higher pressures to eject blood into the aorta. Adapting to this higher afterload leads to left ventricular hypertrophy, typically in a concentric fashion with a reduced cavity size. Eventually the left ventricle maladapts as it cannot cope with the increased afterload

and the end diastolic pressure rises, leading to higher pressure in the left atrium and

hence within the lungs. Overall, the fixed orifice of the stenotic valve, means that it is

difficult to increase cardiac output with exercise and so this leads to exertional

shortness of breath, angina or syncope. It has been well known for nearly 50 years

that with the onset of these symptoms, there is a rapid decline towards death if

untreated.[3] (See Figure 1.1) In very late progression of the disease the ventricle may

begin to dilate and thin, reflecting the high wall stress and at this stage the patient's

clinical condition is likely to have signficantly deteriorated.

VALVULAR AORTIC STENOSIS IN ADULTS
AVERAGE COURSE
(Post Mortem Data)
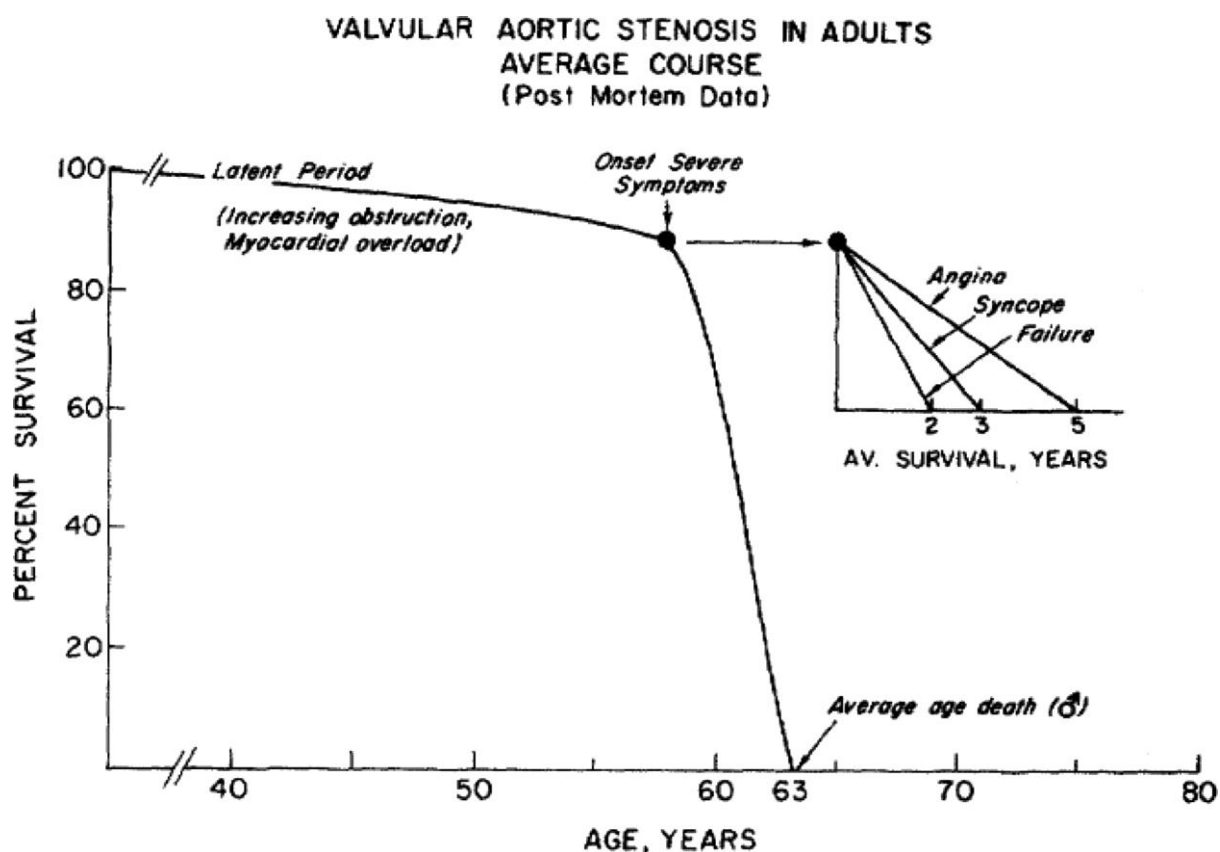
Figure 1. 1: Natural history of aortic stenosis. *Picture courtesy Shah et al, DOI*
https://doi.org/10.1161/CIRCULATIONAHA.111.079368 (reproduced with permission)

Diagnosis

Diagnosis of aortic stenosis can be clinical, with the most common finding being an

ejection systolic murmur, typically radiating from the aortic area to the carotids and

which peaks in mid to late systole. Along with this, as the stenosis progresses, the

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second heart sound becomes softer and even absent. The pulse also becomes slow rising, reflecting the slow ejection of blood from the left ventricle. In bicuspid aortic valves there may be an ejection click auscultated as well. A narrowed pulse pressure may be found, although this is less so in the elderly who have a poorly compliant vasculature.

Current diagnosis is principally based on echocardiography, through which the anatomy and physiology of the valve can be studied. The stenotic valve typically appears as calcified with restricted leaflet excursion. The left ventricle may be seen to be hypertrophied and there may be dilatation of the aortic root. On continuous wave Doppler, the velocity across the valve will be raised. Severe aortic stenosis is classified as a valve area of <1.0cm^2, peak velocity of >4m/s and mean gradient of >40mmHg. However, gradients may be reduced where there is poor left ventricular function, which therefore needs to be taken into account when making the diagnosis. In cases where there is poor LV function, a low-dose dobutamine stress echo may be performed to confirm the diagnosis of severe aortic stenosis in cases where the gradients are low.

Treatment - medical

There is no medical therapy for this condition. Given the similar pathophysiology to atherosclerosis, trials of statins have been perfomed to see if this alters the progression of the disease. However, 2 large randomised controlled trials have shown negative results, along with a more recent meta-analysis.[4-6] One of the theories to explain these results are that the statins are given too late in the progression of the condition to really alter the pathophysiology. It is possible that if started early, they may reduce the initial inflammation, but by the time even mild stenosis is present, the process is too far progressed to be altered.

Treatment - surgical

The only effective treatment is to replace the aortic valve. Although the Hufnagel valve was implanted in the descending aorta in the 1950's for severe aortic regurgitation,[7] the first orthotopic aortic valve replacement (AVR) was performed surgically in 1960 with survival for only a few days.[8] However it was only the advent of cardiopulmonary bypass in the 1960s which meant that the procedure could be performed safely with longer survival. AVR can be performed with either a mechanical or bioprosthetic valve, typically through a median sternotomy and it is the second most common cardiac surgical procedure performed after coronary artery bypass grafting.

There are 3 common types of mechanical valve - the ball-in-cage type (Starr-Edwards), single tilting disc valve (e.g. Medtronic-Hall, Bjork-Shiley) and bileaflet valves (e.g. St. Jude). The latter are the most commonly used now due to the best flow dynamics. All of these valves have been shown to have good long-term outcomes with evidence of prosthesis function for over 30-40 years.[9]

Bioprosthetic valves are either manufactured from typically bovine or porcine pericardium or porcine aortic valve tissue, or can be homografts. Stented valves are most commonly used with a metallic frame, although stentless valves are also available which were designed to improve haemodynamics and durability by removing the metal frame. More recently, sutureless valves have been developed which can be implanted without suturing the new valve into position, therefore reducing cardiopulmonary bypass and overall operating time.

Long-term data from several studies shows that AVR significantly improves survival compared to the natural history of the disease.[10,11] It is now a routine operation in all cardiac surgical units globally and in the UK the published data shows a mortality of just 1.55% for isolated AVR in 2015 (Ref. http://bluebook.scts.org/#ActivityRates) and until fairly recently, this was the only option for these patients. Despite these excellent results, the mortality rates do increase with age and co-morbidities and

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available data does not account for the refusal of surgery to high-risk patients; studies suggest approximately one third of those with severe aortic stenosis were not treated.[12] Of these some may have significant co-morbidities making any intervention on their aortic valve futile, but many could have benefitted from intervention.

Balloon Aortic Valvuloplasty (BAV)

Initially, to treat some of these higher risk patients, BAV was performed, with the first cases reported by Dr Alain Cribier in 1986.[13] In this procedure, a balloon is dilated across the aortic valve under rapid ventricular pacing (done to reduce ventricular contractility and prevent balloon dislodgement). Initial results were promising and the technique was rapidly taken up in many centres.[14] However, longer term studies of this treatment in fact show high rates of restenosis and little benefit if no further intervention is performed.[15]

Transcatheter Aortic Valve Implantation (TAVI)

The first report of a percutaneously implanted valve actually dates back to 1965 when Davies et al. implanted a valve into dogs with experimentally induced aortic regurgitation.[16] However, modern TAVI was really pioneered by Andersen and his team with the first implantation of a balloon-expandable, catheter-mounted aortic valve into pigs in 1992.[17] The first human percutaneous valve implantation was in fact into the pulmonary position by Bonhoeffer in 2000,[18] while it was only in 2002 that Cribier went on to develop and implant the first percutaneous aortic valve following on from Andersen's original concept. He successfully implanted the first valve in a lady in France in 2002.[19] This was done via a trans-septal anterograde approach. Since then the technique has improved, with a progression to the much simpler retrograde approach, with the first publication in 2006 by Cribier et al. showing marked improvements in valve area and reductions in transvalvular gradients using this technique.[20] The rapid evolution of technology means that the

majority of patients can undergo this procedure via the femoral artery, as the current sheath sizes for the smallest valves are now reduced to 14 French, compared to the 24 French sheaths used in the early versions of the valves. In those without adequate femoral access, the valve can also be delivered via the subclavian/axillary artery or transapically/transaortically via a minithoracotomy.

There are several valves currently in use with a CE mark. The first 2 valves to be commercially available were the balloon-expandable Edwards Sapien valve (Edwards Lifesciences), based on Cribier's original model, and the self-expanding Core Valve (Medtronic). These have also undergone several iterations, with the latest models being the Edwards Sapien 3 valve and the Core Valve Evolut R. However, there are several other valves commercially available, including the Lotus valve (Boston Scientific), The Direct Flow Valve (Direct Flow Medical, now withdrawn), Jena Valve (Jena, now withdrawn), Acurate Neo valve (Symetis) and Portico valve (St Jude Medical), with several others at different stages of development. Each has its own advantages and disadvantages, but overall there is an aim to reduce the sheath size needed, reduce paravalvular aortic regurgitation and in some cases allow repositioning of the valves if not ideally deployed in the first instance.

Commercialisation of this technology has resulted in widespread uptake with approximately 30% of AVR in Europe being transcatheter procedures (unpublished data presented at EuroPCR 2011) and no doubt this is increasing. To date TAVI has largely been reserved for patients considered at high risk of or contraindicated for SAVR. Early reports suggest excellent short term outcomes in terms of morbidity and mortality, with early UK registry data (upto 2009) showing a 30 day mortality rate of 6.9% where the average logistic EUROSCORE was over 30%.[21] More recently, the UK in-hospital mortality rate for all TAVI cases in 2016 was 1.84%, despite no definitive evidence that the patient risk profile was improving (British Cardiovascular Intervention Society website, https://www.bcis.org.uk/wp-

content/uploads/2017/08/TAVI-slide-deck-to-2016-data-for-web-as-02-08-2017.pdf).

In a published randomised controlled trial, TAVI had significantly improved outcomes compared to medical management in inoperable patients, with a reduction in 1 year mortality from 49.7% to 30.7%.[22] More recently the results of the randomised PARTNER-A trial have shown non-inferiority in all-cause mortality of TAVI vs. SAVR in patients at high surgical risk at 2 years[23] and the randomised US Pivotal CoreValve study showed improved survival in TAVI patients compared with SAVR at 1 year.[24]

Despite this major advance in treatment for aortic stenosis, there is limited data on the neurological or cognitive impact of the procedure, yet it has been reported to have a relatively high incidence of stroke and there is evidence of significant embolic risk during the procedure.

1.2 Data on cognitive outcomes of SAVR and other open-heart surgery

Cognitive decline following cardiac surgery has been well described in the past, although the reality of this is now considered controversial. Previously, it was believed that cognitive decline was common and indeed when evaluated with objective cognitive testing, it has been reported following open heart surgery, including aortic valve replacement.[25,26] There was evidence that this impairment persisted when compared with controls even up to 5 years post-procedure with rates quoted at 50% at discharge, 36% at 6 weeks, 26-33% at one year and 42% at the end of 5 years[27] - with more sensitive tests revealing more deficits.

More recent work has called this into question.[28-30] In fact, it appears there were significant biases in previous research, meaning that much of the cognitive decline noted may have in fact been due to a cognitive trajectory that was not influenced by the cardiac surgery, as seen in a well-conducted longitudinal study.[30] In this study, patients undergoing coronary artery bypass grafting (CABG) were matched with a medically managed cohort and no differences in cognitive profile were seen, suggesting that background cognitive decline was responsible for any change. The

majority of previous studies lacked a suitable control group. A recent meta-analysis suggested that there is no deleterious effect of cardiac surgery on long-term cognitive function and there may even be a slight improvement following surgery.[28] Much of the cognitive decline described was actually very early and tests may have been affected by post-surgical delirium,[29] which has been seen in 30% of patients undergoing cardiac surgery.[31]

However, the elderly may be more prone to cognitive decline than the populations studied, which are predominantly a younger group of CABG patients with a mean age of 58-68 in the studies assessed in a meta-analysis,[28] with many studies excluding patients >70 years due to the likely presence of baseline cognitive deficits.[25,32] Any decline would be particularly concerning in the elderly where there are more baseline cognitive deficits and there is likely to be a faster rate of cognitive decline even without intervention. This is particularly important in the era of TAVI where the patients being intervened upon have a mean age of 80 years or more.[21,33]

Theories for why cognitive decline may occur include[29]:

1. generation of microemboli in the cardiopulmonary bypass (CPB) circuit

2. embolization during manipulation of the heart and aorta (the latter which may be atheromatous)

3. reduced cerebral perfusion pressures and non-pulsatile blood flow while on CPB

4. systemic inflammation generated by the CPB circuit[34]

5. the effects of general anaesthesia.

Given these factors, in theory methods for ameliorating these effects should reduce post-operative decline. There is a suggestion that the use of appropriate filters in the CPB circuit may reduce microemboli.[35] Reduced cerebral perfusion pressures and non-pulsatile blood flow and systemic inflammation should not be such an issue with off-pump CABG, where CPB is not used. However, this has not proven to be case, as described in 2 separate meta-analyses.[28,36]

1.3 Stroke risk of TAVI

Trial and registry data of stroke risk

Despite the reduction in mortality, there is still a significant stroke risk and in the TAVI vs. medical therapy trial the 30 day risk of major stroke with TAVI was 5% compared with 1.1% in the medically managed group.[22] In high-risk surgical candidates in the TAVI vs. surgery trial, TAVI was associated with an approximately two-fold increased risk of stroke or TIA compared with SAVR (5.5% vs. 2.4%, p=0.04) at 30 days.[33] In the UK registry of all TAVIs performed between 2007-9 the stroke rate was 4.3%,[21] although this has fallen to 2.15% in the latest data for 2016 (BCIS website). Hence reducing the stroke risk during TAVI should be a priority in making the procedure more acceptable.

Strokes following TAVI typically (more than 50%) occur within 2 days of the procedure and are primarily procedure-related. Between 1 and 12 months post-procedure, patient factors including generalised heavy atherosclerotic burden, recent cerebral ischaemic event, and higher NYHA class are the primary determinants of risk. [37]

Why does TAVI cause stroke

As during other types of cardiac procedures, periprocedural stroke during TAVI is likely to be ischaemic and embolic.[38,39] Embolization of atherosclerotic material, clots, and other debris can occur during any phase of the procedure, including scraping of debris from the aorta during catheter placement (which occurs in more than 50% of percutaneous revascularisation procedures).[40] In fact even just crossing the stenotic aortic valve has been shown to cause embolization, hence it is no longer routinely performed for diagnosis of aortic stenosis where there is adequate data from echocardiography.[41]

However, the primary source of emboli during TAVI is likely to be the calcified aortic valve itself and evidence for this was provided by a study using transcranial Doppler

ultrasound (TCD) during TAVI.[42] Each of the 83 patients had evidence of cerebral microemboli. The highest number of emboli were observed during direct manipulation of the calcified aortic valve and crushing of the leaflets and aortic annulus during implantation. Relatively few emboli were observed during other phases of the procedure including valve passage, stiff wire positioning, balloon aortic valvuloplasty (BAV) balloon passage, BAV itself, or passage of the valve delivery system.

Studies have found no influence of approach (transapical or transfemoral) on the incidence of stroke or the generation of focal cerebral ischaemic perfusion defects on MRI after correction for baseline risk.[33,43,44] Implant type (balloon-expandable vs. self-expanding) does not appear to significantly influence stroke rate during TAVI.[45]

What is unknown about why TAVI causes stroke

Early results of randomised controlled trials showed that stroke rate at 30 days and 1 year were higher in TAVI than SAVR.[33] This prompted many observers to speculate the cause of the higher incidence of stroke, especially since it seemed the risk was ongoing, not just related to the index procedure. Theories have been put forward that the stroke risk was related to the increased amount of prosthetic material in the aortic root from TAVI devices. The cause maybe new onset atrial fibrillation (AF), since many patients in sinus rhythm have episodes of AF following TAVI, particularly in transapical cases.[46] However, the most recently published randomised controlled trial of TAVI vs SAVR using the CoreValve system (US CoreValve Pivotal Trial) showed that the total stroke rate was 4.9% in the TAVI arm and 6.2% in the SAVR arm at 30 days (p=0.46) and 8.8 vs. 12.6% at 1 year (p=0.10).[24] This may relate to the use of a different valve or more likely, as the study is more recent, it relates to increased operator experience and the majority of cases being performed transfemorally. The stroke rate remains high for both groups, TAVI and SAVR, and it may simply reflect an underlying high-risk population.

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Trials looking at anti-thrombotic regimens post-TAVI may help in deciphering how best to reduce this late stroke risk. It is possible that the use of prolonged dual-antiplatelet therapy, warfarin or one of the newer anti-coagulant agents may be of therapeutic benefit, although equally none of these may reduce the risk.

1.4 Measuring cerebral embolization during TAVI

There are two methods which have been used to attempt quantification of embolization to the brain as a result of the TAVI procedure, Diffusion Weighted Magnetic Resonance Imaging (DW MRI) and Transcranial Doppler (TCD). These are described below, including the findings of those studies in which they have been used specifically in TAVI, as well as for other procedures.

1.4.1 TAVI and new ischaemic lesions on DW MRI

DW MRI is a highly sensitive and specific technique to visualise acute ischaemia.[47] Acute ischaemia presents on DW MRI as a hyperintense area against the dark background of normal tissue, allowing detection of even small lesions. DW MRI has an average sensitivity of 94% and specificity of 97% in detecting infarction in humans.[48,49] It has been used extensively as a surrogate for cerebral embolization after catheter-based and surgical cardiovascular interventions.[47,50] As a measure of acute or subacute cerebral ischemia, DW MRI lesions can appear within minutes but certainly within 24 hours of the initial insult and usually disappear within 7-14 days of onset.[51]

The Valve Academic Research Consortium (VARC) notes that "There is growing acceptance that neuroimaging is an important biomarker for the diagnosis of neuronal injury and stroke, and diffusion-weighted MRI is generally considered the procedure of choice in the context of acute neurological syndromes."[52] It is well recognised that these lesions are common in the general population, seen in 28% of older patients without a clinical history of stroke in 1 study.[53] In a study of surgical

valve replacement (mostly aortic), new ischaemic brain lesions on DW MRI were

seen in 47% of patients (14/30 patients).[54]

DW MRI studies showing new ischaemic lesions (see table 1.1)

There have been a few studies using DW MRI to detect new ischaemic lesions after

TAVI. Table 1.1 highlights the important details of these studies.

Study	Number of patients	Excluded patients	New lesions	Number of lesions/pt	Volume/size of lesions/pt	Lesion location	Enzyme rise	Strokes	Cognitive changes	TCD	Surgical comparison
Kahlert et al. 2010[55]	32 (22 ES, 10 MCV)	3 died, 5 needed PPM	19/22 ES, 8/10 MCV	4.0 ES, 2.6 MCV	81mm3 ES, 61mm3 MCV		Not collected	Nil	No changes in MMSE/NIHSS post-TAVI or at 3/12	Not performed	21 SAVR pts (younger, less co-morbid group), new lesions in 10/21, av no of lesions/pt 1.6, av vol 224mm3, 1 stroke
Ghanem et al. 2010[56]	22 (all MCV)	2 died, 4 needed PPM, 1 unstable, 1 claustrophobic	16/22	4.7 (mean)	94.6mm3		No rise in neuron specific enolase	1 cerebellar ataxia, 1 dysarthria (resolved by 3/12), 1 left hemiparesis	Not collected	Not performed	Nil
Arnold et al. 2010[57]	25 (all TA ES)	1 died, 1 needed PPM	17/25	4 had 1 lesion, 6 had >5 lesions	4 upto 5mm, 11 upto 10mm, 2 >10mm		Not collected	1 persistent signs of cerebellar and occipital infarction, 4 had transient impairment	Not collected	Not performed	Nil
Rodes-Cabau et al.2011[43]	60 (all ES, 29 TF, 31 TA)	5 died, 6 PPM/TPM, 6 refused, 3 unstable	41/60	3 (median)	91% <1cm, none >5cm		Not collected	2 patients (1TA, 1TF)	No changes in MMSE/NIHSS post-TAVI	Not performed	Nil
Fairbairn et al. 2012[58]	31 (all MCV, 26 TF, 5 SC)	3 PPM, 1 claustrophobic, 1 unable to lie flat, 4 did not undergo TAVI	24/31	2 (median)	2.05 ml/pt		Not collected	2 (1 gait ataxia, 1 expressive dysphasia)	Not collected	Not performed	Nil
Samim et al. 2015[59]	42 (26 ES, 16 MCV, 37 TF, 4 TA, 1 SC)	6 PPM, 1 claustrophobia, 15 Embolic protection, 1 haemodynamic instability	38/42	4.5 (median)	20.2mm3/ lesion or 132.3mm3/pt	47% cortical, 35% subcortical, 18% cerebellum/ brainstem	Not collected	1 TIA (dysphasia)	Not collected	Not performed	Nil
Alassar et al. 2015[60]	62 (Of total 85 pts - 95% MCV, 5% ES, 75% TF, 21% Tao, 4% SC)	23 (not defined)	47/62	2 (median)	7.27mm3 total	Widely distributed (29.1% Parietal, 25.5% Frontal, 21.8% Cerebellum)	Not collected	1 Stroke (major)	Improvement at 3 months from baseline	Mean 134 HITS	32 SAVR pts (younger, less co-morbid group), new lesions in 23/32, median no of lesions/pt 1, av vol 6.95mm3, 1 stroke (major)

Table 1. 1 Studies showing DW MRI findings in patients undergoing TAVI. ES Edwards Sapien, MCV Medtronic CoreValve, MMSE mini-mental state examination, NIHSS National Institute for Health stroke scale, PPM permanent pacemaker, SAVR surgical aortic valve replacement, SC Subclavian, TA Transapical, Tao Transaortic, TF Transfemoral, TIA transient ischaemic attack, TPM temporary pacemaker

Implication of these lesions

The clinical significance of asymptomatic DW MRI lesions is unknown. In population-based studies, the presence of clinically silent brain infarcts has been associated with frailty indices, reduced cognitive ability, depressive symptoms, and an increased risk of subsequent stroke.[61] Several studies have found an association between DW MRI lesions and neuropsychological deficits after conventional valve surgery,[49,54] and DW MRI lesions have been associated with postoperative cognitive deficits and embolic stroke.[49,62] There are however various other studies which suggest that there is no association between DW MRI lesions and cognitive deficits. This includes studies of TAVI[43,55] and studies of AF ablation.[63,64] However, these studies may have been underpowered or have used less sensitive cognitive tests.[65]

Understanding the impact of these multiple embolic lesions on cognitive function outcomes following TAVI is an important pre-requisite to the procedure's wider introduction into lower risk populations.

1.4.2 Trans-cranial Doppler (TCD) based studies

What is TCD and what it shows

TCD is an ultrasound-based technique whereby the intracranial cerebral arteries (most commonly the middle cerebral artery) can be insonated to evaluate blood flow to the brain. It can detect microembolization through these vessels and is the only current technology available to do this in realtime.[66,67] It does this because microemboli cause an increase in reflected Doppler energy, the product of a relative Doppler power increase and its duration.[68] TCD can thus detect active emboli, which has been shown in some studies to relate to the risk of stroke.[69] Emboli are known to arise in all cardiac surgical procedures, as a result of pre-exisiting atherosclerotic plaque, thrombogenesis from the foreign surfaces of cardiopulmonary bypass, air from the cardiopulmonary bypass circuit, and generation of pericardial fat globules.[70] TCD has thus been used in various studies of cardiac and vascular interventions to

detect cerebral embolization, particularly coronary artery bypass surgery, other open-heart surgery and carotid endarterectomy.[71]

One of the biggest weaknesses of TCD is that it requires an adequate temporal window. It is known that this worsens with age as the temporal bone thickens and is also worse in women. One study showed that good unilateral windows could only be obtained in 90% of men and 53% of women over the age of 60, and bilateral windows in 81% of men and 40% of women.[72] In the TAVI population where the average age is over 80, this is likely to be even worse.

How do we interpret TCD signals for embolization?

Microembolic signals (MES) or high-intensity transient signals (HITS) can be detected by transcranial Doppler (TCD). There is a consensus on the detection of MES by TCD. It is established that MES[73]:

1. can be identified as short lasting (<0.01–0.03 s) unidirectional intensity increase

3. intensity increase (>3 dB) within the Doppler frequency spectrum

4. intensity increase is focused around 1 frequency.

5. appear randomly within the cardiac cycle

6. produce a "whistle," "chirping," or "clicking" sound when passing through the sample volume.

TCD in cardiac surgery and the relationship of emboli with cognitive outcomes

Several studies into the correlation between number of emboli and cognitive outcomes following cardiac surgery have been performed with conflicting results, with some showing a good correlation and others failing to show this correlation. There is however significant heterogeneity between the studies in terms of number of patients, types of procedure and types of cognitive tests used, as well as follow-up duration and loss to follow-up. Several of the studies have focussed on traditional CABG with the use of cardiopulmonary bypass compared with the use of off-pump

CABG. A meta-analysis concluded that there was no evidence that off-pump CABG resulted in better neurocognitive outcomes, despite the evidence from some smaller studies.[74] Also, even if there is a difference between the two groups, it is not possible to be sure that this association is only due to embolization and not another difference between the two techniques. One final important issue about many of the studies below is that they have small numbers of patients, postulated to be too few for enough statistical power to show a valid end-point, if such an effect really exists.[27]

1. Pugsley et al.[25] performed a study to look at the effects of an arterial line filter in the cardiopulmonary bypass circuit for patients undergoing CABG. 100 patients were randomised, 50 to the filtered group and 50 control patients. The group with the filter had significantly fewer emboli on TCD and in those with <200 HITS, only 8.6% had neuropsychological deficits, whereas in those with >1000 HITS, 43% had a deficit.

2. Clark et al.[75] showed that the number of emboli correlated with the decrease in total score for those patients undergoing CABG, with patients having >60 emboli showing a change in score of -3.3±0.6, while those having <30 emboli had a change in score of 1.1±0.2.

3. Sylivris et al.[76] showed that patients with a higher embolic load had more significant early neuropsychological defects, in those patients undergoing CABG.

4. Bokeriia et al.[77] showed that there was a significant relationship between cognitive decline and number of emboli in patients undergoing open-heart surgery, defined as those having an intracardiac repair rather than just coronary artery bypass grafting. Specifically they noted that those with large numbers of emboli in the left MCA had verbal memory decline while those with more emboli in the right MCA had more nonverbal memory deficits.

5. Braekken et al.[32] showed a higher number of MES in patients with cognitive deficits vs. those without cognitive deficits among patients undergoing valve replacement. This correlation was not found in patients undergoing CABG, although

the number of patients in that group was only 14, so significantly underpowered to show an effect.

6. Diegeler et al.[78] showed a significantly higher number of emboli in those undergoing conventional CABG vs. those undergoing off-pump CABG and a similar effect on neurocognitive testing with many fewer deficits in the off-pump group.

7. Stroobant et al.[79] showed no correlation between number of HITS and cognitive decline.

8. Browndyke et al.[80] performed a study on patients undergoing either CABG or valve replacement. This showed that patients demonstrated a mild decline in attentional functioning and learning efficiency at the 7-10 day follow-up, but these difficulties essentially returned to baseline by the 1-month follow-up. Intraoperative microemboli counts were not significantly associated with postsurgical neuropsychological functioning in either the CABG or valve replacement group. Interestingly they performed the same battery of tests on age-matched healthy volunteers, who performed better at all time points in the study.

9. Motallebzadeh et al.[81] also compared on-pump and off-pump CABG and looked at cerebral emboli and cognitive function. There were significantly more emboli in the on-pump group than the off-pump group and at discharge the cognitive scores were significantly worse in the on-pump group. However, there was no difference in the scores at 6 weeks or 6 months, suggesting that the problems are not persistent.

10. A further study by Lund et al.[82] of on-pump vs off-pump CABG again demonstrated a significant reduction in the number of microemboli on TCD (16.3 vs 90.0, p<0.001) but no difference in neurocognitive decline or even brain MRI lesions.

11. Eifert et al.[83] performed a small study on 24 patients, with half randomised to the use of an aortic filter. The number of MES was 4 times higher in the filter group, despite 75% of patients showing evidence of trapped debris in the filter, put down to microbubble formation in the filter. No differences were noted in neurocognitive tests between the groups, or different numbers of new ischaemic lesions on brain MRI.

12. Jacobs et al.[84] showed no correlation between the number of HITS and the extent of neuropsychological decline, which was present at 8-12 days post-operatively but had resolved by 3 months.

13. Fearn et al.[85] performed cognitive tests on 70 patients and found an association between number of HITS and memory loss. However, changes which were noted at 1 week post-operatively had mostly resolved by 2 months.

14. Whitaker et al.[34] showed a significant reduction in the number of HITS when using a filter in the bypass circuit, but not effects on rates of cognitive decline at 6-8 weeks post-operatively.

15. Neville et al.[86] performed a study on both CABG and valve replacement patients (266 in total) and only demonstrated a significant correlation between number of emboli and neuropsychological decline on 1 test out of 11, the letter cancellation test. No differences were seen on the other tests despite a significant difference in the number of emboli seen in the valve replacement group (approximately 4 times higher than in the CABG group). They however used carotid emboli count, whereas all the other studies used transcranial Doppler insonating the middle cerebral artery. Another study which used carotid emboli did show a significant correlation between increased emboli number and neurobehavioural change.[87]

16. At 5 years, Stygall et al.[88] showed that the total number of emboli observed correlated with the extent of neuropsychological decline. They noted that the cause may not be the emboli, but the relationship between the number of emboli and the extent of atheroma present (not measured in that study).

TCD in cardiac catheter-based procedures

TCD has also been performed during cardiac catheterisation and interventional procedures. The major studies in this field are outlined below:

1. Leclercq et al.[89] performed TCD in 49 patients undergoing left heart catheterisation. This showed emboli in the majority of patients, usually doing left

ventriculography or contrast injection into the coronary arteries. They concluded that these emboli must therefore be mostly gaseous in origin.

2. Crawley et al.[90] showed in a randomised trial of carotid angioplasty vs. carotid endarterectomy, that despite the increased incidence of emboli during angioplasty, there was no evidence of a worse decline in neuropsychological performance. This may also be due to the additional emboli being gaseous rather than solid.

3. Bladin et al.[91] showed that during PTCA, 70% of microemboli occured during contrast or saline injections. There were 48.7±36.7 emboli/patient in this study. There were no neurological sequelae noted in these patients.

4. Pacchioni et al.[92] compared the number of emboli generated in left vs. right radial artery diagnostic coronary angiography, in patients randomised to each access site. This showed a significant increase in the number of emboli during right radial catheterisation (61 vs 48, p=0.035), with the only factor on multivariate analysis predicting this being the number of catheter exchanges.

5. Jurga et al.[93] compared radial vs. femoral approach with regards to coronary angiography. This showed a significantly higher number of emboli when angiography was performed via the radial approach than via the femoral approach.

TCD data in TAVI patients

It is known that crossing the calcified aortic valve can lead to embolization, resulting in ischaemic lesions seen on MRI.[41] The primary source of emboli during TAVI is likely to be the calcified aortic valve itself as evidenced by a transcranial Doppler (TCD) study where all patients had evidence of cerebral microemboli. The highest number of emboli were observed during direct manipulation of the calcified aortic valve and crushing of the leaflets during implantation.[42] Studies have found no influence of approach or implant type on the incidence of stroke or the generation of focal cerebral ischaemic perfusion defects on MRI, after correction for baseline risk.[33,43-45]

1. The largest study of TCD in patients undergoing TAVI was published by Kahlert et al.[42] In this study 83 patients underwent TCD examination, 32 had the Medtronic CoreValve (MCV) via transfemoral (TF) access, 26 had the Edwards Sapien (ES) valve via TF access and 25 had the ES valve via a transapical (TA) route. The mean number of emboli was 528.7 in the whole cohort. Looking at individual groups, the MCV group had 605.6 HITS/patient, compared to 482.2 in the TF-ES group and 478.6 in the TA-ES group. The most common times overall for HITS were valve implantation (214.1) and valve positioning (173.7). The positioning was more common in the TF-ES (259.9) and TA-ES (206.1) groups than the MCV (78.5) group. Conversely during deployment HITS were more frequent in the MCV (397.1) group than TF-ES (88.2) or TA-ES (110.7) groups. In this study basic cognitive tests were performed (MMSE and MOCA), with no significant decline seen.

2. Erdoes et al.[94] performed a TCD study on 44 patients. They showed no difference in number of HITS on each side. The overall number of HITS per patient was 548/patient, median of 255 on the left side and 274 on the right side. With regards procedure type, there were overall 580 HITS in MCV TAVI and 412 HITS in ES TAVI (this study did not differentiate between TA and TF access, although 5 had TF-ES and 12 had TA-ES). Most HITS were seen in deployment (256 in MCV, 158 in ES, $p=0.027$)) although this was not divided into positioning and deployment separately. They however also showed a large number of HITS during instrumentation pre-valvuloplasty (155 in MCV, 136 in ES, $p=0.66$). No cognitive tests were reported in this study.

3. Reinsfelt et al.[95] performed a TCD study on 21 patients, with the aim of correlating number of HITS with a serum marker of brain injury, S100B. Their division of the timings however differed from previous studies even more, with only 3 categories of instrumentation, valvuloplasty (which also included device positioning) and actual valve deployment. This showed a total number of HITS (done unilaterally using the right MCA only) was 282/patient, with all patients undergoing an MCV TAVI. They

found that 106 HITS occured during instrumentation, 62 during valvuloplasty and 115 during prosthesis expansion. Their data also showed a positive correlation between total number of HITS and the S100B serum level (r=0.68). No cognitive tests were performed.

4. Szeto et al.[96] performed TCD in 28 patients to look at any differences between transfemoral (18 patients) and transapical (10 patients) TAVI. Unilateral HITS were recorded in 12 patients and bilateral in 16 patients, where the better side was chosen for statistical analysis, hence the final values reflect only 1 side per patient. The total HITS were 375 (TF) and 440 (TA) - no significant difference. They recorded wire manipulation in the arch/crossing the valve, balloon valvuloplasty, valve transit and positioning and valve deployment. The most number of HITS were in stages 1 and 3. The total included HITS not within the particular recorded sections of the procedure (personal communication with lead author, not mentioned in paper), a departure from the other studies.

5. Drews et al.[97] looked at 50 patients undergoing transapical TAVI. They differentiated between HITS and MES, suggesting but not stating that MES are solid. In this study, there were 471 HITS in the left MCA and 435 in the right MCA, but only 62 MES in the left and 78 in the right.

6. Alassar et al.[60] performed TCD in a total of 60 out of 85 recruited TAVI patients. The mean number of HITS per patient was 134, compared to 212 per patient during SAVR. There were no differences between the left and right side. The maximum number of HITS occured during device positioning and implantation (mean 67 per patient) and the next largest number during BAV.

What is the meaning of these studies in TAVI

TCD studies have clearly shown that there is extensive embolization during the procedure. The various studies suggest that probably the most important time for the emboli occuring is during the implantation of the valve, with data from Kahlert et al.[42]

suggesting that the Edwards valve causes most emboli during positioning while the Core Valve causes most emboli during actual valve deployment. This is no doubt in part because the positioning is more crucial for the Edwards valve as it so much shorter than the Core Valve and so more likely to be misplaced. Conversely, the self-expanding nature of the Core Valve on the other hand means deployment takes much longer than the much more rapid balloon expansion of the Edwards valve. This data is likely to be most useful in trying to influence the design of the valves to reduce embolization from the valve. It may also be useful in the context of embolic protection devices, since it gives us an insight into when most emboli occur and therefore at what time the protection is needed. It is interesting to note that although much is made of scraping atheroma from the aortic arch, there is little evidence that manipulation of these bulky devices through the aortic arch causes many emboli to be released, at least to the brain.

What is unexplained

There is still very little information about the exact nature of the emboli released. While some of the studies have attempted to exclude gaseous emboli from analysis by not including those released during contrast injections, the reality is that many microbubbles are trapped within the catheter and devices despite flushing them with saline prior to insertion. Also many times injection of contrast is used during valvuloplasty and also deployment of the valve, particularly with the Core Valve, since injections are done while the valve is being released and so it would be impossible to separate these emboli out purely based on timing. Categorising the type of emboli would be useful.

Importance of embolus detection and differentiation by TCD

Automated embolus detection is very useful, since it should reduce error in recording the total number of emboli generated. Embolic differentiation further allows

categorisation into solid and gaseous emboli. However, performing this accurately has many challenges. These include the presence of background Doppler speckle due to clustering of red blood cells and movement of the probe or tissue.[98] Solid emboli cause small shifts in the Doppler signal which need to be differentiated from these artefactual movements.

There are 4 principles on which Doppler detection and differentiation works[98,99]:

1. Quarter Doppler Shift - the Doppler shift is quarter greater with 2.5MHz than 2.0MHz probes (1.25 vs 1 MHz). Artefacts show several peak intensities but not this Doppler shift.

2. Maximum Duration Limit - this is the maximum time it would take an embolus to travel through the sample volume under study. It cannot exceed this if it is an embolus. This time limit is higher for higher-intensity signals.

3. Reference Gate - A second sample volume at least 10 mm from the main sample volume - artefacts would be detected in both gates simultaneously (<4ms apart), whereas emboli will be detected in each gate at separate time points or not at all in the second gate.

4. Bidirectional enhancement - Artefacts normally cause bidirectional enhancement of Doppler power as the tissue resonates in both directions, whereas emboli should predominantly cause a signal in one direction.

In a study to verify the accuracy of automatic embolus detection, the software used in DWL machines (DWL Compumedics, GmbH) showed a sensitivity in vitro of 100% and a specificity of 99.3%.[98] In vivo, the sensitivity was 98.6% and the specificity was 97.2%. The main problem identified was that the software was inaccurate when there were large numbers of emboli passing through the sample volume very close to each other, such as in gaseous or contrast injections.

A further attempt at differentiating solid from gaseous emboli was evaluated by Rodriguez et al.[100] This suggested that non-gaseous (presumed solid) microemboli in

patients with mechanical heart valves had lower relative intensities and could reliably be distinguished by using a cut-off of 16dB. However, this is not used in the currently available software.

Differentiation between solid and gaseous emboli is important, as small gaseous emboli are known to have minimal clinical relevance in terms of cognitive outcomes,[86] whereas solid emboli do have significant relevance.[101] Differentiation between these two types of microemboli is based on the principle that solid emboli reflect more ultrasound at higher frequency, whereas the opposite is the case for gaseous emboli.[98,99] This principle is used in multifrequency TCD instrumentation where the vessels are insonated simultaneously with 2.5 and 2.0MHz and can be used for the differentiation between gaseous and solid emboli,[98] although the accuracy of this software is still a matter of debate.[35,98,100]

Despite the above technological improvements in the area of HITS detection, it is still impossible to reliably distinguish the composition of solid emboli (particles of fat, platelet aggregates, or particles of atheroma).

Use of embolic differentiation software in cardiac surgical studies

There are limited studies to date using the embolic differentiation software, possibly due to its relative novelty, the cost of the software compared to software which just automatically detects emboli and the controversy surrounding its validity. However the following studies have used embolic differentiation software:

1. Abu-Omar et al.[35] performed a study on patients undergoing either off-pump CABG, conventional CABG or an open non-CABG surgical procedure. They showed different rates of solid emboli, with only 12% solid emboli in the off-pump group, but 26% in the on-pump group and 20% in the non-CABG surgery group. Although they could not draw any definitive conclusions from this, they speculated that this technique could be useful in evaluating novel neuroprotective strategies. No cognitive function tests were reported.

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2. Zanatta et al.[102] showed a larger number of solid microemboli between an open CPB circuit with vacuum compared to a closed CPB circuit. There were also a higher number of solid microemboli in the right vs. the left hemisphere. No cognitive function tests were performed in this study either.

To date, no studies using this software have been performed in TAVI.

1.5 Aortic valve calcification

Why aortic valve calcification may be relevant

It is established that embolization is a common event in TAVI.[42] The material which embolises is likely to be a mixture of thrombus, atheroma and also probably valvular material from the native aortic valve which is crushed to the sides of the aortic wall during the procedure.[40-42] The majority of patients undergoing TAVI have degenerative aortic valves which are usually heavily calcified. Hence, the embolization from the valves may well be due to the severity of the valve calcification noted, so potentially a calculation of the aortic valve calcification (AVC) could estimate embolic and hence stroke risk.

Another important feature of valve calcification is that it reflects an increased atherosclerotic burden and is associated with cardiovascular disease including coronary artery disease.[103] Indeed severity of AVC has been strongly associated with increased mortality, independent of the severity of aortic stenosis assessed by aortic valve area or transvalvular gradients.[104] Calcification of the aorta has been associated with an increased risk of stroke[105] and aortic annular calcification correlates with a higher incidence of silent brain infarcts.[106] Similarly, cognitive decline is higher in those patients in the general population who have a higher degree of atherosclerotic calcification.[107] Therefore, AVC measurement may predict which patients are at higher risk of peri-procedural stroke or cognitive decline and this may be independent of embolic phenomena related to the TAVI procedure.

Which methods have been used to assess this in previous studies - aortic valve studies in general and TAVI studies in particular

Aortic valve calcification can be assessed by either CT or echocardiography.[108,109] The majority of recent studies (the number no doubt reflecting the increasing importance of TAVI where CT is now the most common method for valve sizing) have focussed on the use of CT and have used the Agatston scoring method, as used for coronary artery calcium scoring.[110-112] This has a major advantage of being simple to perform with little intra- or inter-observer variability.[110] The results show that the level of calcification is a significant predictor of poor outcome, in particular it predicts the presence of moderate or severe aortic regurgitation.[112,113] *However, there is no information on the association between the degree of aortic calcification as estimated by Agatston calcium score and the incidence of cerebral embolization or cognitive decline.*

1.6 Cognitive function tests

Batteries of tests used in surgical studies

The consensus statement published in 1995 on the study of post-operative cognitive decline has formed the basis of the majority of studies in this field.[114] Cognitive assessments have moved on considerably since then and in particular, there are now much better computer-based assessments of cognition available which have in fact been around for some time.[115] Looking at the neurological injury associated with cardiac surgery, it is unlikely that there would be a specific pattern of deficits to be seen following TAVI. This is because the main proposed mechanisms of microembolization, systemic hypoperfusion and systemic inflammation should not necessarily show any particular localisation, although the different mechanisms do have some preferential areas they affect.[28] There were more emboli noted in the frontal and parietal lobes in one study of DW MRI and cardiac surgery.[116] Emboli are more likely to affect areas of the brain supplied by deep white matter end-arteries in

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borderzone areas, therefore affecting psychomotor processing speed.[117] Also, systemic hypoperfusion should in theory affect the hippocampus preferentially, as that is particularly susceptible to hypoperfusion and therefore memory is likely to be affected.[118] Even though brain injury may be diffuse, it is unlikely to be severe enough to cause deficits in less sensitive measures like the Mini-Mental State Examination (MMSE). Rather, there is likely to be a need for detailed testing in multiple functional domains, including time-sensitive measures of attention and processing speed.[29] A recent meta-analysis showed a transient slowing of processing speed in cognitive tests following CABG.[28]

The consensus statement published in 1995[114] actually attempted to rationalise the tests performed and therefore give consistency in outcomes of different studies. They recommended the 4 tests below and then advised that people could use other appropriate tests in their battery, depending on the clinical situation. They also advised an early post-surgical test within 8-10 days and then another at least 3 months following the procedure when cognition is likely to be stable. Despite this, the post-surgical tests have been performed at different time points ranging from pre-discharge to 3 years, leading to differences in interpretation.

The tests advised in the statement were:

Grooved Pegboard : this assesses fine motor speed as the individual simply has to place pegs in holes as quickly as possible.

Digit Symbol Test : requires the individual to draw the correct symbols to match numbers as quickly as possible according to a 'key' that is left in front of them – assesses psychomotor speed.

Trails A/B Test : is also a test of psychomotor speed that additionally requires a greater degree of planning and working memory (executive functions). It requires the individual to draw lines to connect letters and numbers in a pre-specified sequence.

RAVLT – Rey Auditory Verbal Learning Test : assesses short-term memory for supraspan word lists.

One of the main criteria for choosing these particular tests was that in 1995 computers were not so widely used and therefore paper-and-pencil tests were chosen. Clearly 20 years later things have changed considerably and so now computer-based tests need to be considered as the preferred testing mechanism.

Studies of cognitive function after TAVI

While there is evidence that the embolic risk associated with TAVI is one cause of stroke, there is less data about the impact on cognitive function. Cumulative lesion load may contribute to gradual cognitive decline. In a DW MRI study of vascular dementia, patients with a recent deterioration showed an increased incidence of diffusion abnormalities.[119] Similarly, another observational study suggested that microemboli might even be significant in the development of Alzheimer's disease.[120] Two small early studies of DW MRI lesions after TAVI have failed to identify focal neurological deficits (using the National Institutes of Health Stroke Scale rating) or measurable impairments of neurocognitive function (using the MMSE).[43,55] However, these tests are both screening examinations and thus perhaps not as sensitive to the subtle changes in cognition likely to occur. More recently, three further studies have looked at cognitive change with more detailed cognitive tests:

1. Ghanem et al.[121] looked at a group of TAVI patients.

In total, 125 patients had a baseline evaluation, of these 111 were available at 3 days and this was the study group. The patients had cognitive tests at baseline (pre-TAVI) and then at follow-up at 3 months, 1 year, 2 years post-procedure (44 patients were studied at 2 years). The tests performed were the repeatable battery for the assessment of neuropsychological status (RBANS). The RBANS contains 12 subtests measuring language, attention, visual and constructional skills, immediate memory, and delayed memory. RBANS test scores are transformed into age-, sex- and education-corrected standardized index scores for the 6 cognitive domains assessed and are also integrated into a total score (mean=100 and SD=15). A

postprocedural decline at 3 months of >1 SD compared with a subject's score before TAVI was defined as cognitive decline in this study.

5.4% had clinically significant decline at 3 days. In 2.7% this persisted during follow-up and there were 3.6% patients who had late-onset cognitive decline at any future time-point. 91% of patients showed no decline at any point in the study. In general the patients who had cognitive decline early, showed a steady decline suggestive of a stable trajectory in these patients. Procedure duration and severe renal impairment were correlated to cognitive decline, but not baseline cognitive function. 27% had mild cognitive impairment (MCI) prior to TAVI but they did not differ in rate of cognitive decline compared with those without MCI.

Of the test cohort, 50.4% underwent pre and post- DW MRI. Thirty-six patients had evidence of embolization, 20 did not. No difference in cognitive trajectory between those who had emboli compared with those without emboli and also those who did not have DW MRI. However, older age correlated with cognitive trajectory.

2. Knipp et al.[122] compared the cognitive outcomes between non-randomised patients undergoing transapical TAVI and surgical AVR, using a historical surgical control group from an earlier study by the same research group.[54] The tests used were different for the 2 groups, since it was felt the elderly patients could not cope with more extensive cognitive tests. In the TAVI group, the MMSE and then 3 further detailed tests were performed, namely the digit span subtest of the Wechsler Memory Scale-revised, wordlist test and the Regensburg verbal fluency test. In the surgical group, a much more extensive battery was used.[54] The tests were performed at baseline, early post-procedure and then at 3 months follow-up. In the TAVI group there were 27 patients, against 37 in the SAVR group. The assessments in the TAVI group were performed on average 5.4 days pre-procedure, 10.7 and 115.6 days post-procedure. 4 patients died and 1 had a stroke, leaving 22 available at discharge and 18 at follow-up due to a further 2 deaths and 2 patients refused follow-up. Overall there was no significant change from baseline at either discharge

or follow-up in the overall cohort. In individuals, there were 18% scores reduced by Z -2 or more at discharge and 28% at 3 months.

In the surgical group all 37 were tested at discharge and 34 at follow-up. 7 domains declined at discharge, but all resolved by 3 months with in fact 2 going above baseline (cognitive flexibility and reasoning). Overall there were 46% scores showing a decline at discharge, but only 6% at 3 months.

MRI scans were also available for some patients - 17/27 TAVI patients pre- and 12/27 post-procedure. In the SAVR group, 100% pre- and 95% post-procedure scans were available. Scans were performed on average at 11.7 days post-TAVI and 6.5 days post-SAVR. Lesions were found in 58% of TAVI and 34% of SAVR patients. However, there was no relationship between cognitive decline and presence of lesions and no obvious relationship between clinical factors and probability of having lesions. No major differences in lesion volume or location were discovered between 2 groups. Additionally, there was no relationship between early cognitive impairment and risk of later impairment.

3. Alassar et al.[60] compared cognitive function changes between TAVI and SAVR in non-randomised groups. The SAVR cohort was significantly younger with a lower risk profile. The same tests were used for both groups - the battery used was based on the Consensus statement.[114] The tests were performed at baseline and then at 3 months post-procedure.

There were a total of 85 patients in the TAVI group and 42 in the SAVR group, of which 71 and 36 patients respectively completed the tests at 3 months. Overall there was a strong trend towards a significant difference in the baseline individual cognitive characteristics between the 2 groups, with higher scores in the SAVR group. At 3 months there was a significant improvement in the scores of the 2 groups, with a greater improvement in the SAVR group compared to the TAVI group, which was predominantly due to a greater improvement in the memory score.

There were no correlations between the change in cognitive score in either group with the number of emboli on TCD, the number or volume of new ischaemic lesions on DW MRI or cerebral desaturation.

Implication of these studies and their lack of sensitivity

These studies have shown that TAVI has no significant impact on cognitive function - within the limitations of the tests used. This is relevant, since compared to older surgical data it suggests TAVI causes less cognitive impairment. However, Knipp et al.[122] suggest that even in surgical patients cognitive function recovers by 3 months (as opposed to the progressive decline seen in older studies) and Alassar et al.[60] suggest that cognitive function even improves significantly in surgical patients. For the elderly group of patients who comprise the majority of current TAVI patients, the lack of cognitive impairment is very encouraging.

Without the use of cognitive outcomes in a large randomised trial of TAVI vs SAVR, it is hard to determine whether there truly is a difference between the cognitive impact of the two treatments, especially given the exclusion of older patients in previous surgical studies. If there is a significant difference, this would further help in decision making between the two treatments, especially considering the similar outcomes relating to mortality and morbidity.[23]

1.7 Neuroprotection

Given the risk of stroke in TAVI, one important consideration is whether this can be ameliorated. Since cerebral embolization is an important mechanism for stroke during TAVI, prevention by using embolic protection devices needs to be considered. There is precedent for this, with an extensive experience of using embolic protection devices (EPD) in carotid artery stenting (CAS). While this is not directly comparable with TAVI, in that there is direct manipulation of plaque in CAS, it does give an indication of the problems faced with regards embolization. In CAS, the use of EPD

reduces the risk of brain embolism by approximately 60%[123] and stroke by 40%,[124] hence they are routinely used in many centres. These devices use different mechanisms of action, with distal artery balloon occlusion, flow reversal methods and filters, of which the first two are not relevant to TAVI. However, the use of a filter that catches/deflects the debris is more relevant and it is in this way that devices have been designed for use during TAVI.

To date, 3 difference devices have been designed for specific use in TAVI. These are outlined below:

1. Embrella device (Edwards Lifesciences, Irvine, CA, USA)[125,126]

This device is delivered via 6 French right radial artery access and is a deflector mesh which sits in arch of aorta covering the brachiocephalic and left common carotid artery origins. The device is 58 mm long and 25 mm wide. The original study was performed in 4 patients with severe AS, all of whom had a BAV and 3 who went on to have a TAVI with the Edwards Sapien valve. None of the patients had a neurological event, although 1 patient had a 5mm cortical infarct in the right temporal lobe on MRI. The total extra procedure time was 13 minutes using this device.

A more recent study enrolled 15 patients who underwent TAVI with the device and compared it to 37 earlier patients who had undergone TAVI without the device. This showed that the total number of lesions on DW MRI increased in the intervention group (9 vs 5), although the lesion size was signficantly reduced (9.7 vs. 17.8µl) and there were no patients with large total infarct size (>1000µl) in the intervention arm. In the intervention arm there were more lesions in the right side of the brain, while they were evenly distributed in the control group. This suggests that the device was protective against large emboli, although it may cause small emboli during deployment.

2. Claret CE Pro (Claret Medical, Inc. Santa Rosa,. CA, USA)[127]

This device is delivered via a 6F right radial/brachial artery sheath and has a proximal >9mm filter in the right brachiocephalic artery. Through this, a >3 mm distal

filter (non-proprietary) must be steered into the left common carotid artery, which in the only clinical trial to date used the Spider FX device in 90% of cases.

The only published study was performed in 3 centres, with successful use in 35/40 cases. Seven patients received a 1st generation device with no guidewire and the rest received a 2nd generation device with a guidewire lumen and modified curved shape. There were 38 Corevalves and 2 Edwards Sapien valves implanted. The device was delivered via the radial artery in 5 cases and via the brachial artery in 35 cases.

For the 1st generation device, out of 7 patients, in 5 the device could be placed into the aortic arch. Out of these, in 2 cases it could not be advanced into the carotid, hence only worked in 3/7 cases in total. The mean delivery time was 12.4 mins. Two patients had radial artery complications preventing device delivery.

With the 2nd generation device, 30/33 devices were delivered into the aortic arch (failure in 3 was due to a tortous brachiocephalic). Of these, 26/30 could have both filters placed; in 2 patients an incompatible 2nd filter was used, in 1 there was operator error and in 1 there was unsuitable left common carotid anatomy. The mean delivery time was significantly reduced at 4.4 minutes. The mean extra contrast volume used was 19.6 mls. Two patients had brachial artery aneurysms requiring surgical repair. There were no peri-procedural neurological events. However, there was 1 minor stroke at 30 days and there were 2 major strokes at 4 hours and at 27 days.

3. Tri-Guard device (Keystone Heart, Herzliya, Israel)[128]

This device is delivered via a 9F sheath in the femoral artery and unlike the other 2 devices which leave the left subclavian artery unprotected, this device covers all 3 great vessels.

The first-in-man study enrolled 15 patients, 11 male, with a mean age of 79.3 yrs. Nine TAVIs were performed transfemorally and 6 transapically, all using Edwards Sapien valves. In all cases a BAV was performed prior to valve implantation. The

device was implanted successfully in all 15 cases, needing an extra 7 minutes per case.

There was 1 TIA at 2 days. Ten patients had pre- and post-brain MRIs, with 3.2 new ischaemic lesions per patient in this study compared with 7.2/patient in 20 previous patients who had a TAVI without the device. Distribution of lesions was equal in the left and right cerebral and cerebellar hemispheres.

As well as these 3 devices, the Embol X device (Edwards Lifesciences, Irvine, CA, USA) has been used once for a trans-aortic TAVI.[129] This device is in fact an older, commonly used device in cardiac surgery.[130] In the case published, it was placed through an additional puncture 2 cm above the main access site (for the Ascendra system). There were no clinical events and no new lesions on brain MRI in this case.

What does the future hold for these devices

Embolic protection devices have shown reasonable ease of deployment in the studies above and in some cases there are indications that this may result in a reduction of surrogate markers for stroke, with reduced volume or number of lesions on DW MRI. However, none of these studies was done in the context of a clinical trial and therefore there is no randomised controlled trial data to show that the devices do definitely reduce embolic risk. One major contention is that comparison was made to historic controls and there is clearly a temporal trend towards a lower stroke risk, so the reduced degree of cerebral ischaemia may just be related to general improvement in TAVI technology, procedural technique and operator experience. Given the current stroke risk associated with TAVI (2-5%, with lower rates in more recent trials) and the reduction in lesion volume which could be expected (50-65%), it is unlikely that a suitably powered trial will be performed to prove reduction of risk for clinical stroke for any device. Hence the use of surrogate markers of efficacy such as TCD or DW MRI is likely to be most useful in evaluating these devices.

1.8 Summary of background information

There is good evidence that the stroke risk in TAVI is similar to SAVR from the latest randomised studies, even though the early data suggested the risk in TAVI was higher. The cause is likely to be embolic in many patients, although the cause of late strokes in the TAVI population is still unclear. We have a significant amount of data on embolic risk from studies of new DW MRI lesions and TCD, although the type of emboli (solid or gaseous) is not known. We also do not know of the importance of aortic valve calcification in determining embolic risk. The use of embolic protection devices in TAVI is still under investigation to see if embolization can be reduced and the early data is promising. However, it will be some time before we have enough evidence for their clinical utility, in particular data on exactly which patients would be most likely to benefit from their use.

Moreover, there is still limited data on the cognitive outcomes of the procedure, despite encouraging recent data on mortality and stroke risk. The cognitive impact of the procedure is particularly important, as this could have significant implications in an elderly group of patients.

2. Aims and objectives

The aim of this thesis is to evaluate the cognitive and neurological impact of TAVI, in particular the role of embolization during the procedure and the impact on cognitive function as assessed by detailed, computer-based cognitive tests.

Objectives:

1. Evaluate the timing and pattern of cerebral embolization during TAVI, based on transcranial Doppler (TCD)

2. Correlate embolization to the brain with the degree of calcification of the aortic valve and root

3. Assess whether there is cognitive change as a result of TAVI using detailed computer-based cognitive function tests

4. Use the data collected from the cognitive study to power a randomised study evaluating cognitive change in TAVI versus SAVR.

3. Materials and methods

This chapter will assess the methods used in experiments which form the body of this thesis, highlighting the merits and deficiencies of each and explaining how each method was chosen.

Ethical Approval and Written Consent

Prior to starting the observational studies, ethical approval was obtained from a National Research Ethics Committee, with the approval number *13.LO.1086.* All patients entering the observational studies provided prior written consent. Some of the work was also performed under the consent for taking part in the DEFLECT-1 study.[131]

3.1 Transcranial Doppler (TCD)

The background to TCD has been described in Section 1.4.2.

3.1.1 Methods used during pilot study

This pilot study was performed to assess feasibility of performing TCD within our catheterisation laboratory setting, with the intention of then performing a more comprehensive TCD study. It provided me an opportunity to learn how to perform TCD, in particular, how to search for suitable temporal windows for TCD, which is known to be difficult in many people, in particular the elderly and females.[72] Additionally, using this pilot data the best time points to detect emboli could be assessed for future use.

TCD was performed using a single probe M-mode monitoring system, the ST3 (Spencer Technologies, Seattle, WA, USA). The probe was fixed in position using a head frame, following manipulation to insonate the left middle cerebral artery (MCA). Recordings were then made manually for the number of emboli occurring at different time points during the procedure. Where there were large numbers of emboli occurring at the same time and these were too numerous to count independently, these were recorded as "curtains" of emboli. The time points chosen to count the emboli were (applicable to all patients):

1. Insertion of pigtail catheter

2. Catheter insertion and wire crossing the valve

3. Catheter crossing the valve and wire/catheter exchange

4. Balloon insertion/inflation and deflation/removal

5. Valve insertion and positioning

6. Valve deployment and removal

7. Wire removal/late emboli

In selected patients where steps had to be repeated, these were also recorded. The total number of emboli was then calculated for each patient as the sum of the emboli at each point, adding in the number of "curtains" of emboli per patient. These particular time points were chosen, on the basis that they were distinct and each potentially could be a cause of embolization.

3.1.2 Methods used during observational study

Following completion of the pilot work, a more comprehensive study of TCD in TAVI was started. The aim of this study was to gain further information about the most important time points for embolization during the procedure. It is likely that only solid emboli have any significant neurological impact. With the availability of embolic differentiation software, the frequency of solid emboli at any particular time point could also be assessed. We could also assess whether there was any predilection for left or right cerebral emboli and whether there were any differences in embolization patterns and quantity between males and females. We also aimed to see if any clinical or procedural factors determined the extent of embolization.

Methods:

TCD was performed on consecutive patients undergoing TAVI, where possible. I performed all set-up, recording and analysis. The TCD system used was the multigated Doppler BoxX system (DWL Compumedics Germany GmbH), using a Lam Rack headset and two dual-frequency 2.0/2.5 MHz pulsed wave Doppler

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probes (DWL Compumedics Germany GmbH). This was attached by means of an Ethernet cable to a dedicated laptop with the latest QLab (version 2.10) software.

Set-up

After taking consent from the patient, first their suitability for TCD was assessed by means of a 2.0MHz hand-held probe that was used to detect the presence of a temporal window for adequate TCD signals. Once unilateral or bilateral temporal windows were identified, the size-adjustable Lam Rack headset was attached and the probes were used to insonate the middle cerebral artery on each side and then the probes were fixed using a locking mechanism. Depths used were 48 to 55 mm and sample volume 8 to 12 mm. This was done prior to the patient coming from their ward bed to the catheterisation laboratory. The headset was then removed. Once the subject had been anaesthetised/deeply sedated for the TAVI procedure, the headset was re-positioned and with some minor adjustments the middle cerebral arteries were again insonated. A sweep speed of 6 seconds display duration was chosen, and the Doppler velocity range spectrum was adjusted to the expected maximum velocity. Doppler velocity and power M-mode spectrograms were monitored simultaneously for both sides (when both could be insonated). If a unilateral temporal window was found then only this was used.

In the catheterisation laboratory itself, the TCD machine was placed beneath the cath lab table and connected to the laptop by an Ethernet cable. The probe cables were run from the box, along the side of the patient upto the head-end where the probes were attached to the headset.

Data acquisition

The TCD machine was used to record near continuous signals from the start of the case until all catheters were removed. We did not record baseline embolization at rest or at a time point following the procedure, as a previous study had already shown no emboli occurring at these times.[42] The recording itself was broken up into the component parts of the procedure in order for the data to be analysed for each

part separately, which required a stopping and starting of data recording. This was adjusted from the pilot study and also based on the requirements of the DEFLECT-1 study (see 3.1.3).

For most cases, these parts were:

1. catheter insertion

2. retrograde crossing of aortic valve and catheter exchange

3. inserting balloon (where performed)

4. balloon valvuloplasty (where performed)

5. retrograde passage of the valve through the aortic arch

6. positioning the valve

7. deploying the valve

8. removing the valve delivery system

In some cases, a particular step needed to repeated more than once. In each case the number of emboli were counted separately. Exceptionally in some cases where 2 components followed on from each other in particularly quick succession, there was not enough time to stop and start the recording without losing data so the 2 components were taken together. Timing of contrast injections was noted and also marked on the recordings.

Analysis and Data Recording

Analysis of the TCD data was done offline using the QLab 2.10 software. Each component part of the procedure was analysed separately and the data recorded in an Excel spreadsheet.

For each part of the procedure in turn, the TCD signals were reviewed. The software automatically marked when emboli occurred (Solid or Gaseous) and differentiated them from Artefact, counting the total number of solid and gaseous emboli for each component part of the procedure. Each marking for an embolus was taken in turn and checked offline to make sure it was recording an actual event, which could be seen visually as a disturbance in the cerebral blood flow tracing and could also be

heard using the audio playback (heard as a clicking sound). If there was an embolus at that point, then the original marking (Solid or Gaseous) was kept, otherwise, it was re-labelled as Artefact. Once this had been done for all the marked emboli in the recording, the final total number of Solid and Gaseous emboli were recorded in an Excel spreadsheet. This process was then repeated for each component part of the procedure. No attempt was made to differentiate the Solid and Gaseous emboli manually, since it was important to use the software's own analysis, to ensure consistency throughout the study.

Statistical analysis

Data was tabulated into an Excel spreadsheet and then transferred to SPSS v16 for further analysis. Median and interquartile range (IQR) were calculated for continuous TCD data, given the skewed distribution of emboli as seen in the pilot study. For background characteristics with continuous variables, mean and standard deviation were used since the data were normally distributed. The Mann-Whitney U (non-parametric) test was used to compare means between left and right sided embolization and male and female patients. The unpaired T test (parametric) was used to compare data for differences between clinical categorical variables. Correlations were calculated for the number of emboli against continuous variables.

3.1.3 TCD methods during the DEFLECT-1 study

The technique for TCD was the same as in the observational study, although the time points differed slightly to allow for the evaluation of the insertion and removal of the embolic deflection device. Further details specific to the study have been described later (see Chapter 4.3).

3.2 Cognitive testing

The background to cognitive testing used in surgical studies has been detailed in Section 1.6. Given the advance in computer-based testing since the Consensus

statement was published 20 years ago, it was decided that these needed to be used in this study.

CANTAB Eclipse cognitive testing - rationale of test choice

The consensus statement suggested considerations about the composition of the test battery to be used, which are still useful. These are:[114]

1. The cognitive domain of the test

2. The sensitivity and reliability of the test

3. The time taken to perform the test

4. The degree to which learning may occur in the test

5. The availability of parallel forms of the test

6. The physical effort required to perform the test

7. The overall battery of the cognitive domains assessed in the battery

The CANTAB eclipse system is a computer-based system first developed in Cambridge University nearly 30 years ago and has over 20 different tests which can be selected for use. There are several key advantages of these over traditional "paper-and-pencil" tests. The majority of tests are independent of language, there is limited training needed for the operator, data collection is automated reducing operator bias in interpretation and the tests are available in multiple languages meaning that multi-centre international studies can be performed reliably. All patients undergo the Motor Screening test (MOT) to assess whether they are able to use the touch screen computer or not. After that, the battery of tests has to be chosen and this battery is then used by inserting a memory stick "key" into a dedicated touch screen computer to activate a license. All scores for the tests are calculated by the system itself and tabulated, for download by the test users later on. All the tests provided in the CANTAB system have been extensively evaluated and used in clinical studies, with over 1500 publications to date having used the tests. Most of

the tests have an in-built practice part which is not assessed, to make sure there is little learning effect by repeated testing.

Given the considerations above in selecting tests for use in our battery (and information from the Consensus statement), we decided that the tests needed to be selected so that:

1. The total test battery would not take more than 1 hour

2. There must be at least 1 test which is known to be sensitive at picking up mild cognitive impairment (MCI) or early dementia, given the age of the patients we plan to study

3. There must be tests which correspond to the consensus battery to allow some comparison with past studies - hence motor speed, psychomotor speed, executive function/decision making and verbal short-term memory would be assessed

4. At least 1 test should test frontal and parietal lobe function as these are known to be the most common sites of embolization

Given these factors, the following tests were chosen for use in our study (which were calculated to take approximately 50-55 minutes to perform):

1. Motor Screen, MOT (2 mins) - Introductory test to screen for visual, movement and comprehension difficulties

2. Choice Reaction Time, CRT (7 mins) - Alertness and motor speed

3. Rapid Visual Information Processing, RVP (7 mins) - Attention - this is a sensitive test of parietal and frontal lobe dysfunction and general performance

4. Paired Associate Learning, PAL (10 mins) - tests visual memory and is sensitive to age-related memory loss, mild cognitive impairment and Alzheimer's

5. Spatial Working Memory, SWM (8 mins) - tests frontal lobe and 'executive' function including heuristic strategy

6. Verbal Recognition Memory, VRM (7 mins) - tests immediate and delayed recall, under free recall and forced choice recognition conditions

7. Stop Signal Task, SST (14 mins) - tests decision making and response control, measures ability to inhibit a pre-potent response.

Why CANTAB is a better testing system than traditional batteries of tests

One of the main advantages of the CANTAB system is the ability of a computer to perform all the measurements, removing the need for the neuropsychologist performing the tests to make any assessment, which could in theory introduce bias into the test results. Secondly, the use of a specific script for giving instructions, means there should be no variability in how the instructions are delivered to the patient. The tests used can be adjusted to suit different populations, for example a more complex test protocol in younger patients, although clearly this should not be done for different patients in a particular study and could in theory cause problems if studies are compared if different protocols were used. One major advantage is that many of the tests have different complexities, so that a level can be chosen that would be better suited to an elderly population (e.g. the RVP test has a mode with larger numbers on screen).

Specific methods:

Patients attending clinic for potential TAVI were screened for suitability to enter the study. Patient recruitment was mostly limited by time available in clinic, due to the time needed to perform the cognitive tests.

Inclusion criteria:

- Patients undergoing TAVI and willing to participate in the study, even if already enrolled in another study

Exclusion criteria:

- Motor, visual or auditory impairment leading to patient being unable to use a touchscreen computer
- Patient not willing to attend follow-up appointments upto 1 year post-TAVI

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Time points for the cognitive tests:

Initially, the time points chosen were:

a. initial visit pre-TAVI

b. 2nd pre-TAVI (at either an appointment for an angiogram or CT scan or pre-assessment) - the reason for 2 baseline tests was to see the impact of learning with use of the system.

c. 6 weeks post-TAVI (or whenever the 1st clinic visit was, since some patients delayed their initial visit of their own accord or due to medical reasons)

d. 6 months

e. 1 year.

However, once 17 patients had undergone the 2 pre-TAVI tests, it was decided to analyse the data, to see if any significant differences had arisen and hence determine the necessity of these 2 baseline test time points. Given a lack of significant difference, the initial test was abandoned to reduce the burden of cognitive assessments on an elderly group of patients (see Chapter 6).

Demographic data for all patients was also collected. Initially the plan had been to perform TCD in all these patients where possible, however due to a change in practice very early in the study from performing TAVI under general anaesthesia (GA) to local anaesthesia (LA), the TCD headset became too uncomfortable to wear for the entire procedure for those patients under LA. Hence this was abandoned. Similarly, the original plan had been to perform pre- and post-procedure brain MRIs in a subset of these patients to try and correlate any cognitive deficits with areas of the brain affected. Again, this was abandoned due to lack of funding, despite being in the original protocol and ethics application. Taking the pragmatic approach, that cognitive change was the most important outcome of the study, it was commenced. TAVI was performed using standard methods as described earlier, under LA for the majority of patients.

Statistical analysis

Data was tabulated using Microsoft Excel 2007 and then analysed using both Excel and SPSS v16. Baseline characteristics of the patients were assessed. Then differences between time-points were analysed using paired t-tests.

3.3 Cardiac CT calcification

The background to the importance of aortic valve/root calcification and the use of cardiac CT has been described in Chapter 1.5.

Calcium scoring was done using the standard Agatston scoring method. This involved taking a non-contrast CT scan with 3mm slice thickness as is standard for coronary calcium scoring, performed as part of the work-up CT for TAVI. This was then imported into a GE workstation with automated software for scoring (SmartScore).

Each slice which involved the aortic valve and root was then analysed and colour coded marking was performed to distinguish between calcium in the valve itself and in the aortic root. Once each slice had been analysed, the software calculated a total score for each - the valve and the root. These were tabulated in Microsoft Excel 2007.

To ensure data consistency, intraobserver variability was calculated, by looking at 9 of the same scans at an interval of 3-6 months. I was blinded to the first set of scores I had previously calculated to avoid bias.

Statistical analysis:

The data was analysed using Excel 2007 and SPSS 16.0 to assess basic parameters such as mean and standard deviation. The interclass correlation coefficient (ICC) was used to assess intraobserver variability. Correlations were made between the Agatston calcium score and the number of emboli on TCD, using Spearman's rank correlation due to the nonparametric distribution of the number of emboli. Analysis was also performed with baseline characteristics of continuous

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variables, to assess whether there were any important predictors of calcification in the valve.

3.4 Brain MRI

Brain MRI is a useful tool in assessing the extent of neurological damage, as detailed in Chapter 1.4.1.

Brain MRI was used in the DEFLECT-1 study (see Chapter 4.3 for details). However, due to issues of time and funding, we were not able to perform brain MRI scans in the studies described in this thesis.

4 Transcranial Doppler Studies

4.1 TCD pilot work

Background and methods:

The rationale and methods for this study have been described in Chapter 3.1.1.

Results:

I was able to insonate the MCA in a total of 13 patients, of which 2 had poor windows with unreliable readings obtained. Therefore the readings for 11 patients were recorded. The median number of emboli at each time point are shown in Figure 4.1. Additionally, in some patients there were large showers of emboli at certain points which could not be accurately recorded and were recorded in my data as showers of emboli. Although this can not be represented on the graph, there were a median of 4 such showers of emboli in each patient in addition to the number in the graph. In 3 patients, additional time points had to be added due to extra procedures performed (one per patient) at time points labelled as 2nd wire insertion, 2nd balloon insertion/inflation and 2nd valve implantation. In the graph, these emboli have been added to the 1st time each procedure was carried out. Of the 11 patients, 2 had a Medtronic CoreValve implanted and 9 had the Edwards Sapien XT valve implanted. From the data in Figure 4.1, it can be observed that the most common time points for embolization were valve insertion, valve deployment, catheter exchange and balloon valvuloplasty in that order. There was a clear difference in timing of the emboli between the 2 patients who underwent a Core Valve implantation compared to the 9 who underwent Edwards Sapien valve implantation. The Core Valve patients had a similar number or fewer emboli at valve positioning compared to implantation, while the Edwards patients had far greater numbers of emboli on average during positioning than deployment.
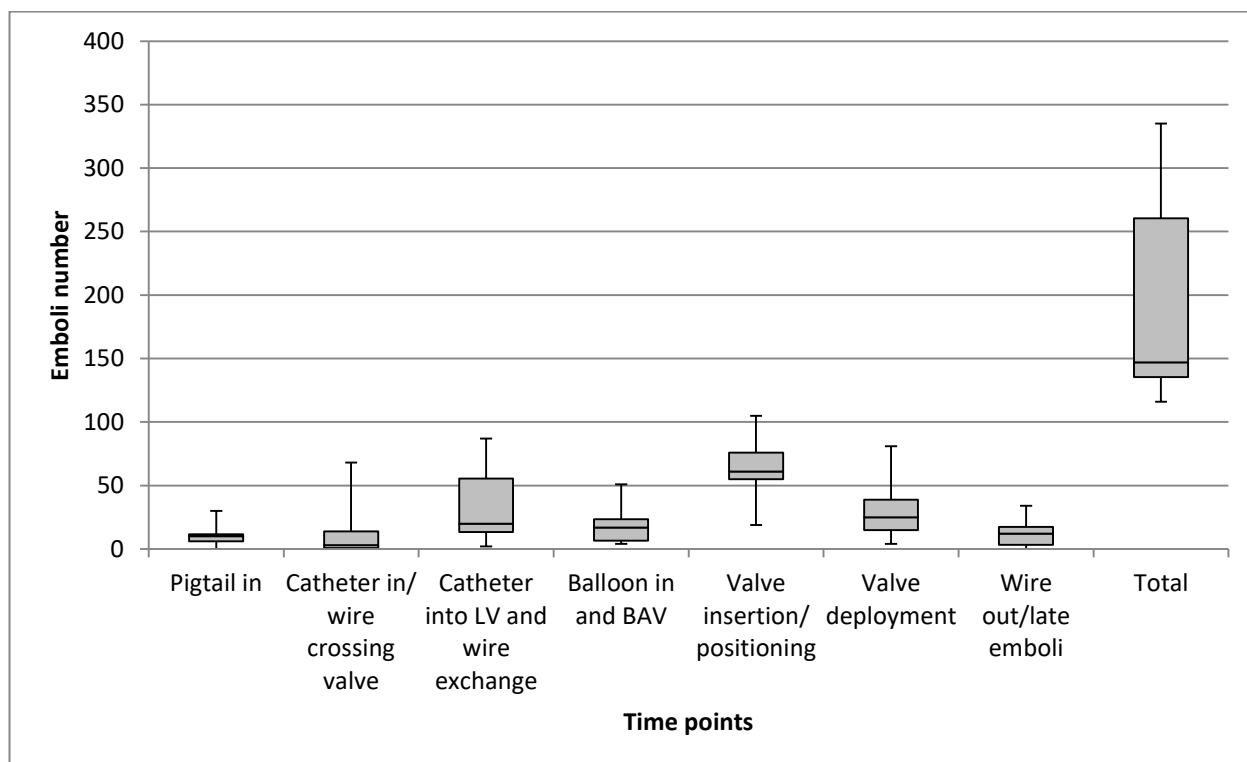
Figure 4.1: Box and whisker plot of number of emboli at each time point during TAVI, pilot data.

Discussion:

It is evident that numerous emboli are generated during the TAVI procedure and they are spread throughout the procedure, although the largest number are found around the time of the actual valve implantation. This would fit with the expectation that the main risk of embolization is during valve implantation, when the native valve tissue is crushed by the newly implanted device and therefore may embolise. However, there were also a large number of emboli during catheter exchange as well, which we could expect to be gaseous in origin, given that despite flushing the catheters, there are still likely to be microbubbles entrapped within the catheters, which may be released during exchange. Given the TCD system used, there was no mechanism of distinguishing between solid and gaseous emboli, hence we were unable to confirm the likely composition of these emboli. This would be important in further work to assess the significance of embolization during TAVI.

Limitations:

In this pilot study, clearly there were several limitations that needed to be addressed. Firstly, the emboli were counted manually and not recorded, meaning that the data cannot be checked and any inaccuracies reviewed. Secondly, using a manual counting system, it was impossible to actually count the number of emboli during showers of emboli or "curtains", making the total number of emboli recorded inaccurate, indeed systematically undercounting the number. Thirdly, emboli were always taken from unilateral signals as we only had a left MCA probe and at this point we had no information as to whether emboli were more frequent on one side than the other and indeed whether this had significance in terms of the procedure. Finally, there were numerous emboli during what would appear to be relatively benign components of the procedure like catheter exchange. Without the ability to differentiate the type of emboli (solid or gaseous), it is not possible to ascertain the significance of just the number of emboli generated at each time point.

Based on this pilot data and with this experience, a more comprehensive study of TCD was performed in patients undergoing TAVI. For this, another TCD machine was acquired, which had software with the capability to automatically count emboli and differentiate between solid and gaseous emboli.

4.2 Observational TCD study in TAVI

Background and methods:

The rationale and methods used for this study are described in detail in Section 3.1.2. Patients were selected as consecutive patients undergoing TAVI, within the limitations in recruitment described in that section (relating to lack of consent, lack of suitable TCD windows, lack of operator for TCD).

Results:

Baseline characteristics:

63 patients had TCD performed in the study period from May 2012 to May 2014. A total of 152 patients underwent TAVI during this time, 65 female and 87 male patients. TCD was attempted in a total of 106 patients, 46 patients did not have TCD attempted due to operator unavailability or the procedures being performed as emergencies. TCD was attempted in a total of 39 female and 67 male patients, in whom it was possible in 10 female and 53 male patients, i.e. 25.6% female and 79.1% male patients had adequate temporal windows for TCD. Other characteristics are described in Table 4.1.

Characteristic	n=63	
Continuous variables	*Mean*	*s.d.*
Age (years)	80	8.3
Body mass index (BMI)	27.2	5.2
Logistic Euroscore	19.1	12.6
Euroscore 2	7.58	7.48
Creatinine (µmol/l)	153.3	113.1
Aortic valve area (cm2)	0.77	0.28
Mean gradient (mmHg)	41.3	13.2
Peak gradient (mmHg)	66.9	20.5
Categorical variables	*No*	*%*
Male	53	84.1
Previous MI	17	27.0
Previous cardiac surgery	21	33.3
Previous PCI	8	12.7
Pulmonary disease	17	27.0
Diabetes	20	31.7
Peripheral vascular disease	9	14.3
Stroke/TIA	14	22.2
Current/Ex-smoker	39	61.9
Impaired LV function	28	44.4

Table 4. 1: Baseline characteristics of the group in this study. *LV left ventricular, MI myocardial infarction, PCI percutaneous coronary intervention, TIA transient ischaemic attack*

Procedure details/outcomes (see Table 4.2):

The majority of patients during this TCD study had an Edwards Sapien XT or

Edwards Sapien 3 valve implanted. Approximately half the patients underwent a

BAV as part of their procedure, which will be explored in greater detail in Section 4.4.

All patients had a successfully deployed valve and only 2 needed a post-implantation

balloon dilatation due to the severity of AR.

One patient needed a valve-in-valve TAVI procedure for device migration, within 1 hour of the original procedure. However, TCD monitoring had been discontinued at this point and could not be re-started due to the emergency nature of the situation. One patient needed conversion to full sternotomy for cardiac tamponade. There were no procedural deaths or strokes in this cohort.

Procedural details	n=63	
	No	*%*
Valve implanted		
Edwards Sapien XT	42	66.7
Edwards Sapien 3	13	20.6
CoreValve	4	6.3
Direct Flow	2	3.2
Lotus	2	3.2
BAV performed	30	47.6
Deployment success	63	100.0
Post-dilatation	2	3.2
	Mean	*s.d.*
Procedure time (mins)	113	36.2
Fluoroscopy time (mins)	15.4	8.4
Radiation dose (µGy/m2)	4083	2780

Table 4. 2: Procedural details of the TAVI procedures performed in this study. ***BAV balloon aortic valvuloplasty***

TCD outcomes:

Of the patients assessed, 39 had adequate bilateral TCD windows, 14 had only a left-sided window and 10 only a right-sided window. Differences in total emboli were calculated between the left and right side for those 39 patients who had adequate bilateral windows. The median (IQR) of total emboli on the left side was 348.0 (262.5-477.5) and right side was 355.0 (263.0-511.5) (difference p=0.41).

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This indicates that there is no clinically significant difference in emboli number between the 2 sides. Therefore, I felt it was reasonable to use the average number of emboli on each side for analysis, which was done for the rest of the data (see Table 4.3).

The data was also analysed to see if there were any significant differences between male and female patients. The data showed the number of emboli occuring in males (n=43) and female (n=10) was (median (IQR)):

Male: Solid 76.0 (61.3-110.5), Gaseous 267.0 (202.8-369), Total 343.0 (269.8-478.8)

Female: Solid 82.0 (53.1-143.8), Gaseous 338.3 (158.3-425.4), Total 437.5 (210.8-561.9)

p values for the differences: Solid 0.970, Gaseous 0.918, Total 0.880.

Time point	n=	Solid	Gaseous	Total
		Median (IQR)	Median (IQR)	Median (IQR)
Insertion of diagnostic catheters	61	4.0 (0.5-14.0)	11.5 (3.0-44.5)	15.0 (3.5-58.5)
Cross valve/exchange catheters	63	15.0 (6.0-33.5)	61.0 (26.0-99.0)	74.0 (31.0-132.0)
Insert balloon	30	1.8 (0.9-3.0)	6.3 (2.8-9.0)	8.3 (4.0-11.6)
Balloon valvuloplasty	30	3.3 (1.8-9.3)	15.0 (6.1-39.1)	18.8 (8.0-45.4)
Valve transition through arch	54	1.0 (0.0-1.6)	3.3 (0.0-8.6)	3.8 (0.0-10.8)
Valve positioning	63	27.0 (16.5-40.5)	86.0 (57.5-127.5)	112.0 (74.0-173.0)
Valve deployment	62	2.5 (0.5-10.3)	8.0 (2.0-41.1)	11.3 (2.9-53.9)
Remove delivery system	59	7.5 (4.0-13.0)	23.5 (11.0-42.0)	31.5 (14.0-53.5)
Late emboli	55	5.0 (1.5-10.0)	22.5 (6.0-30.0)	28.0 (8.5-38.0)
Total	63	**76.0 (61.0-112.0)**	**278.5 (202.0-372.0)**	**356.5 (267.5-490.5)**

Table 4. 3: Number of solid, gaseous and total emboli occurring at each time point during TAVI

Relationship between number of emboli and background characteristics or outcomes

There was no relationship between the number of emboli observed (total or solid) and any of the characteristics listed in Table 4.3.

There were no deaths to hospital discharge in the patients analysed but there were 2 strokes (during hospital stay for the procedure, but neither during the procedure itself). These 2 patients had 490.5/146.5 and 210.0/63.0 total/solid HITS per side - well within the normal number of total and solid emboli seen in the group as a whole (from Table 4.3).

There was also no relationship between the number of total/solid emboli observed and the total or fluoroscopic time of the procedure.

Discussion:

Regarding the group of patients in this study, it is important to note the percentage of male and female patients in whom TCD was possible. It is clear that adequate temporal TCD windows were much harder to obtain in females, and this has been well described in the literature, especially in patients over 60 years of age.[72] In fact in our group the patients were much older, with a mean age of just over 80 years. Hence the much lower percentage of female patients in this group compared to what would be expected. Otherwise, the group characteristics can be seen to be very similar to those in the registry of patients undergoing TAVI in the UK.[21]

The majority of valves implanted in this study are of the balloon-expandable variety, either Edwards Sapien XT or Edwards Sapien 3 valves. Hence the data obtained primarily relates to these valves rather than the other commonly available self-expandable Medtronic Core Valve or the newer valves studied, the Direct Flow Medical or Lotus valves. BAV was performed in approximately half of the patients studied, but on the whole this was not a decision based on individual patient characteristics. Rather, it was based on a change in practice from performing a BAV

to not performing a BAV. This is analysed in more detail later. The fact that no patients in this cohort had a procedural stroke means that it is not possible to assess whether patients having a stroke would have a different pattern of embolization, which we might expect.

Although obtaining data from both left and right middle cerebral arteries in all patients would have been ideal, this was difficult due to poor windows in older patients. To avoid further compromising the number of patients in the study (given the number without even an adequate unilateral temporal TCD window), it was decided to see whether there were any differences in the number of HITS detected on each side in those with bilateral windows. This data showed that there was no significant difference. Hence I felt that it was appropriate to use the average number of HITS per side for analysis when 2 sides were available, or just the number on 1 side where unilateral windows were available. Finding that there is no difference in left and right sided embolization is however important when evaluating embolic protection devices, since they should equally protect both sides of the brain. What TCD does not indicate, is the risk of embolization to the posterior circulation, since it assesses only the anterior circulation.

Our data obtained for total emboli showed significantly higher numbers than in the largest study to date of TCD in a TAVI cohort.[42] In that study, they excluded emboli that were detected during catheter flushing, contrast injection and other parts of the procedure likely to be associated with large numbers of gaseous emboli and therefore for bilateral TCD obtained a total of 482.2 emboli (i.e. 241.1/side) for the transfemoral Edwards Sapien cohort, which make up the vast majority of our data. Given our software to differentiate between the emboli, it was felt that we should not exclude times where larger numbers of gaseous emboli were likely. However, even during catheter insertion and exchange when most emboli should be gaseous, there were still a large number of solid HITS identified. It is likely that actually the software was unable to accurately differentiate HITS at these timepoints. Hence the data

would have been better analysed by excluding times when catheter flushing and contrast injections were most frequent. This could be difficult to do accurately however, since at certain times contrast injections occur when important steps of the procedure are being carried out e.g. valve deployment.

Similar to the paper discussed above, we also found that the majority of HITS in ES valves occurred when the valve was positioned. The significance of this is hard to establish. It is possible that the reason is that as the valve is pushed into the native valve, several emboli occur as particles of the valve tissue are displaced. However, it is also possible that at this point as the valve is somewhat squeezed into native valve tissue, that actually microbubbles trapped in the TAVI valve are released. This does not happen with the CoreValve on positioning as the valve is still sheathed. Conversely, with the CoreValve the emboli occur on valve deployment as the valve is unsheathed. This could be as the valve expands it displaces old valve tissue which then embolises. However, it could also be because at that point the microbubbles trapped in the valve are released. Although our software should have been able to distinguish between these 2 possibilities, in reality this does not seem to have happened. The likely reason is that the large number of emboli during contrast injections occurring at important times during the procedure have diluted the important information we intended to obtain.

Limitations:

The major limitation of TCD is the inability to find adequate temporal windows. One study showed that good unilateral windows could only be obtained in 90% of men and 53% of women over the age of 60, and bilateral windows in 81% of men and 40% of women – given the thicker temporal bones in women at older ages.[72] We observed this in our cohort or rather had even more problems with obtaining adequate temporal windows particular in women, where the patients were even older than in the article referenced here.

With the removal of the headset between set-up and re-positioning, there was occasionally difficulty with finding the temporal windows again, especially if they were hard to find in the first place. However, given the discomfort wearing the headset for long periods of time in an awake patient, it was not practical to keep the headset on for a long period prior to the procedure. The other issue was that the headset could be displaced at various points during the procedure, such as when the TOE probe was inserted or manipulated. The Lam Rack headsets used in theory provided a greater degree of stability than the standard headsets, but this was still a problem in some cases.

In terms of the interpretation, the main issue arose during showers of emboli, which mostly occurred during contrast injections. During these showers it was not possible to accurately count the number of emboli manually or even automatically. Hence the number of emboli during these episodes was taken directly from the automatic counter. It is likely that the differentiation ability of the software during these episodes was inaccurate. Thus counting the emboli during these periods may have diluted the quality of the data.

Conclusions:

TAVI implantation is associated with a large number of embolic events, detected as HITS on TCD. For implantation of transfemoral Edwards Sapien valves, the largest number of these occur during valve positioning within the native aortic valve leaflets. Embolic differentiation can be performed on TCD recordings, but appears to be beset with problems related to the large number of gaseous emboli which occur during catheter exchange and contrast injections. Accurately distinguishing the reasons for embolization is therefore not easily possible. Hence in studies looking at embolization to the brain during TAVI, diffusion weighted MRI data is likely to be more useful.

4.3 TCD in the DEFLECT-1 study (part of the Methods/Results/Discussion sections adapted from Baumbach et al.[131])

Background

Stroke is one of the most devastating complications of TAVI, as described in the introduction. Given the likely role of embolization during the procedure as a cause of this,[38,39] embolic protection may reduce this risk. The TriGuard embolic protection device (EDD), formerly known as the SMT device, has previously been tested in a small study[128] and the DEFLECT-1 study was designed as a multi-centre observational study to assess the safety of this device for cerebral embolic protection.[131] This study had received approval via the National Research Ethics Committee. My role in this study was performing TCD for all the patients. I could then use this information to compare the TCD findings with the MRI findings.

Methods

Methods of EDD device usage during TAVI

At the start of the procedure, a 9 French arterial sheath was inserted in the contralateral femoral artery (to the side used for valve implantation), through which the EDD was advanced to the aortic arch and deployed to cover the ostia of the 3 major cerebral vessels. The EDD was removed after completing the TAVI procedure.[131]

TCD methods

I performed and analysed the TCD for the DEFLECT-1 study. The TCD was set-up as described earlier (see Methods in Section 3.1.2), using the Doppler BoxX device (DWL Compumedics Germany GmbH). Given the procedural differences between typical TAVI cases and this cohort, the following additional time points were also used for data collection:

70

a. Pre-EDD insertion

b. EDD insertion and unsheathing

c. Removing the EDD
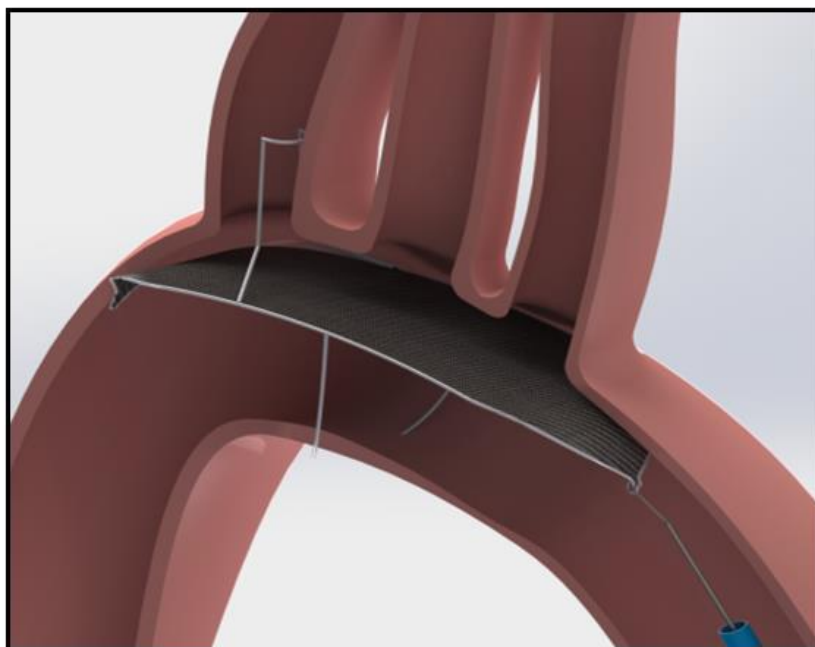
Figure 4. 2: Illustration of the Keystone Heart TriGuard Embolic Deflection Device positioned in the aortic arch

DW-MRI of the brain was performed up to 21 days pre-procedure and at 4±2 days post-procedure according to a standardized acquisition protocol. DW-MRI images were reviewed and analyzed using validated methods by a neuroradiologist blinded to clinical characteristics and temporal sequence of the scans. All lesions were independently adjudicated by a second imaging physician. Axial DW-MRI images and corresponding apparent diffusion coefficient (ADC) maps, as well as corresponding T2-weighted images, were reviewed for the presence of lesions with high signal intensity on DW-MRI. Acute ischemic lesions were defined as areas of high signal intensity on DW-MRI with corresponding areas of low signal intensity on the ADC maps. For each patient, the total number of lesions at pre- and post-procedure time points was recorded and the total number of new lesions calculated.

For each positive lesion, the volume of each lesion was recorded. Lesion volumes were summed across each patient to yield total lesion volume.[131]

Statistics

Data was tabulated using Microsoft Excel 2007. Statistics, including correlations between TCD and MRI performed using the Pearson correlation coefficient, were calculated using SPSS v16.

Results

A total of 37 subjects were enrolled at 6 sites in Europe and Brazil. A total of 42 valves were implanted in 37 patients (3 valve-in-valve, 1 valve-in valve–in-valve). The Medtronic CoreValve was used in 27/42 (64.3%) cases and the Edwards Sapien valve in 15/42 (35.7%), all implanted transfemorally. TAVI implantation was successful in 36/37 (97.3%) subjects. One patient required urgent conversion to SAVR after failed implantation of 2 Medtronic CoreValves, complicated by severe aortic insufficiency. A total of 41 EDD devices were used in 37 patients. The EDD and delivery sheath were inserted, deployed and retrieved intact in all 41 attempts – in 4 patients more than one device was required as the first device did not sit well in the arch. No obstruction to cerebral blood flow or interference of the EDD with balloon aortic valvuloplasty or TAVI was reported. The device was successfully positioned to cover all three cerebral inflow vessels prior to passage of the TAVI catheter in 33/37 (89.2%) cases, remained in position through prosthetic valve deployment and implantation in 28/37 (75.7%) cases, and remained in proper position after removal of the TAVI delivery system in 23/37 (62.1%) cases. Two patients had a stroke. One stroke occurred the day following urgent surgical conversion after failed TAVI. The second stroke occurred in a patient whose procedure was complicated by loss of ventricular capture from a temporary pacing

lead in the setting of complete heart block, which required cardiopulmonary resuscitation.

TCD monitoring was attempted in 25 subjects and interpretable in 18 subjects. The total count of MCA HITS for each step of the procedure (sum of right and left sides) is reported in Figure 4.3. Procedural HITS were detected during all steps of the TAVI procedure. Most HITS occurred during passage of the stiff guide wire (25%), balloon valvuloplasty (13.6%) and positioning (11.7%) and deployment of the prosthetic valve (30.3%), while removal of the TAVI delivery system contributed 6.3% of HITS. Deployment of the sheath needed for delivery of the EDD resulted in a relatively small number of HITS, while introduction and positioning the EDD delivery system produced a higher number of HITS. Solid HITS during this period were comparable to the number observed during guidewire and pigtail catheter passage over the aortic arch.
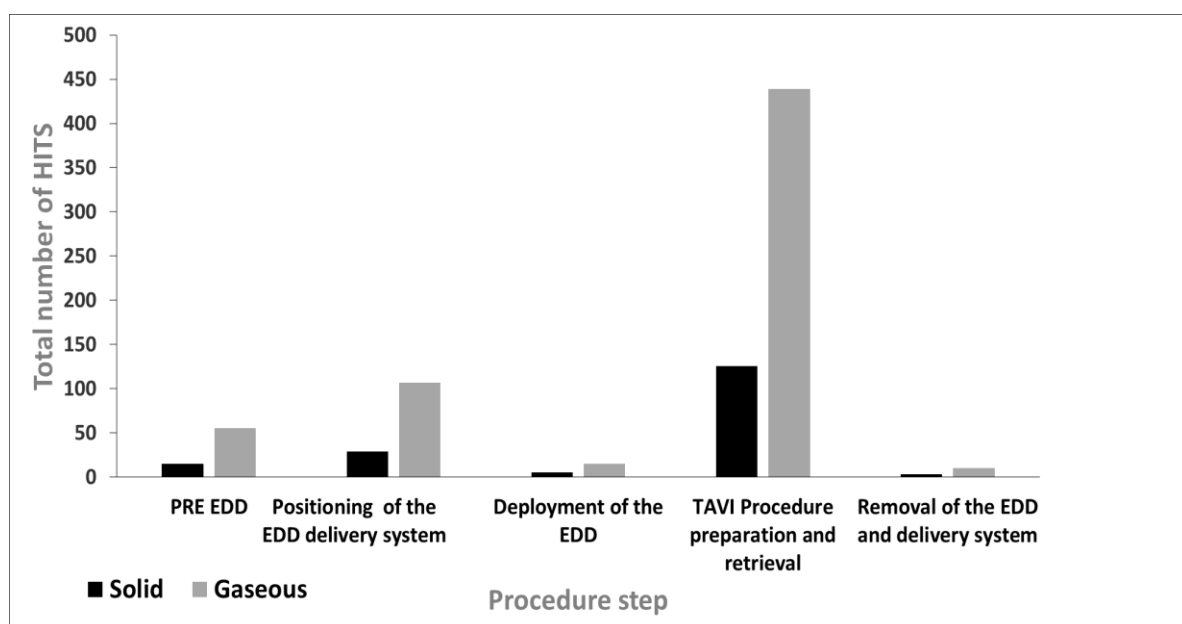

Figure 4. 3: Total number of solid and gaseous middle cerebral artery HITS by procedure stage

MRI correlation

Out of 18 patients in whom TCD was interpretable, 13 also completed the full MRI protocol with a pre- and post-TAVI scan. Of these 13 patients, 10 had new lesions with an average of 7.3 (range 1-28) lesions/patient and 1.03 (range 0.16-3.94) cm^3/patient. There was no correlation between the number of solid, gaseous or total emboli with the total number or volume of new lesions (all p>0.5).

Although not my work, for completeness I have included a summary of the study's MRI results here. Out of 37 patients in total, 28 patients completed the MRI protocol. The proportion of patients with new ischemic lesions was 22/28 (78.6%) patients. This rate was not significantly different from the percentage derived from historical controls of unprotected TAVI (76%; p=NS). Average new single lesion volume was non-normally distributed; median was 0.11 [0.04-0.18] cm^3. Mean new single lesion volume was 62% lower compared to historical controls (0.13±0.13 vs. 0.34 cm^3). Average maximum single lesion volume was also not normally distributed; median was 0.18 [0.045-0.39] cm^3. Median number of new ischemic lesions was 3 [1.0-7.0]. Median total lesion volume was 0.43 [0.09-1.06] cm^3; mean total lesion volume was 53% lower than historical controls (0.77±0.96 vs. 1.64 cm^3). Lesion distribution was slightly biased to the left cerebral circulation (60% vs. 40%); the most common affected vascular territory was the MCA (47%), followed by the posterior cerebral artery (22%), posterior inferior cerebellar artery (17%), anterior cerebral artery (13%), or other (2%).[131]

Discussion

Previous studies of TCD (including my own work), demonstrate that the majority of microembolization occurs during balloon valvuloplasty and TAVI prosthesis positioning and deployment, with relatively little subsequent generation of emboli.[42] This study confirms that the majority of solid embolization occurs during TAVI deployment (78%), however, 6.3% of TCD HITS occurred during TAVI delivery

system removal. Thus truly optimal embolic protection should include complete procedural coverage, including removal of the TAVI delivery system. Importantly, positioning and removal of the EDD resulted in a minimal increment of solid HITS beyond background levels.

The DW MRI data demonstrated reduced lesion volume compared with historical controls despite there being a similar number of total lesions. This suggests that the EDD does stop larger emboli reaching the brain, clearly a promising conclusion. However, there is clear evidence that the stroke rate from TAVI has reduced over time, so these findings may just reflect that change. The only way to be sure whether there is a significant difference attributable to the device is a randomised controlled trial of the device against a control group (which formed the basis of the later DEFLECT-3 study).[133]

The lack of correlation between MRI lesions and TCD is interesting. It may reflect the small numbers of patients. However, more likely it relates to the fact that TCD does not differentiate particle size and so the reduction of a few large particles embolising to the brain would not make a significant difference to the HITS count, whereas it makes a big difference to the volume of infarction on DW MRI. This once again points to the importance of using DW MRI to assess embolization during TAVI, rather than TCD.

4.4 TCD to assess differences between performing TAVI with and without balloon aortic valvuloplasty (BAV)

Introduction:

As part of the TAVI procedure, a balloon aortic valvuloplasty has traditionally been performed and is a manufacturer recommendation as well as being mandated in study protocols.[22,33,134] Theoretically it could help with ensuring easy passage of the new valve through the old one and allow better deployment with reduced paravalvular leak, as well as help in sizing of the valve.[135] However, the necessity of this is unknown and certainly now sizing is predominantly done using 3 dimensional

computerised tomography (3D CT) or even 3D transoesophageal echocardiography (3D TOE).[136,137] Conversely, avoiding the BAV could theoretically reduce time taken for the procedure, reduce ionising radiation exposure and reduce the number of cerebral emboli that occur during the BAV procedure.[138]

There is evidence that performing TAVI with the self-expanding Core Valve (Medtronic, Minneapolis, MN) can be done safely and effectively without a BAV.[139,140] There is also some data showing this for transapical implantation of the balloon-expandable Edwards Sapien XT valve.[141] Some anecdotal data does exist for this technique in transfemoral cases but there is no detailed information on the success of this technique to date.[142-144]

The aim of this study was to see whether there were any differences in embolization on TCD in patients who underwent balloon-expandable TAVI implantation, with and without BAV. To broaden this study, I aimed to evaluate differences between the 2 groups in terms of procedural success and safety as well as total procedural and fluoroscopic time.

Methods:

I retrospectively evaluated all first-time TAVIs performed via the transfemoral route for predominant aortic stenosis using the balloon-expandable Edwards Sapien XT (ESXT) and Edwards Sapien 3 (ES3) devices from March 2012 to July 2014. BAV was routinely performed until May 2013, after which it was discontinued by operator preference. Hence patients were excluded who had either another concomitant intervention or who were having a valve-in-valve procedure for bioprosthetic valve failure.

The TAVI procedures were performed using standard methods, with the majority of patients under general anaesthetic and using transoesophageal echocardiographic guidance, but latterly some under local anaesthetic with transthoracic echocardiography only. Transcranial Doppler (TCD) monitoring was performed

during the procedure where adequate temporal windows were present, to assess the degree of embolization.

Data was collected on patient demographics, Valve Academic Research Consortium (VARC)-2 defined composite endpoints (both deployment success and early safety), total and fluoroscopic time and the number of total and solid emboli as detected using TCD. Categorical variables were analysed using the Fisher exact test and continuous variables by the unpaired T-test using SPSS v16.0 (SPSS Inc., Chicago IL, USA).

Results:

In the period selected for this study, a total of 165 patients underwent TAVI using a balloon-expandable valve. We excluded 1 patient who underwent a concomitant balloon mitral valvuloplasty, 3 patients who underwent transapical valve deployment, 6 patients who underwent a valve-in-valve TAVI procedure for bioprosthetic valve failure and 1 patient who underwent a valve implant into a heterotopic heart transplant to prevent aortic regurgitation into the native heart. The study group therefore comprised a total of 154 patients.

Seventy-six patients underwent prior BAV (Group 1) and 78 patients had no prior BAV (Group 2). Patient characteristics are presented in Table 4.5. There were no differences in the majority of baseline characteristics, except for more male patients having no BAV and the number of patients having an ESXT or ES3 valve. The number of male patients having no BAV appears to have resulted from more TAVI referrals for male patients more recently. The increasing number in the recent group having an ES3 valve implanted is a result of a gradual change to using this valve. However, there were also no differences in the same characteristics listed in Table 4.4 between the groups undergoing TAVI with either of these two valves.

Variable	BAV (n=76)	No BAV (n=78)	p value
Age (yrs)	82.2	80.6	0.26
Gender (%Male)	47.4	66.7	**0.02**
Body mass index (kg/m2)	27	27.6	0.48
Logistic Euroscore	19.1	20.5	0.51
Euroscore 2	7.3	7.6	0.80
Previous MI (%)	25	24.4	1.00
Previous cardiac surgery (%)	19.7	24.4	0.56
Previous PCI (%)	15.8	14.1	0.82
Creatinine (µmol/l)	127.1	133.3	0.65
Renal disease (%)	13.2	15.4	0.82
History of TIA/CVA (%)	23.7	20.5	0.70
Pulmonary disease (%)	26.3	20.5	0.45
Diabetes mellitus (%)	22.4	26.9	0.58
Impaired LV function (%)	28.9	43.6	0.07
Sapien XT valve (%)	89.5	55.1	**<0.001**
Peak gradient (mmHg)	71	67.8	0.37
Mean gradient (mmHg)	46.3	41.9	0.90
Aortic valve area (cm2)	0.7	0.74	0.29

Table 4. 4: Baseline characteristics. *BAV balloon aortic valvuloplasty, CVA cerebrovascular accident, LV left ventricular, MI myocardial infarction, PCI percutaneous coronary intervention, TIA transient ischaemic attack*

VARC-2 defined endpoints (see Table 4.5)

There were no differences in the rate of VARC 2-defined deployment success. This is defined as absence of procedural mortality, correct positioning of a single prosthetic heart valve into the proper anatomical location and no patient-prosthesis mismatch or moderate/severe regurgitation. In three patients who had not undergone a BAV there was some difficulty in crossing the valve (two patients with an ESXT valve and one with an ES3 valve). In each of these cases partial inflation of the distal tip of the balloon within the valve enabled crossing of the native aortic valve without subsequent deployment problems.

Similarly there were no differences in the rate of VARC 2-defined early safety. This is defined as (at 30 days), all-cause mortality or stroke, life-threatening bleeding, acute kidney injury stage 2 or 3, coronary artery obstruction needing intervention, major vascular complication or valve-related dysfunction requiring repeat procedure. Specifically, there was no difference in 30 day mortality, although there was a strong trend towards a lower stroke rate at 30 days in those not having a BAV (p=0.06). There were no significant differences in any of the other specific endpoints encompassed in the VARC-2 early safety endpoint, or differences in the requirement for permanent pacing or length of in-hospital stay.

There was a significant reduction in both total procedure time and fluoroscopy time in those not undergoing a BAV, as seen in Table 4.5.

Variable	BAV (n=76)	No BAV (n=78)	p value
Deployment success (%)	93.4	94.9	0.74
Early safety (%)	78.9	84.6	0.41
Moderate-severe AR (%)	5.3	0	0.06
Post-deployment balloon dilatation (%)	2.6	2.6	1.00
Procedure time (mins)	125.6	104.9	**0.01**
Fluoroscopy time (mins)	18.3	13	**<0.001**
Radiation dose (µGy/m2)	4681.3	3419.3	0.13

Table 4. 5: Outcomes. *AR aortic regurgitation, BAV balloon aortic valvuloplasty*

Embolization results (see Table 4.6)

TCD data was only available in a limited subset of these patients (n=53), due to difficulty insonating adequate temporal windows or operator availability. In the subset analysed, there were no differences between the 2 groups in terms of number of emboli - either solid, gaseous or total emboli. In fact it was noted that looking specifically at embolization during valve positioning (the most significant time point for embolization), on average 119.2 HITS were detected in the BAV group but 169.0

in the non-BAV group (p=0.03). In the BAV group an average of 8.0 HITS were detected during balloon positioning and 26.3 during balloon valvuloplasty itself, so the total HITS in the BAV group during BAV and valve positioning was 152.5.

Time of TCD analysis	BAV (n=24)	No BAV (n=29)	p value
Total Solid HITS	81	95.3	0.26
Total Gaseous HITS	276.8	339.1	0.13
Total Solid and Gaseous HITS	357.9	434.4	0.14
Total emboli - balloon positioning	8.0	NA	NA
Total emboli - BAV	26.3	NA	NA
Total emboli - Valve positioning	119.2	169.0	**0.03**
Total emboli - Valve deployment	16.5	15.8	0.89

Table 4. 6: TCD outcomes *BAV balloon aortic valvuloplasty, HITS high-intensity transient signals, TCD transcranial Doppler*

Discussion:

BAV as part of the TAVI procedure using balloon-expandable valves appears to be unnecessary, since it does not improve procedure success or patient safety. In terms of the theoretical benefits, the problem of crossing the stenosed valve was rarely seen and even then, it was easily overcome by slight inflation of the distal balloon tip. The other cited benefit of prior BAV in improving the landing zone for the valve is probably not relevant in balloon-expandable valves, since these valves are being actively expanded using a balloon unlike self-expanding valves. Our data certainly supports this. In contrast, with self-expanding valves there is evidence that inadequate balloon dilatation is correlated with increased aortic regurgitation, which certainly suggests that omitting BAV would likely result in increased AR.[112] Finally, the advantage of improved valve sizing is less relevant in an era where CT valve sizing has become standard in most centres. The lack of significant paravalvular leak

or frequent annular rupture in the vast majority of patients suggests that valves were sized correctly.

Clearly there may still be some patients who could benefit from a BAV. Looking at our patients in more detail, among the last 67 patients once not performing BAV had become our standard practice, there were still 2 patients who did have a BAV. One of these patients was in cardiogenic shock with the TAVI procedure being performed as an emergency and it was felt they should have a BAV while the valve was being prepared. In the other patient, there was very severe calcification of the valve and there was a concern about coronary obstruction during valve implantation and hence a BAV was performed with a simultaneous contrast injection to see if there was still coronary blood flow. Hence, even now there may be selected patients where a BAV is felt to be indicated.

The reduced total procedural time and reduced fluoroscopic time observed was expected, given the omission of part of the procedure. Reduced radiation exposure is important for operators and with TAVI gradually moving into a younger population, reduced radiation is also important for patients. The advantages of reduced procedural time is self evident in any catheterisation laboratory, for patients, operators and management.

The most surprising result perhaps was that omitting BAV did not reduce the observed rate of embolization. Embolization during TAVI is known to occur as a result of native valve calcium, thrombus, etc. being dislodged by dilatation of the valve and subsequent valve implantation.[55] As can be seen from these results, there appear to be similar numbers of emboli occuring during valve implantation in the non-BAV group as there are during BAV and valve implantation combined in the BAV group. This suggests that any particulate matter which embolises during BAV is then not present anymore to embolise when the valve is implanted. Also, BAV itself clearly is less important in terms of embolic phenomenon than valve deployment as noted here and in Chapter 2.2. Considering clinical relevance, the PARTNER B

study showed that stroke was much less common in the medically managed group than the TAVI group (1.1% vs 5.0% at 30 days), where 83.8% of the medically managed group underwent a BAV at some point after randomisation for the trial.[22]

Limitations:

This is a retrospective study where there is the possibility of bias between the 2 strategies since patients were not randomised in the 2 groups. Also, since omitting BAV is a more recent adjustment to the technique, the fact that overall operator experience has increased and technology has improved, as evidenced by the recent more frequent use of ES3 valve, means that some of the benefits attributed to omitting BAV might be due to confounding factors. For these reasons, only a randomised trial of the 2 strategies would give a definitive answer as to which strategy is better and indeed this is ongoing with the EASE-IT study (albeit only for ES3 valves implanted transapically).[145]

Conclusions:

Balloon-expandable TAVI valves can be safely implanted transfemorally without prior BAV, without a reduction in VARC-2 defined deployment success or early safety. Without performing a BAV there is a significant reduction in the total procedural and fluoroscopic time but there is no significant difference in the rate of embolization on TCD.

5. CT study

5.1 CT calcification assessment and correlation with TCD data

The background to the importance of aortic valve and root calcification has been described earlier (see Chapter 1.5).

Methods: The methods used for CT assessment have been described earlier (see Chapter 3.3). CT calcium scoring was performed for all patients who had undergone TCD during their TAVI, where a suitable CT had been performed. In some cases, CTs were used for TAVI planning which were done in other hospitals and in some of those cases the appropriate non-contrast sequence had not been performed, meaning they had to be excluded from the analysis.

Results: Out of a total of 63 patients who had TCD performed, a total of 45 patients underwent a cardiac CT that included an appropriate non-contrast sequence.

The baseline characteristics of the patients undergoing CT are given in Table 5.1.

Characteristic	n=45	
Continuous variables	*Mean*	*s.d.*
Age (years)	80.0	8.3
Body mass index (BMI)	27.2	5.2
Logistic Euroscore	19.1	12.6
Euroscore 2	7.6	7.5
Creatinine (µmol/l)	153.4	114.0
Aortic valve area (cm2)	0.78	0.28
Mean gradient (mmHg)	41.3	13.2
Peak gradient (mmHg)	67.0	20.6
Categorical variables	*No*	*%*
Male	40	88.9
Previous MI	12	26.7
Previous cardiac surgery	14	31.1
Previous PCI	4	8.9
Pulmonary disease	14	31.1
Diabetes	14	31.1
Peripheral vascular disease	5	11.1
Stroke/TIA	10	22.2
Current/Ex-smoker	29	64.4
Impaired LV function	18	40.0

Table 5. 1: Baseline characteristics of patients undergoing TCD and non-contrast cardiac CT. *LV left ventricular, MI myocardial infarction, PCI percutaneous coronary intervention, TIA transient ischaemic attack*

The mean Agatston calcium (Ca) score was:

Aortic valve: 3382.4±1944.4

Aortic root: 754.9±900.7

Total score: 4124.9±2197.2

Intraobserver variability:

The interclass correlation (ICC) was:

Total calcium score: 0.998

Aortic valve calcium score: 0.998

Aortic root calcium score: 0.948.

Correlations with TCD (using Pearson's correlation):

Correlations with TCD findings:

Total cases with both HITS and Ca score: 45

Total HITS vs Total Ca score   - 0.190 (p=0.211) – see Figure 5.1
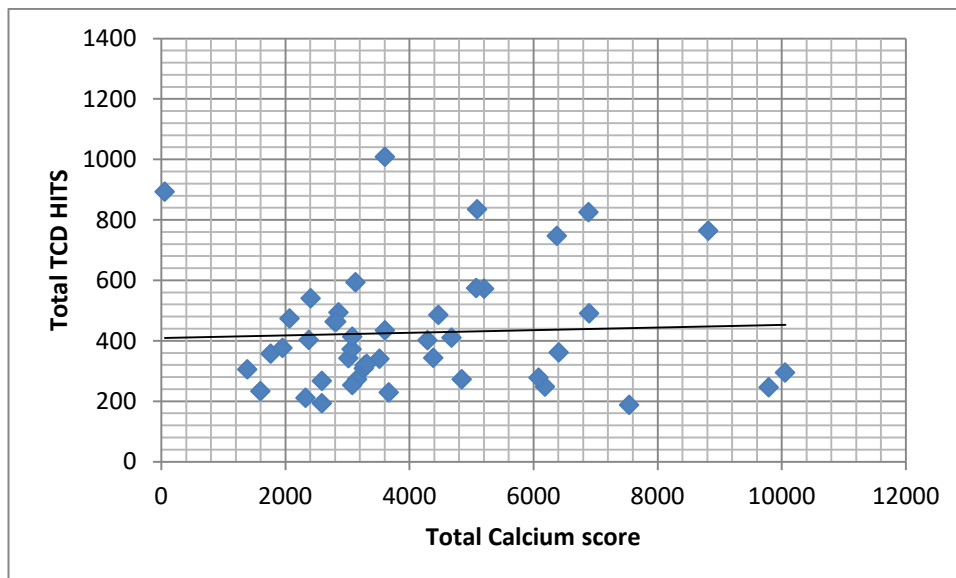

Figure 5. 1: Correlation between Total Calcium score and TCD HITS

Solid HITS vs Total Ca score - 0.235 (p=0.120)

Total HITS vs Valve Ca score - 0.222 (p=0.142)

Solid HITS vs Valve Ca score - 0.303 (p=0.043) – see Figure 5.2
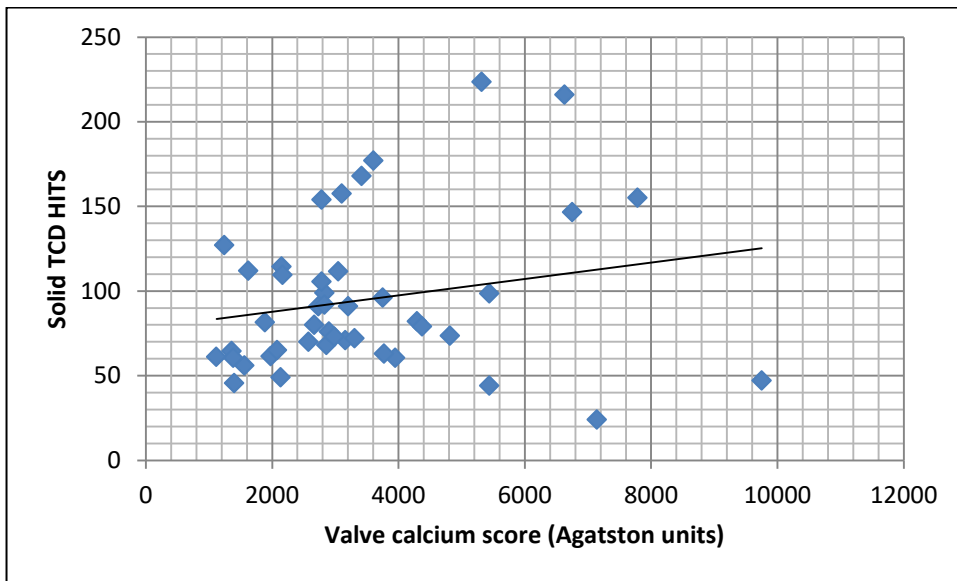
Figure 5. 2: Correlation between Valve Calcium score and Solid TCD HITS

Solid HITS during valve positioning vs Valve Ca score - 0.312 (p=0.037) – see

Figure 5.3
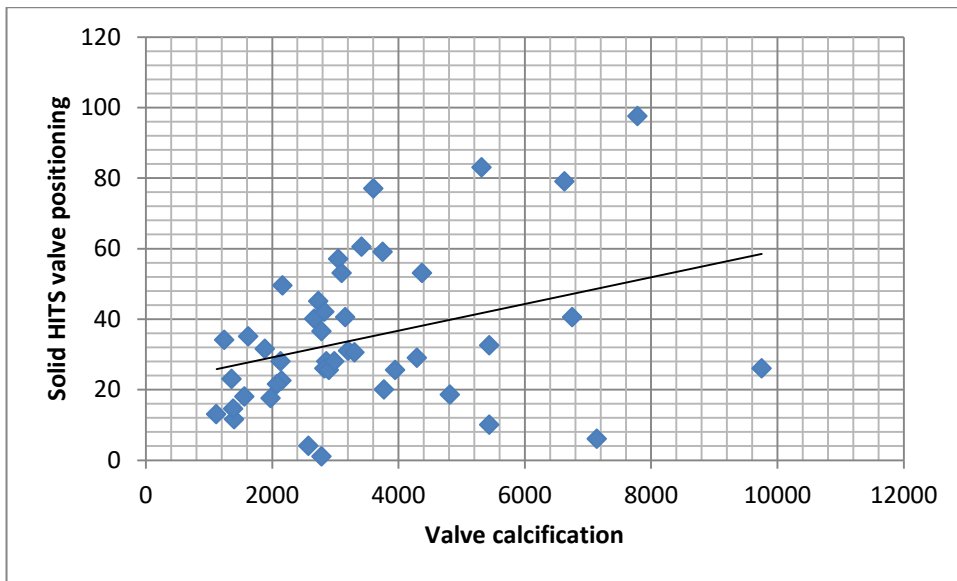
Figure 5. 3: Correlation between Valve Calcium score and Solid TCD HITS during valve positioning

These results show that there were positive correlations between the number of solid HITS on TCD and the valve Ca score. In particular, the strongest correlation was between the number of HITS during valve positioning and valve Ca score. Although not given here, solid TCD HITS did not correlate with any other part of the procedure.

Discussion:

Our mean aortic valve calcium scores were slightly higher than those for patients with severe AS in a major study looking at aortic valve calcification in severe aortic stenosis (3382 vs 2931) - taking the patients with concordant severe AS and high gradients on echo from the study as a comparison.[110] The likely higher calcium load may well relate to the older age of our patients (80.0 vs 74.0 years) and the predominance of males in our group (88.9% vs 57% in the comparison group from the study quoted). It has been shown in a previous study that for the same severity of aortic stenosis, males have a higher aortic valve calcium score even when indexed for body surface area.[146]

Although only performed on a small number of patients, the intraobserver variability noted was reassuring, in that there was very little difference in total calcium score between the 2 observations. Clearly there was slightly higher variation in the aortic root calcium score, but this is likely because the total number was smaller and there can be some difficulty in separating the valve from the root when calculating the independent calcium scores.

The positive correlation between the valve calcium score and the number of solid TCD HITS fits with the hypothesis that there is significant embolization of solid particles when performing a TAVI. In particular the maximum number of emboli occur during positioning of the valve and the number of solid emboli released during this action correlated well with the calcium score of the aortic valve. The calcification, which reflects the more diseased state of the valve, is greater in valves which embolise more solid matter. The correlation should be weaker between the total calcification and embolization, since calcification in the aortic root should not much affect embolization, given that the root is not really manipulated during valve deployment and this is indeed what these results demonstrate.

6. Cognitive Studies

6.1 Cognitive outcomes of TAVI

The background to this study has been described in Chapter 1.2 and 1.6. The general methods used for cognitive testing are described in Chapter 3.2 using the CANTAB Eclipse system, including the rationale behind the choice of tests.

In this study I aimed to evaluate the change in cognitive function as assessed by cognitive function scores in a cohort of patients undergoing TAVI, from baseline to multiple time-points post-procedure. Furthermore, I intended to evaluate whether this testing method was appropriate in TAVI patients and could therefore be used for future studies, in particular a cognitive sub-study of the UK TAVI trial.

Specific methods:

Patients attending clinic for potential TAVI were screened for suitability to enter the study. Patient recruitment was mostly limited by time available in clinic, due to the time needed to perform the cognitive tests.

Inclusion criteria:

- Patients undergoing TAVI and willing to participate in the study

Exclusion criteria:

- Motor, visual or auditory impairment leading to patient being unable to use touchscreen computer

- Patient not willing to attend routine follow-up appointments upto 1 year post-TAVI

Time points for the cognitive tests:

Initially, the time points chosen were:

a. initial visit pre-TAVI

b. 2nd visit pre-TAVI (at either an appointment for an angiogram or CT scan or pre-assessment) - the reason for 2 baseline tests was to see the impact of learning with use of this system.

c. 6 weeks post-TAVI (or whenever the 1st clinic visit was, since some patients delayed their initial visit of their own accord due to ill health, inconvenience, etc.)

d. 6 months

e. 1 year

However, once 17 patients had undergone the 2 pre-TAVI tests, I decided to analyse the data, to see if any significant differences had arisen and hence determine the necessity of these 2 baseline test time points. Given a lack of significant difference, the initial test was abandoned, as described in more detail below.

Initially the plan had been to perform TCD in all these patients where possible. However, due to a change in practice very early in the study from performing TAVI under general anaesthesia (GA) to local anaesthesia (LA), the TCD headset became too uncomfortable to wear for the entire procedure for those patients under LA. Hence this was abandoned. Similarly, the original plan had been to perform pre- and post-procedure brain MRIs in a subset of these patients to try and correlate any cognitive deficits with areas of the brain affected. Again, this was abandoned due to lack of funding, despite being in the original protocol and ethics application. Taking the pragmatic approach, that cognitive change was the most important outcome, the study was commenced.

TAVI was performed using standard methods as described earlier, although under LA for the majority of patients.

Statistical analysis:

Data was tabulated using Microsoft Excel 2007 and then analysed using both Excel and SPSS v16. Baseline characteristics of the patients were assessed. The 2-tailed

paired Student T-test was used to analyse the differences between time points. We also aimed to use a repeated measures ANOVA test to look at changes over time.

Results:

A total of 39 patients were recruited to the study for initial testing. Of these 31 actually entered the study. Those who did not were for the following reasons:

1. Death before or during the procedure (2 patients)

2. No TAVI procedure performed (2 did not require treatment after complete investigation, 1 went for surgery)

3. TAVI and follow-up performed in private setting (1 patient)

4. Patient unable to complete tests (1 patient)

5. Patient found tests unsatisfying (1 patient).

Patient demographics are given in Table 6.1.

Characteristic	n=31	
Continuous variables	*Mean*	*s.d.*
Age (years)	83.3	5.2
Body mass index (BMI)	28.8	7.4
Logistic Euroscore	14.5	7.7
Euroscore 2	4.3	3.3
Creatinine (µmol/l)	137	94.8
Aortic valve area (cm2)	0.72	0.19
Mean gradient (mmHg)	42.1	14.9
Peak gradient (mmHg)	67.7	16.7
Categorical variables	*No*	*%*
Male	16	51.6
Previous MI	6	19.3
Previous cardiac surgery	4	12.9
Pulmonary disease	9	29.0
Diabetes	10	32.3
Peripheral vascular disease	4	12.9
Stroke/TIA	5	16.1
Current/Ex-smoker	14	45.2
Impaired LV function	6	19.3

Table 6. 1: Baseline characteristics. *LV left ventricular, MI myocardial infarction, TIA transient ischaemic attack*

For the initial part of the study, change between the two baseline time-points was analysed. There were 17 patients who underwent these two batteries of tests. As seen in the table below, there was only a significant difference in 1 field of 1 test (Paired Associate Learning 6 shapes), which would not be significant applying a Bonferroni correction, given that this field was not pre-specified. Given this lack of evidence of a learning effect with our test battery, we decided that we did not require two baseline tests to be performed, making the process simpler in terms of assessing patients' cognitive function before the TAVI procedure. For further
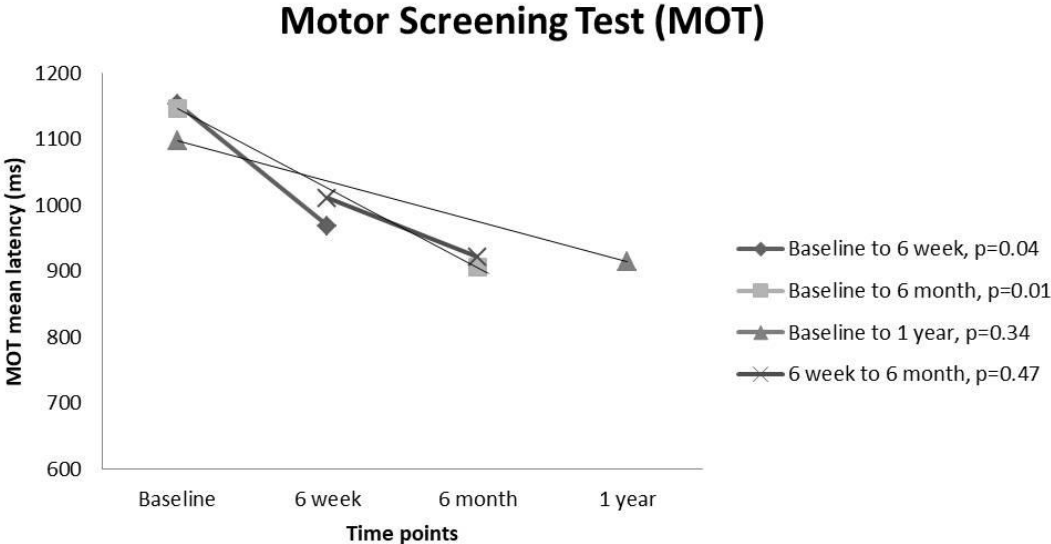
analyses, it was decided to use the patients' most recent pre-TAVI assessment as the baseline (if they had undergone two pre-TAVI assessments).

Of the 31 patients who entered the proper study, 1 dropped out due to ill-health and inability to attend any follow-up appointments. Nine missed the 6 week time point, 12 missed the 6 months timepoint and only 10 attended the 1 year follow-up. Reasons for missing assessments were:

a. patient had lack of time when attending appointments (5 patients)

b. discomfort with performing the tests (4 patients at 7 follow-ups)

c. felt ill at time of appointment (2 patients at 3 follow-ups)

d. missing appointments altogether (6 patients)

e. death (1 patient died after their 6 week follow-up but before their scheduled 6 month follow-up visit)

f. all other tests were missed due to lack of operator availability, this particularly affected the 1 year follow-ups during the patients recruited later in the study due to a move of the clinical TAVI service from The Heart Hospital to Barts Heart Centre

Graphs of key cognitive data are given in Figure 6.1 (a-g). The full dataset has been included in Appendix 1. It must be noted that the variable data points at each time point are due to different patients missing different assessments.

Figure 6.1: Graphs of key cognitive data

a.

b.

c.

Paired Associate Learning (PAL)

Legend:
- Baseline to 6 week, p=0.03
- Baseline to 6 month, p=0.01
- Baseline to 1 year, p=0.01
- 6 week to 6 month, p=0.16

X-axis: Time points
Y-axis: PAL total errors

d.

Rapid Visual Processing (RVP)

Legend:
- Baseline to 6 week, p=0.38
- Baseline to 6 month, p=0.05
- Baseline to 1 year, p=0.66
- 6 week to 6 month, p=0.08

X-axis: Time points
Y-axis: RVP A'

e.

Spatial Working Memory (SWM)

f.

Stop Signal Task (SST)

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g.

Verbal Recognition Memory (VRM)

Although the initial plan was to perform a repeated ANOVA test to look at differences in cognitive domains over time, it became evident that due to a lack of consistent follow-up, there would be too many missing data points for this to be a meaningful tool. Hence this analysis was not performed.

Discussion:

Cognitive function change is a potentially key area where there is limited information in the TAVI cohort. Studies to date have concentrated on using the battery of tests outlined in the Consensus document.[114] This is the first study to use the CANTAB Eclipse system of cognitive assessment, using a battery of tests designed specifically for the TAVI population demographic and focussing on areas of cognition most likely to be affected.

Although there are clear limitations of this study due to poor follow-up rates, it is evident from the results that there are some significant changes in cognition from baseline to follow-up. We can see that both the 6 week and 6 month follow-ups show significant differences in the MOT mean latency, PAL total errors and SSRT. All of

these tests show an improvement in cognitive function, while no areas show significant cognitive decline. Given the lack of differences when 2 baseline tests were conducted, it is reasonable to attribute these improvements to the procedure than a learning effect. One strong feature of the CANTAB Eclipse system is that the majority of tests (other than VRM) have a practice phase built into them and so this should reduce any practice effect which may otherwise have existed.

In terms of cognitive domains, the MOT and the SSRT results relate to reaction times. The PAL total errors is a marker of visual memory and is thought to be a sensitive test for age-related change and Alzheimer's. Our results suggest that the TAVI procedure may be able to improve this, something that could have the potential to further improve the lives of elderly patients, over and above the physical benefits that are well-documented for this procedure. These findings are similar to those noted by Alassar et al,[60] who also noted an improvement in memory, although more apparent in an SAVR cohort than the TAVI cohort.

Limitations

There are several limitations of this study, the main one being the poor rate of follow-up, for which there are several reasons as described in the results section above. Overall the number of patients is small in any case, so only large differences are likely to have been detected. Also, the patients were not recruited consecutively due to time constraints and so it is possible there was a selection bias. Finally, with the poor follow-up rate, it is possible that patients who refused the follow-up tests may have been those who would have performed poorly.

Conclusions:

This study has shown that even in a small cohort of patients, there is evidence of cognitive improvement in certain domains. Reassuringly, there was no evidence in any domain of cognitive decline at any time-point from 6 weeks to 1 year post-

procedure. This study has also shown the feasibility of performing such tests using the CANTAB Eclipse system in TAVI patients, despite the advanced age of many of them.

Going forward, clearly it is important that larger numbers of patients are recruited to try and detect any discernible differences in cognition caused by TAVI. Ideally such a study should focus on those domains where we have already seen some noticeable improvement or trend to change from baseline, since a smaller battery of tests and the resulting reduced time taken may make the study more palatable to those participating (both researchers and subjects). Then moving further on, these tests could be incorporated into further trials of both TAVI and also TAVI versus SAVR. If this is possible, it would be the first time detailed assessments of cognitive function would be made in a group of randomised patients who need aortic valve replacement for severe aortic stenosis. Hopefully this would help us better guide patients needing intervention on their aortic valve as to which treatment is better for them.

7. Future directions

Following on from this body of work, there are several areas which could be addressed further. In particular there is scope for incorporating the cognitive function tests into other larger studies of TAVI and other cardiac procedures. There would also be scope for looking at biomarkers for neuronal injury in future studies and correlating these with the cognitive outcomes. Finally, this work could be used to further assess the benefits of neuroprotective strategies. Each of these possibilities is discussed below.

7.1 Cognitive assessment

There is growing evidence for either no decline or even improvement in cognitive function following TAVI, with several studies now showing this,[60,121,122,148] as well as my data presented here. What is really lacking now, is a comparison with SAVR in a randomised controlled trial (RCT), since all such comparisons have been between groups with different baseline characteristics.[60,122] This would clearly be very important as TAVI is being performed more frequently globally and yet we do not know the cognitive impact compared to surgical AVR. However, the findings here are promising. Our plan was initially to perform such a study in the UK TAVI trial, but unfortunately this was not logistically possible. Hopefully, we will be able to perform such a study in future, in conjunction with another RCT of TAVI versus SAVR, whether industry-sponsored or not.

7.2 Biomarker assessment

Neurological injury following TAVI should result in the release of blood biomarkers due to cell damage, in the same way that troponin is released from cardiac myocytes following myocardial infarction. Only two studies have attempted to look at this to date. One study showed no rise in neuron specific enolase,[56] whereas another study showed a rise in S100B which correlated with HIT count on TCD.[95] The main limiting factor here is that there is no consensus on which biomarker of neurological injury

best characterises the extent of damage. At this point in time, with a lack of consensus in this matter, such a study would not be beneficial. However, it is likely that in future such markers will become available as research into stroke progresses and these could then be used for such a study of TAVI and/or SAVR as well. For now we will have to rely on imaging biomarkers like DW-MRI.

7.3 Embolic protection

There is emerging evidence of the safety of embolic protection devices in TAVI from two studies.[133,149] However, there is limited data on the clinical benefit of these devices. Both these studies have shown a reduction in volume of lesions on DW-MRI, while one study showed a benefit in terms of cognition, which was not shown in the other study. Due to the increased time needed to place these devices, the requirement for operator experience and the cost, it is likely that these devices will only ever be used in select patients. How to choose those patients is yet to be determined and subgroup analyses of future larger studies could be important, in order to select who is particularly likely to benefit. The CANTAB Eclipse system could be useful in such studies, as an easier method for cognitive function assessment than traditional tests, which has the added benefit that they should be cheaper to perform as well.

8. Conclusions

TAVI is a procedure showing exponential growth worldwide for the treatment of symptomatic severe aortic stenosis and in some cases asymptomatic aortic stenosis and even aortic regurgitation. We know that stroke is a frequent, albeit reducing, major complication of this procedure and the most important proposed mechanism which is embolization, may also cause cognitive decline.

In this thesis I have shown several important aspects relating to TAVI, cerebral embolization and cognition. I have shown the frequency of embolization using Transcranial Doppler and the importance of differentiating between solid and gaseous emboli. Next, I have shown using this technique, that TAVI using a balloon-expandable device can be performed safely without prior balloon dilatation of the valve. I have also shown that the degree of aortic valve calcification relates to the extent of cerebral embolization. Finally, I have shown that using the CANTAB Eclipse cognitive function test battery is feasible in this elderly population and there is some preliminary evidence that there is an improvement in cognition following TAVI.

With this information, there is scope to extend this field of research into looking at the effects of neurological damage following TAVI and ways of mitigating this. In the long-term, this information should help us making more informed choices when treating patients with aortic valve disease, particularly when there is a need to choose between transcatheter or surgical aortic valve replacement in older patients.

9. Acknowledgements

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12 Appendix 1: Full cognitive dataset

Name of test	MOT			CRT				PAL		RVP				
Test component	Mean lat	Med lat	Mean error	Mean lat	Med lat	SD correct lat	Percent correct	Total errors	Total errors 6 shapes	A'	Prob hit	False alarms	Mean lat	Med lat
1st test	1139.07	997.36	11.49	425.70	402.65	139.88	98.41	47.76	21.71	0.78	0.29	4.88	684.44	643.03
2nd test	1124.44	881.35	11.62	421.00	406.56	106.79	98.88	48.41	16.53	0.80	0.34	8.71	656.59	656.16
p-value	0.90	0.20	0.89	0.78	0.79	0.18	0.39	0.90	0.02	0.65	0.31	0.23	0.83	0.44

Name of test	VRM				SWM		SST							VRM	
Test component	Free correct	Free novel	Imm corr	Imm false pos	Between errors	Strategy	SSRT	Mean corr	Med corr	Direction err	Prop corr stops	SSD 50%	Del corr	Del false pos
1st test	4.53	0.12	21.29	0.65	27.82	18.88	289.53	806.15	741.62	5.53	0.61	452.09	21.69	1.19
2nd test	5.00	0.06	21.41	0.82	27.00	18.94	271.40	751.83	695.12	5.00	0.54	423.72	21.56	1.94
p-value	0.27	0.58	0.95	0.56	0.72	0.92	0.37	0.14	0.19	0.72	0.11	0.36	0.39	0.09

Table 12.1: Comparison of two pre-TAVI CANTAB test batteries for differences

Name of test	MOT			CRT				PAL		RVP				
Test component	Mean lat	Med lat	Mean error	Mean lat	Med lat	SD correct lat	Percent correct	Total errors	Total errors 6 shapes	A'	Prob hit	False alarms	Mean lat	Med lat
Baseline test	1153.89	896.73	11.01	445.04	431.73	111.74	98.77	47.27	17.55	0.81	0.37	10.23	655.13	629.84
6 week test	968.63	807.14	10.52	433.68	412.20	125.50	98.45	35.77	17.09	0.82	0.38	7.24	632.19	579.57
p-value	0.04	0.10	0.56	0.72	0.56	0.36	0.47	0.03	0.86	0.38	0.96	0.46	0.49	0.21

Name of test	VRM				SWM		SST						VRM	
Test component	Free correct	Free novel	Imm corr	Imm false pos	Between errors	Strategy	SSRT	Mean corr	Med corr	Direction err	Prop corr stops	SSD 50%	Del corr	Del false pos
Baseline test	5.41	0.05	22.55	0.77	26.91	18.82	266.31	783.07	713.68	3.82	0.57	447.37	21.82	1.18
6 week test	5.00	0.38	22.10	0.67	29.76	19.52	233.53	739.12	699.90	4.52	0.57	466.37	21.38	1.05
p-value	0.40	0.02	0.20	0.38	0.16	0.15	0.03	0.11	0.67	0.44	0.83	0.41	0.53	0.61

Table 12.2: Comparison of baseline and 6 week CANTAB test batteries for differences

Name of test	MOT			CRT				PAL		RVP				
Test component	Mean lat	Med lat	Mean error	Mean lat	Med lat	SD correct lat	Percent correct	Total errors	Total errors 6 shapes	A'	Prob hit	False alarms	Mean lat	Med lat
Baseline test	1146.97	897.95	11.01	416.39	405.61	103.96	98.63	51.84	19.21	0.80	0.36	8.84	662.91	627.37
6 month test	904.99	773.11	11.47	401.37	384.79	111.72	98.16	39.05	21.16	0.83	0.41	4.58	609.83	577.74
p-value	0.01	0.00	0.64	0.35	0.17	0.68	0.11	0.01	0.36	0.05	0.33	0.13	0.18	0.21
Name of test	VRM				SWM		SST						VRM	
Test component	Free correct	Free novel	Imm corr	Imm false pos	Between errors	Strategy	SSRT	Mean corr	Med corr	Direction err	Prop corr stops	SSD 50%	Del corr	Del false pos
Baseline test	5.11	0.05	21.32	0.63	28.11	19.05	257.45	702.39	635.63	4.63	0.54	378.18	21.33	1.44
6 month test	4.42	0.11	21.95	0.63	26.47	19.00	220.61	661.45	617.71	3.95	0.56	397.10	20.89	1.39
p-value	0.11	0.33	0.62	1.00	0.50	0.94	0.03	0.22	0.55	0.42	0.44	0.49	0.37	0.90

Table 12.3: Comparison of baseline and 6 month CANTAB test batteries for differences

Name of test	MOT			CRT				PAL		RVP				
Test component	Mean lat	Med lat	Mean error	Mean lat	Med lat	SD correct lat	Percent correct	Total errors	Total errors 6 shapes	A'	Prob hit	False alarms	Mean lat	Med lat
Baseline test	1096.82	840.35	10.96	392.47	379.90	106.56	98.50	49.50	14.30	0.83	0.41	5.30	601.64	580.70
1 year test	914.12	742.55	11.08	392.94	380.17	94.29	98.78	25.40	13.60	0.82	0.45	11.90	719.17	652.65
p-value	0.34	0.12	0.92	0.70	0.77	0.51	0.40	0.01	0.79	0.66	0.50	0.22	0.10	0.37

Name of test	VRM				SWM		SST						VRM	
Test component	Free correct	Free novel	Imm corr	Imm false pos	Between errors	Strategy	SSRT	Mean corr	Med corr	Direction err	Prop corr stops	SSD 50%	Del corr	Del false pos
Baseline test	4.50	0.10	20.80	0.40	22.90	19.50	283.63	741.54	686.65	4.80	0.53	403.02	21.56	1.78
1 year test	5.67	0.33	22.44	0.78	23.89	19.56	218.89	686.70	649.83	3.00	0.53	430.94	21.33	1.89
p-value	0.30	0.35	0.05	0.40	0.64	0.84	0.04	0.19	0.34	0.10	0.89	0.58	0.87	0.92

Table 12.4: Comparison of baseline and 1 year CANTAB test batteries for differences

Name of test	MOT			CRT				PAL		RVP				
Test component	Mean lat	Med lat	Mean error	Mean lat	Med lat	SD correct lat	Percent correct	Total errors	Total errors 6 shapes	A'	Prob hit	False alarms	Mean lat	Med lat
6 week test	1010.64	841.93	10.29	432.22	411.87	125.87	97.93	38.00	17.93	0.83	0.43	9.71	613.00	560.61
6 month test	921.76	759.88	11.64	391.43	374.25	113.62	97.93	42.43	23.93	0.85	0.46	4.21	599.28	578.39
p-value	0.47	0.21	0.10	0.64	0.73	0.93	1.00	0.16	0.01	0.08	0.62	0.23	0.81	0.74

Name of test	VRM				SWM		SST						VRM	
Test component	Free correct	Free novel	Imm corr	Imm false pos	Between errors	Strategy	SSRT	Mean corr	Med corr	Direction err	Prop corr stops	SSD 50%	Del corr	Del false pos
6 week test	5.21	0.36	21.71	0.79	31.64	19.64	214.01	685.24	639.82	6.07	0.58	425.81	21.14	1.57
6 month test	4.50	0.14	22.07	0.71	26.71	18.57	209.04	656.10	618.96	3.93	0.56	409.93	20.64	1.64
p-value	0.17	0.08	0.31	0.78	0.06	0.25	0.70	0.22	0.31	0.06	0.35	0.40	0.29	0.75

Table 12.5: Comparison of 6 week and 6 month CANTAB test batteries for differences