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The Impact Of Transcatheter Aortic Valve Implantation (TAVI) On Cognition: Evaluating The Relationship Between Changes In Cognitive Function, Cerebral Injury, Physical Ability, And Mood

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THE IMPACT OF TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI) ON COGNITION: EVALUATING THE RELATIONSHIP BETWEEN CHANGES IN COGNITIVE FUNCTION, CEREBRAL INJURY, PHYSICAL ABILITY, AND MOOD

by

Jaclyn Reckow
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This dissertation, submitted by Jaclyn Reckow in partial fulfillment of the requirements for the Degree of Doctor of Philosophy from the University of North Dakota, has been read by the Faculty Advisory Committee under whom the work has been done and is hereby approved.

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October 23, 2015

PERMISSION

Title	The effects of transcatheter aortic valve implantation (TAVI) on cognition: Evaluating the relationship between changes in cognitive function, cerebral injury, physical ability, and mood
Department	Psychology
Degree	Doctor of Philosophy

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Jaclyn Reckow
10/23/2015

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ABSTRACT

Aortic stenosis is a cardiovascular disease affecting 2 to 4% of U.S. adults over age 65 years old (Freeman & Otto, 2006). Aortic stenosis causes angina and syncope eventually leading to heart failure and death (Otto, 2006). Transcatheter aortic valve implantation (TAVI) is an alternative to surgical aortic valve replacement in patients with high surgical mortality risk (Kappetein, 2013). The TAVI is associated with increased cerebral injury, with silent ischemia reported in up to 90% of TAVI patients (Samim et al., 2015). The present study examines the relationship between cerebral injury, cognitive changes, and quality of life in TAVI patients.

Participants ($n = 40$) completed a cognitive assessment one day before the TAVI and at one-month post-TAVI. The primary cognitive measure was the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Additional tests (letter fluency, Trail Making Test, Digit Span Backward and Stroop) were included as measures of executive function and working memory. Measures of functional ability (Physical Self-Maintenance Questionnaire, Functional Activities Questionnaire, Dementia Severity Rating Scale), mood (GDS), and quality of life (Kansas City Cardiomyopathy Questionnaire) were also included. Baseline and follow-up MRIs were completed for 22 participants. Baseline RBANS Total Index scores ($M = 85.26$, $SD = 14.69$) evidenced mild cognitive decline prior to the TAVI. At one month, there was significant improvement on RBANS Language Index ($p = 0.014$), RBANS Fluency ($p = 0.023$), RBANS Figure Recall ($p = 0.027$), GDS ($p = 0.018$), and KCCQ ($p < 0.001$). There was a significant decline on RBANS List Recall (*p* = 0.001). Six participants (27%) obtained new cerebral lesions at one month. Participants with neuronal injury did not differ from those without at one month (RBANS Total Score, *p* = 0.45).

TAVI is related to overall stable cognitive performance and improved quality of life. The relationship between cerebral ischemia following TAVI and negative cognitive consequences is not supported. Further research is required in the cognitive implications following TAVI.

CHAPTER I

INTRODUCTION

Cardiovascular Disease and Cognition

The relationship between cardiovascular disease and cognitive function is well established in previous literature (Katzel & Waldstein, 2001). Cardiovascular disease (CVD) is a broad term encompassing diseases of the heart, blood vessels, and circulation (Katzel & Waldstein, 2001). CVD accounts for the most deaths in the United States per year than any other cause. Stroke, often resulting from CVD, is the third highest cause of death in the United States (Katzel & Waldstein, 2001).

CVD is related to cognitive decline in older adults (Katzel & Waldstein, 2001). For example, hypertension, a predecessor to more serious CVDs, has been shown to negatively affect cognitive function. Hypertension (i.e., systolic blood pressure ≥140 millimeters of mercury (mmHg) and/or diastolic blood pressure ≥90 mmHg) is a risk factor for coronary artery disease, and atherogenesis (i.e., the deposit of plaque particularly on the inner arterial wall) (Waldstein & Katzel, 2001). Longitudinal studies have found that long-term hypertension is related to poorer performance on attention and memory tasks in older adults, and hypertension predicts decline on Wechsler Adult Intelligence Scale visuospatial subtests (Picture Completion, Picture Arrangement, Block

Design, and Object Assembly) and speed subtests (Digit Symbol Substitution) (Elias Robbins, Elias, & Streeten, 1998). Additional longitudinal studies show that midlife hypertension predicted decline on tests of mental status and cognitive flexibility (Waldstein & Katzel, 2001). The relationship between CVD and cognitive decline may also have bidirectional negative consequences. Cognitive decline is a predictor of all cause mortality after hospitalization in adults greater than 70 years old with cardiovascular disease (Farid et al., 2013).

Atherosclerosis is arterial narrowing caused by the accumulation of fatty deposits and fibrous tissue in the vessel wall (Everson, Helkala, Kaplan, & Salonen, 2001). Fibrous plaques may become calcified, which decreases vessel flexibility and increases frailty. Severe complications as a result of atherosclerosis include stroke, ischemia (i.e., areas of restricted blood flow), and heart attack. Carotid atherosclerosis has been shown to result in poorer cognitive functioning in global cognition, nonverbal memory, cognitive flexibility, verbal fluency, and verbal memory (Everson, Helkala, Kaplan, & Salonen, 2001).

Hypoperfusion–lack of adequate blood flow and oxygen to the brain–is often cited as the causal link between CVD and decreased cognitive abilities (Jefferson, Poppas, Paul, & Cohen, 2007). Jefferson and colleagues (2007) examined the relationship between neuropsychological functioning and cardiac output. Seventy-two participants (mean age = 69.14) completed a neuropsychological battery and an echocardiogram. Data from the echocardiogram was used to estimate cardiac output, which is the amount of blood pumped from the heart to the systemic vascular system per minute (Jefferson et al., 2007). When the participants were grouped based on cardiac output (low versus normal), the low cardiac output group performed worse on executive measures (DKEFS Tower Test and DKEFS Trail Making Test) (Jefferson et al., 2007). Increased cerebral perfusion following stenting in the carotid artery significantly predicts cognitive improvement based on the informant behavioral observations in the Informant Questionnaire on the Cognitive Decline in the Elderly (IQ-CODE; Moftakhar, Turk, Niemann, et al., 2005). The IQ-CODE has been shown to correlate with Mini-Mental State examination and episodic memory (Moftakhar et al., 2005).

Cardiovascular Disease Treatment and Cognition

In addition to CVD alone, treatment of CVD may have cognitive implications. Coronary artery bypass grafting (CABG) is a surgical procedure to treat coronary artery disease (CAD), which is caused by progressive narrowing to eventual occlusion in the coronary arteries by artherosclerotic plaque (Newman, Stygall, & Kong, 2001). Studies have found neuropsychological deficits following CABG in the following cognitive domains: memory, attention, visuospatial, language, visuomotor, executive function, and global functioning (Newman, Stygall & Kong, 2001). Cognitive changes following CABG are often inconsistent with each study showing decline in different cognitive domains, and these discrepancies are likely due to differing methodologies. Studies with post testing evaluations within days following the surgery may be measuring confounding factors such as postoperative recovery from anesthesia and surgery (Newman, Stygall & Kong, 2001). Mahanna et al. (1996) assessed cognitive functioning in 232 coronary artery bypass patients 6 days post-surgery and found decline (i.e., a decrease of 20% from baseline on at least 20% of the measures) in 66% of patients. In the same study, 34% continued to show cognitive impairment at 6 weeks and 19.4%

continued at the 6-month follow-up. Studies with postoperative evaluations weeks or months following the procedure measure more stable neuropsychological decline. For example, Sellman, Holm, Ivert, and Semb (1993) assessed cognitive functioning 4 weeks post-surgery in 54 coronary artery bypass surgery patients, and the researchers found cognitive decline in 17% of the patients. In the same study, cognitive decline was stable for 7% of the patients at a 6-month follow-up. Even with similar methodologies and testing intervals, results are still variable in studies examining neuropsychological functioning after cardiac surgery. However, research indicates that risk factors for postoperative decline following CABG include increased age, female gender, and increased severity of cardiac disease (Newman, Stygall, & Kong, 2001).

TAVI Procedure and Cerebral Injury

One type of CVD in the older adult population is aortic stenosis. Aortic stenosis is narrowing of the aortic valve, which is located between the heart's left ventricle and the aorta, and may result in backed up blood flow and increased pressure in the heart (Otto, 2006). Aortic stenosis results from a disease process of lipid accumulation, inflammation, and calcification (Otto, 2006). Aortic sclerosis (i.e., thickening and hardening of the aortic valve and precursor to stenosis) is found in approximately 2% of people age 65-74 years and approximately 48% in people over 84 years old (Freeman & Otto, 2005). The risk of developing aortic stenosis increases with age with 2-4% of adults over the age of 65 meeting diagnostic criteria (Freeman & Otto, 2005). The disease ranges in severity, but those with severe symptomatic aortic stenosis experience angina (i.e., chest pain), syncope (i.e., fainting resulting from a fall in blood pressure), and heart failure (Otto, 2006). Aortic stenosis is typically treated through surgical aortic valve replacement (open heart surgery).

Transcatheter aortic valve implantation (TAVI) is a recently-developed procedure to treat high-grade aortic stenosis in patients with risk factors that preclude the patients from conventional aortic valve replacement (AVR) surgery. To qualify for TAVI, patients must be denied surgical aortic valve replacement by two independent surgeons based on mortality risk (Kappetein et al., 2013). The European System for Cardiac Operative Risk Evaluation (EuroSCORE) and/or The Society for Thoracic Surgeons' risk score (STS score) are used as assessments to evaluate patient mortality risk prior to the procedure. The EuroSCORE includes patient factors (e.g., age, sex, history of chronic pulmonary diseases, etc.), cardiac factors (e.g., unstable angina, recent myocardial infarct, etc), and operation factors (e.g., level of emergency, additional cardiac procedures performed in conjunction, etc.). A high mortality risk as assessed by the EuroSCORE and other risk factors including liver disease, frailty, and severe pulmonary hypertension (Kappetein et al., 2013) are combined with the cardiac surgeon's clinical judgment to decide the patient's candidacy for surgical AVR. The STS score contains multiple risk factors including, but not limited to morbid obesity, prior cardiac conditions, medical conditions (e.g., diabetes, chronic pulmonary obstructive disease, etc.), and type of procedure to predict mortality (Collas, Chong, Rodrigus, Vandewoude, & Bosmans, 2015). Predicting mortality for TAVI patients is difficult, and the STS-score is slightly more accurate in predicting two year mortality in high-risk patients than the EuroSCORE (Collas et al., 2015).

TAVI clinical trials have shown promising results in long-term success with patients (Ussia, Barbanti, Petronio, et al., 2012; Toggweiler et al., 2013). However, compared to AVR, TAVI is associated with higher rates of clinically significant stroke (i.e., cerebral injury that results in overt changes in neurological function) (Hauville, Ben-Dor, Lindsay, Pichard, & Waksman, 2012). Studies examining neurological injury following cardiac procedures show clinically significant stroke following AVR ranges from 0.7% to 5% while stroke following the TAVI procedure ranges from 0% to 10% (Hauville et al., 2012).

Neurological injury (i.e., any number of central nervous system (CNS) injuries, including encephalopathy, stroke, coma, delirium, and neurocognitive decline) is a common concern following any cardiac surgery, particularly in older adults with comorbid risk factors (Newman et al., 2006). TAVI candidates are typically older adults with multiple risk factors, which resulted in their ineligibility for AVR. Even mild CNS injury following cardiac surgery relates to decreased quality of life and cognitive abilities (Newman et al., 2001), and it is associated with increased medical costs (Roach et al., 1996). Previous research identifies a number of risk factors associated with increased major stroke, higher rates of major cardiac or cerebral events, and mortality in TAVI patients. See Table 1 for a list of medical variables that previous studies have associated with CNS injury and cardiac surgery/TAVI.

The increased neurologic injury from TAVI has been associated with increased emboli from the procedure (Arnold et al., 2010). Emboli may include air bubbles, fatty deposits, blood clots, or another object that causes blood flow obstruction. In addition to clinically significant stroke (see above), TAVI may have increased rates of clinically

Table 1.

Medical variables and associated risks for neurological injury or death

Variable	Associated Risk	Reference
Age Unstable angina Diabetes (type I or II and insulin use) History of neurological disease Previous coronary artery bypass surgery History of vascular disease, history of Pulmonary disease	Stroke following cardiac surgery	Newman et al. 2006
Atrial Fibrillation	Stroke and Transient Ischemic Attacks following cardiac surgery	Creswell, 1999
Cerebrovascular disease History of coronary artery disease Higher transvalvular aortic gradient Gender (male) Hyperlipidemia Renal dysfunction Porcelain aorta Increased left atrial appendage velocity Lower aortic atheroma thickness Reduced aortic valve area	Silent Ischemia following TAVI	Kahlert et al., 2010 Rodes-Cabau et al., 2011 Tay et al., 2011
Increased creatine levels Higher EuroSCORE	Mortality following TAVI	Codner et al., 2013
Left ventricular function (ejection fraction <30%) Moderate/severe aortic regurgitation History of COPD	Mortality following TAVI	Moat et al., 2011

silent cerebral injury. Cerebral injuries that occur in the absence of specific neurological dysfunction are considered clinically silent; clinically-silent cerebral injuries are only detected through neuroimaging (Hauville et al, 2012). Neuroimaging techniques identify areas of restricted blood flow known as ischemia. Persistent ischemia may lead to infarcts, which are permanent areas of dead tissue in the brain. Both ischemia and infarcts can be clinically-apparent and clinically-silent cerebral injuries depending on the location of the lesion.

Diffusion-weighted magnetic resonance imaging (DW-MRI) is an imaging technique that is more sensitive to detecting ischemia than the standard MRI (Hauville et al, 2012). The relationship between detected ischemia and true neuronal damage is unclear (Bendszus & Stoll, 2006). Some studies have shown initial ischemic lesions persisted to structural damage at later testing times while other studies have shown lesions on DW-MRI cease without neuronal damage due to resolution of the restricted blood flow. The discrepancies in results are likely due to different times the imaging was completed. Overall, ischemia on DW-MRI that is present more than 24 hours after the initial event are indicative of cerebral infarction (i.e., tissue death due to obstructed blood supply) (Bendszus & Stoll, 2006).

Cerebral Ischemia and Cognitive Function

Studies examining the relationship between silent cerebral ischemia and cognitive functioning have shown small or no effects (Bendszus & Stoll, 2006). Many studies only include measures of global cognitive function (i.e., Mini-Mental State Examination) as measurements of cognitive deficit and more nuanced changes in cognitive areas such as processing speed and mood may be missed (Bendszus & Stoll, 2006).

Studies including more comprehensive cognitive measures show mixed results for effects of lesions detected on DW-MRI. Knipp et al. (2005) administered a neuropsychological battery assessing seven cognitive domains to 39 coronary artery bypass graft surgery patients at baseline, at discharge, and at a three-month follow-up. At discharge, patients exhibited cognitive decline in all domains compared to pretest performance. At the 3 month follow-up cognitive function was regained in all domains, except immediate recall during a verbal learning task, which remained significantly below baseline. Twenty patients (51%) evidenced new ischemic lesions following the procedure. Those with ischemia were no more likely to have persistent cognitive decline at the 3-month follow-up than patients without new lesions (*n* = 19). The ischemic injury did not account for the cognitive decline in the study's sample.

Conversely, Restrepo et al. (2002) found that patients with new lesions on DW-MRI had significantly larger declines on neuropsychological tests of psychomotor speed, language, and visuospatial abilities than patients without new lesions. Restrepo et al. (2002) used pre and post-neuroimaging and cognitive assessment in patients undergoing coronary artery bypass grafting surgery. The cognitive assessment was completed within a week prior to the procedure and within a week after the procedure. The assessment included trail making test B (processing speed), oral and written naming tests, oral reading tests (language), line cancellation, and Bells tests (visuospatial). Thirteen patients completed both the pre and postoperative assessments. Ten patients experienced cognitive decline in at least one test (7 demonstrated decline on one test, 2 patients showed decline in >1 test, and 1 patient showed decline on 5 tests). Four patients showed new diffusion lesions in the postoperative neuroimages, and patients with new lesions on DW-MRI had greater decline (i.e., larger *z*-score change) between pre and postoperative cognitive assessments than patients without new lesions (Restrepo et al., 2002). In comparison to Knipp et al. (2005), the time of post-procedural cognitive evaluations may explain the discrepancy in results. Restrepo et al. (2002) completed the follow-up cognitive evaluation within one week following the procedure while Knipp et al. (2005) had a 3-month follow-up examination. Ischemic lesions may relate to cognitive decline shortly following the cardiac procedure (as found in Restrepo et al., 2002), but the cognitive impact of ischemic lesions could be reduced over time (as found in Knipp et al., 2005). Additionally, surgical effects such as recovery from anesthesia may confound cognitive testing within days following a surgical procedure (Newman, Stygall & Kong, 2001). Ischemic lesions are only one factor to consider when examining cognitive performance following a cardiac procedure.

In patients undergoing a coronary artery bypass grafting (CABG) with on-pump procedure (i.e., a heart-lung artificial circulation system is used and the heart is stopped), ischemic lesions were associated with cognitive dysfunction (Lund et al., 2005). However, ischemic changes were not associated with cognitive decline in patients undergoing the procedure off-pump (i.e., the heart continues beating) (Lund et al., 2005). One hundred six patients were given a neuropsychological evaluation preoperatively, at a 3-month follow-up, and at a 1-year follow-up. Patients were given 10 tests measuring six cognitive domains: Grooved pegboard (motor coordination), Digit Symbol, Trail Making Test (psychomotor speed), Digit Span, Stroop Color-Word Interference Test (attention), Rey Auditory Verbal Learning, Rey Auditory Verbal Learning Recall (verbal memory), Similarities, Controlled Oral Word Association Test (verbal comprehension and fluency), Block Design (visuoconstructive abilities). Eleven of the 54 off-pump patients and 12 of 52 on-pump patients demonstrated cognitive decline at 3 months (Lund et al., 2005). After one year, 13 of the 54 off-pump and 12 of the 52 on-pump patients had continued cognitive impairment. Neuroimaging revealed new ischemic lesions in 13 (12.5%; 9 on-pump; 4 off-pump) of the patients. New ischemic changes were not associated with cognitive decline in either group, but preoperative MRI classification (i.e., normal, borderline, pathologic) was significantly correlated with cognitive decline for the on-pump patients. Preoperative MRI classifications were normal when no cerebral lesions were present, borderline when cerebral lesions were < 5mm, and pathologic when cerebral lesions were >5mm. No patients with normal preoperative MRI had cognitive impairment at 3 months. Twenty percent of patients with borderline preoperative MRI and 27.1% with pathologic preoperative MRI had cognitive decline at 3 months (Lund et al., 2005). The authors state that prior cerebral lesions may result in fewer cognitive resources and a greater susceptibility to negative consequences from ischemia occurring from the procedure.

In another study using coronary artery bypass grafting (CABG) patients, new ischemic lesions were not associated with postoperative cognitive decline (Bendszus et al., 2002). Bendszus and colleagues (2002) administered the d2-letter cancellation test (sustained attention and concentration), Benton Visual retention test (visual short-term memory and visuomotor), Reitan trail-making test A (attention, psychomotor tracking speed, and motor coordination) at 2 days pre-procedure and 3, 6, and 9 days post-surgery. Nine of 35 patients (26%) exhibited new ischemic lesions following CABG. Patients with prior diffuse white matter changes noted in the preprocedural MRI were more likely to experience new ischemic lesions. There was no relationship between new lesions and neuropsychological test performance at the 3-day follow-up (Bendszus et al., 2002). Instead of new ischemic lesions, overall neuronal loss (combined pre- and post-CABG neuronal damage) may account for cognitive changes. The researchers used the biomarker *N-Acetylaspartate* to indirectly measure neuronal injury. *N-Acetylaspartate* is found exclusively in neuronal tissue, and decreased levels are associated with neuronal loss or impaired functioning in neurons. The authors found decreased *N-Acetylaspartate-creatine* ratios were associated with decreased performance on the letter cancellation test, Reitan Trail Making A, and Benton visual retention tasks 3 days postprecedure (Bendszus et al., 2002). When the *N-Acetylaspartate-creatine* levels returned to baseline 10-14 days postoperatively, neuropsychological functioning also returned to baseline.

TAVI, Cerebral Injury, and Cognition

Understanding the cognitive impact of silent ischemia is an important aspect in the TAVI procedure as TAVI patients have a high occurrence of ischemia. DW-MRI studies have found silent ischemic changes in 68% to 90% of TAVI patients, but many studies have not extensively examined cognitive sequelae from these ischemic changes (Rodes-Cabau, Dumont, Boone et al., 2011; Kahlert et al., 2010; Samim et al., 2015). Compared to the standard surgical AVR, the TAVI procedure is associated with higher occurrence of lesions detected by DW-MRI. The observed DW-MRI lesion rate for surgical AVR ranges from 38% to 47% (Spaziano et al., 2014).

Rodes-Cabau and colleagues (2011) examined the difference in cerebral injury in patients following transapical (TA) TAVI (*n* = 31) and transfemoral (TF) TAVI (*n* = 29) procedures. TA-TAVI and TF-TAVI differ in the artery routes taken to access the aortic valve. TF-TAVI is a more commonly used TAVI approach, in which a valve-containing catheter is advanced through the femoral artery and through the aortic arch. The TA-TAVI procedure is used for patients with calcified, diseased, or too small arteries, and consists of avoiding the aortic arch by advancing the catheter through the ventricular apex located at the bottom of the ventricle, inferior to the aortic valve.

DW-MRIs were obtained within 24 hours prior to the TAVI procedure and within 6 days following the procedure (Rodes-Cabau et al., 2011). Sixty patients completed the Mini-Mental State Examination (MMSE) and the National Institutes of Health Stroke Scale (NIHSS). The MMSE is a brief global cognitive function screening that measures several cognitive areas: orientation to place and time, memory registration, attention, memory recall, language, complex commands, and visuospatial ability (Folstein, Folstein, & McHugh, 1975). The NIHSS is a 15-item scale measuring neurological functioning including vision, gaze, level of consciousness, language, sensory loss, dysarthria, facial palsy, extreme weakness, and ataxia (Brott et al., 1989). Pre-procedural DW-MRI results indicated that prior to the procedure, no previous acute ischemic lesions were found, and old silent ischemic lesions were found in 53% of the patients (Rodes-Cabau et al., 2011). Post-procedure imaging results revealed 68% of patients had new ischemic lesions, and most patients with new lesions had multiple lesions sites. The new lesions occurred in both hemispheres (73%) and in anterior and posterior vascular territories (66%). There were no differences between the TA and TF in number or location of new ischemic lesions. New lesions were found more frequently in patients that had a history of coronary artery disease, that exhibited a higher transvalvular aortic gradient (pressure gradient surrounding the aortic valve), and that were male. There were no significant differences in neurological function as assessed by the NIHSS between pre- and post-procedure evaluations for both patients with ischemic lesions and those without. No significant differences were found in cognitive function at baseline (MMSE median = 28, range 16-30) compared to after the procedure (MMSE median = 28, range 17-30, *p* = 0.14). No differences in cognitive function were found between patients without new lesions compared to those with new lesions (*p* = 0.90) (Rodes-Cabau et al., 2011).

Compared to Rodes-Cabau et al. (2011) who found 68% of TAVI patients had new ischemic diffusions on DW-MRI, Kahlert et al. (2010) found 86% of TAVI patients had new ischemic lesions. Kahlert and colleagues (2010) compared imaging and neurological function of patients undergoing a transfemoral TAVI procedure to surgical aortic valve replacement. Neurological function was evaluated using the NIHSS, and cognitive function was assessed with the MMSE at baseline and post-procedure (2.5 to 4.4 days). No statistically significance differences were found between baseline MMSE (*M* = 28.4, *range* = 27.4 to 29.3) and post-procedure MMSE (*M* = 28.2, *range* = 27.3 to 29.1). No significant changes occurred in NIHSS scores between pre and postoperative measurements. Restricted diffusions were found in 86% (19 of 22) of TAVI patients and 80% of surgical aortic valve replacement (8 of 10) patients. A three-month follow-up DW-MRI showed no new restricted diffusion foci beyond lesions initially detected at the postoperative evaluation. Additionally, at the three-month follow-up, NIHSS and MMSE scores remained similar to baseline. Patient risk factors for new foci included hyperlipidemia, renal dysfunction, porcelain aorta, increased left atrial appendage velocity, lower aortic atheroma thickness, and reduced aortic valve area at baseline (Kahlert et al., 2010).

Arnold and colleagues (2010) examined silent ischemia following TA-TAVI procedures. Twenty-five patients completed the pre (6±12 days before) and post procedural (6±2 days after) MRI examinations. Seventeen (68%) of the patients showed new focal diffusion abnormalities. Five of the 17 with new lesions exhibited neurological changes caused by new lesions (Arnold et al., 2010). Neurological changes included reduced awareness (one patient), transitive diplopia (one patient), and transitive psychosis (three patients) (Arnold et al., 2010). Cognitive function was not assessed in the study. In a more recent study, ischemic lesions were found in 90% of patients five days post-TAVI (Samim et al., 2015). Significant predictors for new ischemia were age, hyperlipdemia, and dilation of the implant. Samim and colleagues (2015) did not examine cognitive changes.

Another study found few negative neurological effects immediately following and at a long-term follow-up after a TF-TAVI procedure (Ghanem et al., 2010). Patients completed pre and two post-procedural DW-MRI examinations. The second examination occurred 2.2 ± 0.4, and the third examination occurred 91 ± 5 days after the TAVI procedure. Sixteen patients (72.7%) showed new ischemic lesions, of which, only three patients had ischemia at the second examination that persisted to focal infracted brain tissue at the third examination. Only one patient had persistent neurological deficits at the third examination (NIHSS = 16). Two patients exhibited neurological deficits at the second examination, but not the third examination. These transient neurological symptoms were not correlated with DW-MRI lesions (Ghanem et al., 2010).

The above research indicates that silent ischemia from the TAVI procedure may not have a negative impact on neurological function (i.e., as assessed by the NIHSS) and global cognitive function (i.e., as assessed by the MMSE). Overall, the majority of TAVI patients experience embolic ischemia following the procedure; however, follow-up imaging has shown many lesions resolve (Ghanem, et al, 2010). To date, few studies have used more comprehensive cognitive measures in TAVI patients than the studies reported above.

Knipp et al. (2013) compared postoperative cognitive function after surgical aortic valve replacement (AVR) or transapical aortic valve implantation (TA-TAVI). Comparisons between AVR and TAVI are appropriate because TAVI is a nonstandard procedure used instead of AVR. However, direct comparison between the groups is inherently flawed as the TAVI patients are typically older and have a higher mortality risk than AVR patients. Knipp and colleagues, administered different cognitive batteries to the AVR and TAVI groups, and only a comparison of general pre to post test patterns can be noted. TAVI participants completed the MMSE as a measure of global cognitive function, and the researchers gave measures of verbal short-term memory, verbal working memory, verbal learning and delayed recognition, and verbal fluency at baseline (5.4 ± 8.1 days before the procedure), post-operative (10.7 ± 4.9 days after the intervention), and 3-month (115.6 ± 49.7 days after the intervention) follow-up examinations (Knipp et al., 2013). Patients in the TA-TAVI group were significantly older and had higher estimated operative risks than the AVR group. In the TA-TAVI group (*n* = 27), no significant cognitive changes were found between baseline and post-operative examinations. There was a significant increase ($p < .05$) in MMSE scores and digit span backward scores in the TA-TAVI group between the post-operative and 3-month follow-up evaluations. In the AVR group (*n* = 37), several cognitive domains (rate of information processing, cognitive flexibility, attention, delayed recognition, verbal working memory, visual short-term memory, and logical thinking) showed a significant decline in performance ($p <.05$) between pre-operative and post-operative (10.7 ± 4.9

days after) examinations. All domains with initial decline postoperatively returned to baseline at 3-month follow-up with the exception of cognitive flexibility and logical reasoning. Cognitive flexibility and logical reasoning significantly improved from baseline to the 3-month follow-up ($p < .05$) (Knipp et al., 2013).

Fifty-eight percent of the TA-TAVI patients and 34% of the AVR group evidenced new ischemic lesions on neuroimaging (Knipp et al, 2012). In both the TA-TAVI and the AVR groups, new ischemia was not indicative of cognitive dysfunction ($p = 0.66$). These results support previous studies, in which cognitive function in the AVR group shows decline at the postoperative evaluation, but overall regain of cognitive function with some improvement at the 3-month follow-up. Unlike the AVR group, the TA-TAVI group failed to show any significant decline on cognitive measures. The TA-TAVI group had a significant improvement in global cognitive function (MMSE) and verbal working memory (Digit span backward) between the postoperative and follow-up evaluations; however, the 3 month performance was not significantly different from baseline.

Ghanem et al. (2013) had 111 TAVI patients complete cognitive testing (RBANS) before the procedure, 3 days post, 3 months post, 1 year post, and 2 years post-TAVI. Ghanem and colleagues (2013) also had 56 participants complete MRI protocol pre and 3 days post TAVI. Thirty participants (53.5%) evidenced new embolic events three days following the TAVI. Participants with new embolic events did not differ from those without embolic events in their cognitive trajectories. Despite new embolic injury, cognitive performance remained relatively stable. Ghanem and colleagues examined variables to predict postoperative cognitive decline (POCD), as defined as a significant decrease in RBANS standard score following the TAVI. Ghanem and colleagues (2013) had only 6 participants show decline. T-tests of variables between those without POCD (*n* = 105) and those with POCD (*n* = 6) revealed terminal renal failure requiring hemodialysis and procedure length were significantly different between the groups. Procedure length is used as an indirect measure of the operation complexity (Ghanem et al., 2013).

Participants had an overall improvement in RBANS total score at the 3 days and 2-year follow-up compared to baseline (Ghanem et al., 2013). The researchers did not discuss the transient improvement at 3 days or later improvement at the 2-year follow-up, because the improvements were stated as not clinically significant. Significant improvements were also found on the RBANS Immediate Memory subtest at 3 days post-TAVI and on the RBANS Language subtest at 3 months. A significant decline was observed on the RBANS Visuospatial/Constructional subtest at one year. The RBANS subtest significant changes were transient and the scores remained or returned to baseline at all other follow-ups (Ghanem et al., 2013). Within the 111 participants, the researchers found a subset (*n* =30, 27%) that met criteria for Mild Cognitive Impairment (MCI; as defined as >1.5 SD below expected score on their preprocedural RBANS; Ghanem et al, 2013). The cognitive trajectory of participants with MCI did not differ from those without MCI, and participants with MCI even showed transient improvement in cognition (Ghanem et al., 2013).

Alassar et al. (2015) compared microembolism and cognitive performance in TAVI to surgical AVR. Eighty-five TAVI and 42 surgical AVR patients completed DW-MRI at baseline, 6 days, and 3 months postprocedure. Participants also completed a neurocognitive assessment at baseline and at the 3-month follow-up. The neurocognitive assessment consisted of the following measures: Memory score (complex figure test, auditory verbal learning test), Executive functioning score (trail making test A and B, verbal fluency test), Processing speed (symbol digit replacement, letter cancellation test, grooved pegboard test), and Overall cognitive score (an average of the above measures). The TAVI participants had significantly lower scores on the Memory index than AVR participants at baseline with no other significant differences between the groups. At the 3-month follow-up (TAVI *n* = 71, AVR *n* = 36), overall cognitive function significantly improved in both the TAVI and AVR groups, and the change was significantly larger for the AVR group than the TAVI group (Alassar et al., 2015). The AVR improved significantly more in the memory scale than the TAVI participants (Alassar et al., 2015). Using DW-MRI, new cerebral lesions were found in 76% of TAVI and 72% of AVR patients at the 6-day follow-up (Alassar et al., 2015). Sixty-three percent (37 of 59) of the TAVI patients had lesions remain visible at 3 months (Alassar et al., 2015). The authors report that there was no association between cerebral lesions and cognitive performance.

The present study will include a more comprehensive neuropsychological evaluation than many previous TAVI studies. Included in the evaluation are cognitive measures that are more sensitive to cognitive changes in older adults (e.g., Repeatable Battery for the Assessment of Neuropsychological Status) and will contain additional measures of cognitive domains that are affected by cardiovascular disease (e.g., processing speed and mental control (Saxton et al., 2000)). The present study will also assess depressive symptoms, which previous cognitive TAVI studies have not addressed. Daily functioning measures (i.e., activities of daily living) were also included in the present study to examine how cognitive changes, mood, and TAVI procedure relate to the patients' ability to function.

TAVI and Quality of Life

Activities of Daily Living

Functionality is divided into two areas: basic activities of daily living (BADL) and instrumental activities of daily living (IADL). BADLs include every day self-care activities such as eating, hygiene, dressing, and toileting. IADLs are tasks that allow more independent living, such as medication management, money management, housework, use of communication, and use of transportation. Cognitive deficit prior to cardiac surgery (valve replacement, CABG or combined) predicts changes in IADLs three months after the procedure (Messerotti Benvenuti, Patron, Zanatta, Polesel, Palomba, 2014). Preoperative cognitive status was also a stronger predictor of decline in IADLs at three months than postoperative cognitive decline (Messerotti Benvenuti et al., 2014). Previous studies have indicated that BADL level, frailty, and physical mobility significantly predicted all-cause mortality and major adverse cardiovascular and cerebral events in patients following the TAVI procedure (Stortecky et al., 2012). Patients with reduced BADL may have reduced adaptive capacities and fewer physiological reserves to recover from the TAVI procedure.

Quality of Life

Neurological injury following cardiac surgery potentially decreases quality of life (Newman, Grocott, Mathew et al., 2001). Quality of life (QOL) assessments often include multiple measures of activity level, mood, perceived social support, working status, social functioning, and health status. Level of activity measurements include assessment of ADLs (i.e., personal care, ambulation, and household tasks) as well as general activity level (Newman, Grocott, Mathew et al., 2001). Although often only a component of the QOL assessment, significant changes in ADL can likely greatly influence a person's quality of life.

Fairbairn et al. (2012) examined health-related quality of life (HLQOL) of 102 patients undergoing the TAVI procedure. The patients completed the Social Functioning 12v2 health outcomes questionnaire and the Euro Quality of Life (EQ-5D) questionnaire at baseline, 30 days, 6 months, and 1 year. The EQ-5D measures five dimensions of quality of life: mobility, self-care, pain/discomfort, usual activities, and mood (anxiety/depression). The patients demonstrated an increase in quality of life from baseline to 30 days and to 6 months. A nonsignificant drop in HLQOL occurred from 6 months to 1 year. Predictors of increases in QOL were male gender and the surgeon's experience with the TAVI procedure. The operator experience was an independent predictor of QOL over complications and procedural factors (e.g., transfusion or aortic regurgitation) (Fairburn et al., 2012).

Mood

Depressive symptoms, a component often assessed in QOL, also have important cardiovascular and cognitive implications. Depression increases risk of cardiovascular disease and increases mortality of patients with cardiovascular disease (Lett et al., 2004). Depression also increases risk of stroke (Pan, Sun, Okereke, Rexrode, & Hu, 2011). Cardiovascular disease and cerebral injury can contribute to developing late-life onset depression (Taylor, Aizenstein, & Alexopoulos, 2013).

Self-reported high levels of mood symptoms have also been shown to negatively affect neuropsychological testing following cardiac surgery (Andrew, Baker, Kneebone, & Knight, 2000). Patients undergoing cardiac surgery (*n* = 147) were given a neuropsychological evaluation preoperatively (the day before the procedure) and at discharge (*mean* = 6.5 days) (Andrew et al., 2000). The neuropsychological evaluation included the California Verbal Learning Test (CVLT), Purdue pegboard, Controlled Oral Word Association Test letter fluency, Trail Making Test (TMT) A and B, Wechsler Adult Intelligence Scale - Revised: Digit Symbol subtest, Boston Naming Test, National Adults Reading Test- Revised. Mood symptoms were measured using the Depression Anxiety Stress Scales (DASS). The DASS is a 14 item self-report measure that requires the participant to indicate both severity and frequency of anxious and depressive symptoms. Twenty percent of the patients indicated symptoms of depression following the surgery, of which the majority indicated depression prior to the surgery, as well. Reported anxiety and stress on the DASS was a significant predictor of postoperative mood. Pre and postoperative depression and anxiety significantly predicted deficits on TMT A, CVLT total recall, and CVLT recognition discrimination (cognitive areas of attention and verbal memory). Preoperative mood failed to predict preoperative neuropsychological tests. Although postoperative mood symptoms were significant predictors of neuropsychological deficit on several tests, these relationships were diminished to nonsignificant when preoperative mood symptoms were used as a covariate (Andrew et al, 2000). The above study demonstrates a complex relationship between mood symptoms and neuropsychological measures in cardiac surgery patients. The addition of mood measures in the present study may help identify factors influencing cognition in TAVI patients.

Frailty

Frailty will also be addressed in the present study. Frailty exhibited in the geriatric population is defined as being "characterized by an increased vulnerability to stressors, leading to increased risk of negative health-related events (including falls, disability, hospitalizations, and mortality)" (Houles et al., 2012). Frailty does not have a standardized measure, and studies often use differing criteria to establish frailty (Houles et al, 2012). Physical frailty and cognitive impairment often co-occur (Yassuda et al., 2012), and physical frailty with cognitive impairment is predictive of future disability (Ávila-Funes et al., 2011). Frailty, when assessed combining independence in ADLs, gait speed, grip strength, and serum albumin, is a significant predictor of mortality rates at one year in TAVI patients (Green et al., 2012). Frailty status was not related to TAVI procedural complications immediately following the procedure (Green et al., 2012). Gait speed alone also indicates frailty. Slowed gait speed, defined as walking 5 meters in ≥6 seconds, is an independent predictor of mortality and major morbidity (e.g. stroke, renal failure, etc) in older adults following cardiac surgery (Alfiano et al., 2010).

The Kansas City Cardiomyopathy Questionnaire (KCCQ) (Green, Porter, Bresnahan, & Spertus, 2000) is a 23-item, self-report assessment that measures symptoms (frequency and severity), physical function, self-efficacy and knowledge, social function, and quality of life in patients with heart failure (Green et al., 2000). The KCCQ is valid measure of symptoms and quality of life in patients with aortic stenosis (Arnold et al., 2013). The KCCQ demonstrated adequate reliability and the domains of the KCCQ showed positive correlations with relevant reference measures (Arnold et al., 2013). TAVI patients score significantly higher on the KCCQ overall summary score at one month compared to baseline (*p*<.001, *d* = 0.94; Arnold et al., 2013).

Present Study

The present study will further our understanding of cognitive changes following the TAVI procedure. TAVI is associated with an increased risk of silent ischemic injury (Arnold et al., 2010; Ghanem et al., 2010; Kahlert et al, 2010; Rodes-Cabau et al., 2011). Despite the risk of cerebral injury, many studies have failed to assess cognition or only examined cognitive function through a global cognitive measure (i.e., Mini-Mental State Examination) (Rodes-Cabau et al., 2011; Kahlert et al., 2010). Most studies using the MMSE have failed to find cognitive changes following TAVI. In the studies using more comprehensive cognitive assessment, cognitive abilities appear stable with some improvements (Ghanem et al, 2013; Alassar et al., 2015). Ghanem and colleagues (2013) found improvement on RBANS total score three days and two years after the TAVI. Similarly, Alasssar and colleagues (2015) observed significant improvement at three months post-TAVI in overall cognitive measures and on the memory sub-scale. The present study will also use the RBANS, which has demonstrated sensitivity to cognitive changes in the TAVI population (see Ghanem et al, 2013), and it will include additional measures of processing speed, mental control, and executive function. Processing speed and mental control are cognitive domains negatively affected by cardiovascular disease (Saxton et al., 2000). In the present study, we predict that the participants will show a significant improvement in processing speed, attention, executive function, and mental control. More specifically, we anticipate results similar to Ghanem et al. (2013) with significant improvement on the RBANS Immediate Memory Index and the RBANS Language Index scores.

The present study will also include non-cognitive measures (mood, functional ability, and frailty) that have been associated with cognition and overall quality of life. Research supports improved quality of life following the TAVI (Fairburn et al., 2012). We predict that in addition to improvements in self-reported quality of life, we will also find improvements in functional ability and frailty status.

Previous studies indicate that a subset of new ischemia observed on neuroimaging within days following the TAVI procedure will resolve (Alassar et al., 2015; Knipp et al., 2013). Therefore, the present study will examine neuroimaging at one month to more accurately detect permanent neuronal damage. We predict that the rate of ischemic injury will be lower than previous estimations (e.g., 84% in Kahlert et al., 2010) due to the one-month delay. The cognitive sequelae of ischemia following cardiac procedures are debated (see above). Recent studies using MRI in TAVI patients fail to support that ischemic changes have a significant effect on cognition (Ghanem et al, 2013; Alassar et al., 2015). Therefore, new lesions are predicted to have no relationship with postoperative cognitive functioning. Instead, medical variables, such as procedure length and chronic kidney disease have been associated with post-operative cognitive decline (Ghanem et al., 2013). We predict that the measures of overall medical health (i.e., the Society for Thoracic Surgeons score) and procedural variables (i.e., procedure length) will predict post-operative cognitive performance.

CHAPTER II

METHOD

Participants

The interventional cardiologist at The Sanford Medical Center in Fargo, North Dakota identified patients eligible for the TAVI procedure, and a clinical research coordinator obtained informed consent. Participants completed a baseline cognitive assessment and DW-MRI one day prior to the TAVI procedure and at a one-month follow-up (30.67 day ± 5.46). Participants with diminished capacity to consent were excluded from the study. Patients non-fluent in English were excluded. As the TAVI procedure is an alternative procedure for high mortality risk patients, patients with health-related issues that may affect cognition were not excluded. Specifically, uncontrolled hypertension, coronary artery disease, carotid disease, chronic obstructive pulmonary disease, parkinsonism, history of stroke, history of cancer, history of prior CABG are common in the TAVI population and may affect cognition. However, patients with the above conditions were not excluded, as they are believed to be representative of the population. Patients needing combined heart surgery (i.e., multiple valve disease, patent foramen ovale, etc.) or multiple vascular surgeries (i.e., ascending aortic aneurysm and carotid revascularization) were excluded. To reduce attrition, noncompliant patients, as defined as an inability to complete the Mini-Mental State examination and the RBANS were excluded. Patients were excluded from the neuroimaging portion of the study when an MRI was contraindicated (e.g., claustrophobia, internal ferromagnetic material as a result of trauma, surgery, or implant), but the cognitive evaluation was still completed.

Fifty participants were recruited from Sanford Medical Center in Fargo, North Dakota. Forty participants were seen at one month. Three participants died before the follow-up. Deaths resulted from TAVI complications including embolic event to the bowels (death 2 days post-TAVI), aortic dissection (death 5 days post-TAVI), and during the TAVI procedure (surgical complications). Three participants chose to withdraw at the follow-up: one participant was hospitalized during the follow-up and cited poor health as the reason for withdrawal; one participant failed to attend the follow-up appointment and withdrew when contacted to reschedule. One participant did not tolerate cognitive testing at the follow-up and failed to complete the MMSE and RBANS. Two participants completed the baseline evaluation, but the TAVI procedure was canceled or delayed due to medical conditions or patient decision (i.e., urinary tract infection, decided to forgo the intervention). A scheduling error resulted in one participant failing to complete the follow-up.

Cognitive Evaluation

Participants completed cognitive testing within 24 hours prior to the procedure and 30.67 ± 5.46 days later. The follow-up cognitive assessment was scheduled to coordinate with the TAVI postoperative medical follow-up. The following tests were administered during the first testing session: Mini-Mental State Exam (Folstein, Folstein, & McHugh, 1975), Wechsler Test of Adult Reading (Holdnack, 2001), Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998), Stroop Color-Word Interference Test (Golden, 1978), Trail Making Test A and B (Reitan

& Wolfson, 1993), Letter Fluency (Benton & Hashmer, 1983), Verbal Series Attention Test (Mahurin & Cooke, 1996), Wechsler Adult Intelligence Scale–Fourth Edition (WAIS-IV) Digit Span subtest (Wechsler, 2008), and the Geriatric Depression Scale (Yesavage, Brink, Rose, Lum, & Huang, 1983). The follow-up examination was identical except the Wechsler Test of Adult Reading was not administered. The RBANS has two alternate forms: RBANS-A and RBANS-B. Administration was counterbalanced such that half of the participants completed RBANS-A initially and RBANS-B at the follow-up, and the other half completed RBANS-B during the pre-procedure assessment and RBANS-A during the follow-up. A family member or caregiver completed the informant questionnaires (Functional Activities Questionnaire (Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982), Physical Self Maintenance Scale (Lawton & Brody, 1969), and the Dementia Severity Rating Scale (Clark & Ewbank, 1996)) during the pre- and post-TAVI evaluations.

Cognitive Assessment Materials

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)

The RBANS is a brief cognitive battery developed to screen for cognitive decline in older adults. The RBANS contains 12 subtests and takes approximately 25 minutes to administer. Subtests are combined to yield 5 indices: Immediate Memory, Visuospatial/Constructional, Language, Attention, and Delayed Memory. Indices can be combined to calculate a Total Scale Score. the RBANS test-retest reliability was calculated for retest intervals between 1 and 134 days, and the length of the interval did not significantly affect the test-retest reliability. The RBANS subtest test-retest reliability coefficients range from 0.52 (List Learning) to 0.83 (Coding), and the indices test-retest reliability coefficients range from 0.68 (Visuospatial/Constructional) to 0.80 (Delayed Memory; Randolf, 2012). In construct validity studies, the RBANS subtests correlated with measures of similar cognitive abilities; for example RBANS Visuospatial/Constructional Index correlated highly with the Rey-Osterrieth Complex Figure Copy, and the RBANS Attention Index correlated highly with the Wechsler Memory Scales - Revised Attention/Concentration Index (Randolf, 2012). The RBANS subtests are described below.

1) List Learning and Story Memory subtests comprise the Immediate Memory Index. During List Learning, individuals learn a verbally presented 10-word list over four trials. Scores are recorded for recall after each trial and for total recall over all four trials. In Story Memory, individuals learn a story containing 12 parts or ideas over two verbally presented trials. Scores are calculated by combining story part recall for each trial.

2) Visuospatial/Constructional index contains the subtests Figure Copy and Line Orientation. The Figure Copy requires the participants to copy a 10-part geometrically complex figure. A four-minute time limit is given for Figure Copy, which far exceeds the time necessary for most people to complete the task. Time required to complete the drawing is recorded, but does not influence the Figure Copy score. The participants are instructed that they are timed during the Figure Copy, but that their score is based on the accuracy of the drawing. The Line Orientation subtest requires individuals to correctly identify the matching orientation of two target lines to a 13-line array spanning 180 degrees.

3) The Language index consists of Picture Name and Semantic Fluency subtests. Picture Naming requires the individual to name line drawings of objects. If the individual

misperceives the picture, a semantic cue is given. In Semantic Fluency, participants are presented with a category (e.g., Fruits and Vegetable) and have 60 seconds to generate words within the category.

4) Digit Span and Coding comprise the Attention Index. The Digit Span subtest requires the participant to repeat verbatim strings of digits verbally presented by the examiner. During the Coding subtest, participants quickly match numbers to a series of symbols using a key. Coding is a timed test.

5) List Recall, List Recognition, Story, Recall, and Figure Recall comprise the Delayed Memory Index. List Recall is a free recall measure from the word list presented in List Learning. The List Recognition subtest requires the participant to identify the word list words amongst distracters by providing "yes" or "no" responses. The Story Recall subtest is a free recall task for the story presented in Story Memory. The Figure Recall subtest requires the participant to draw the geometric figure from Figure Copy from memory with no time limit. All delayed recall subtests occur approximately 10-15 minutes after the original stimulus presentation.

The figure copy and recall were scored with awareness to pre and post-TAVI status. Ten percent of the figures were re-scored by a research assistant blinded to the pre- and post-TAVI status. The calculated inter-rater reliability percent agreement was 0.93, indicating adequate scoring agreement.

Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) is a global cognitive screening measure (Folstein, Folstein, & McHugh, 1975). The MMSE consists of brief measurements of multiple cognitive domains, including orientation to time and place, memory encoding and recall, complex attention, language production and reception, and visuospatial/constructional abilities. The MMSE has adequate reliability and demonstrates good validity, as evidenced by high correlations with criteria measures of cognitive impairment (i.e., the Diagnostic and Statistical Manual for Mental Disorders and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Alzheimer's criteria; Tombaugh & McIntyre, 1992). The MMSE is often used as a dementia screening in older adults with scores < 24 representing probable cognitive impairment (Folstein, Folstein, & McHugh, 1975).

Stroop Color-Word Interference Test

The Stroop Color-Word Interference Test (Golden, 1978) consists of three sections, each with a 45 second time limit. In the first section, the participant is required to read a list of color words (e.g., red, blue, etc.) at a rapid rate. In the second section, the participant is presented a list of X's printed in different colors. The second section requires the participant to provide the color of ink the series of X's is printed in (e.g., "XXXXX" printed in red ink and the participant would respond "red") at a rapid rate. For the third section, the participant is presented with color words printed in incongruent ink colors (e.g., the word "red" written in blue ink). The participant is required to rapidly provide the ink color while ignoring the word. The first two sections of the Stroop provide processing speed measures. The third section measures inhibition, an executive function requiring attention and inhibition of prepotent responses (i.e., reading the written word). The test-retest reliability for the three trials are 0.89, 0.84, and 0.73, respectively

(Golden, 1975). The third trial (Word-Color interference) correlates with established measures of prepotent response inhibition and attention (May and Hasher, 1998).

Test of Premorbid Functioning

The Test of Premorbid Functioning (Wechsler Test of Adult Reading: WTAR) requires the participant to read aloud a list of words (Holdnack, 2001). The WTAR words have atypical pronunciations based on common English rules (e.g., ogre). The WTAR is used to estimate overall cognitive ability prior to a cerebral injury, such as traumatic brain injury or degenerative disease. The WTAR demonstrates adequate reliability and correlates well with verbal intelligence quotients (Whitney, Shepard, Mariner, Mossbarger, Herman, 2010).

Trail Making Test A and B

The Trail Making Test (TMT) consists of two subtests (Reitan & Wolfson, 1993). In the first subtest (Trail A), participants are presented a page with circles each containing a number (unordered). The participant is required to connect the numbers in ascending numerical order at a fast rate without error. In the second subtest (Trail B), participants are presented a page with circles each containing a number or a letter. The participant is required to connect the circles in alternating order (1 to A, A to 2, 2 to B, B to 3, etc.) at a rapid rate without error (Reitan & Wolfson, 1993). The test-retest reliability for TMT Part A is 0.79 and 0.89 for Part B (Dikmen, Heaton, Grant, & Temkin, 1999). TMT Part A measures primarily visual search and processing speed; TMT Part B measures both working memory and task-switching performance (Sanchez-Cubillo et al., 2009)

Letter Fluency

In letter fluency, participants are given a letter and asked to generate words that begin with that letter (Benton & Hashmer, 1983). Letter fluency consists of three 60-second trials with a different letter in each trial. Letter fluency is a well-established neuropsychological assessment measure of executive function, verbal ability, and processing speed (Strauss, Sherman & Spreen, 2006, pp. 499- 526).

Verbal Series Attention Test

The Verbal Series Attention Test (VSAT; Mahurin & Cooke, 1996) requires the participant to say series of letters, words, or numbers. Participants are informed that speed and accuracy are important. The VSAT requires verbal recall and/or mental manipulation of overlearned material (e.g., "say the alphabet"; "say the days of the week backward", etc.). The VSAT generates scores for overall time to complete the items and number of errors. The VSAT is a measure of mental control and attention. The VSAT Time score has good test-retest reliability ($r = 0.86$), and adequate construct validity as a measure of attention (i.e., highly correlates with the WAIS-R Freedom From Distractibility factor; Mahurin & Cooke, 1996).

WAIS-IV Digit Span Subtest

For the present study, only the backward subsection of the Digit Span subtest was completed. During Digit Span Backward, the examiner reads a series of numbers and the participant is required to repeat the series in reverse order. The number strings increase in length until the participant can no longer complete the task correctly. Digit Span Backward measures complex attention. The Digit Span backward test is a measure of working memory (Wechsler, 2008).

Geriatric Depression Scale

The Geriatric Depression Scale (GDS) is a 30-item yes/no response, self-report questionnaire developed to measure depressive symptoms in older adults (Yesavage et al., 1983). The test items focus on the psychological symptoms associated with depression and excludes physiological symptoms that are more likely confounded by age and disease. The GDS demonstrates adequate internal consistency and correlates highly with other measures of depression in an elderly sample (Yesavage et al., 1983).

Informant Questionnaires

The informant questionnaires assess the participant's level of functioning through a caretaker's report. The Physical Self-Maintenance Questionnaire (PSMS; Lawton & Brody, 1969) is a multiple-choice questionnaire that assesses level of independence in the following basic activities of daily living (BADLs): toilet use, feeding, dressing, grooming, physical ambulation, and bathing. The PSMS has test-retest reliability of 0.94 and has high correlations with physicians' ratings and other measures of activities of daily living (Lawton & Brody, 1969). The Functional Activities Questionnaire (FAQ; Pfeffer, Kurosaki, Harrah, Chance, & Filos, 1982) measures instrumental activities of daily living (IADLs) such as managing personal finances and meal preparation. The FAQ has high inter-rater reliability and adequately discriminates normal controls from patients with dementia (Pfeffer et al., 1982). Typically, IADLs represent activities that require higher cognitive function than BADLs. The Dementia Severity Rating Scale (DSRS; Clark & Ewbank, 1996) is a multiple-choice questionnaire measuring major cognitive and functional typically impaired in individuals with dementia. The DSRS has good test-retest reliability and correlates highly with cognitive measures and with other validated measures of dementia severity (Clark & Ewbank, 1996).

Frailty Measures

The frailty assessment included the gait speed, the KCCQ, and fatigue/exhaustion. The Kansas City Cardiomyopathy Questionnaire (KCCQ; Green, Porter, Bresnahan, & Spertus, 2000) was used to measure activity level and quality of life. The KCCQ is included in the standard pre and post TAVI evaluations by the heart team. The KCCQ is a 23-item, self-report assessment that measures symptoms (frequency and severity), physical function, self-efficacy and knowledge, social function, and quality of life in patients with heart failure (Green et al., 2000). Two questions from the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977) ("I felt that everything I did was an effort" and "I could not get going") were included at the end of the GDS as a measure of frailty. The two CES-D questions as exhaustion measures have been used in previous research of frailty and surgical outcomes (Makary et al., 2010). Patients rating either question with a 2 (occurred 3-4 days in the past week) or 3 (occurred 5-7 days in the past week) on either question meet criteria for exhaustion. As a measure of gait speed, patients were asked walk 5 meters at walking speed. Participants with ≥6 seconds on the 5 meter walking test met criteria for frailty (Alfiano, Eisenberg, Morin, et al., 2010). Participants responding with a "2" or "3" on either CES-D question and with a gait speed greater than 6 seconds qualified as frail in the present study.

Magnetic Resonance Imaging

MRI data was acquired within 24 hours pre-TAVI and at the 1-month follow-up. A 1.5T magnet utilizing a standard head was used for imaging. Images were assessed for small vessel ischemic change, old infarcts, microhemorrhages, and acute ischemia by a neuroradiologist at Sanford Health. Medically relevant findings from the MRIs, as determined by the radiologist and interventional cardiologist, were shared with the patient as necessary. Data collected from the MRI images will include number new ischemic lesions.

Medical Variables

Variables with prior research to support their use in the present study were extracted from the participants' medical records. Medical variables of interest are listed in completion in Table 1. For purposes of the present study, presence of coronary artery disease, uncontrolled hypertension, history of neurological disease, history of prior coronary artery bypass grafting, chronic kidney disease and chronic obstructive pulmonary disease were extracted from electronic medical records for general demographics of the TAVI patient population health status. As TAVI procedure length potentially influences post-TAVI cognitive outcomes (Ghanem et al., 2013), it was also included in further analyses.

CHAPTER III

RESULTS

Data Screening

All variables were examined for outliers and normality. Using an *a priori* criterion of beyond two standard deviations, no outliers were eliminated from any variables. Normality was assessed using the Shapiro-Wilk test of normality and Fisher's coefficient for skewness and kurtosis measures. Shapiro-Wilk values with $p < 0.05$ indicate the variable is not normally distributed. Fisher's coefficient is calculated using skewness divided by the standard error of skewness, and calculated values outside of ±1.96 indicate the distribution is significantly skewed (Howell, 2010, Chapter 2). The following variables were not normally distributed: RBANS (Line Orientation, Picture Naming, List Recall, List Recognition, Figure Recall), Digit Span Backward, Verbal Series Attention Test, Trail Making A Time, Trail Making B Time, and all informant rating scales.

Variables that failed normal distribution measures were transformed to improve their normality. The type of data transformation was determined by the skewness direction (i.e., positive or negative) and the severity of the skewness (i.e., moderate, substantial, or severe). For positively skewed distributions, data were transformed using formulas in Mertler and Vannatta (2010, p. 32) by attempting transformations for moderate skewness (square root) then substantial skewness (logarithm) then severe skewness (inverse) until normality was achieved. For distributions negatively skewed, data were reflected (i.e., (*K* - *X*), in which the constant (*K*) creates the smallest value of one) before their subsequent transformation (Mertler & Vanatta, 2010, p. 31). Reflection causes the distribution to become positively skewed, and the subsequent transformation (i.e., square root, logarithmic, or inverse) to correct the positive skewness to a more normal distribution (Mertler & Vanatta, 2010, p. 31) The RBANS List Recall Raw distribution was positively skewed (post-TAVI Fisher coefficient = 2.70), and data were transformed using the inverse to achieve normality. The RBANS Figure Recall pre-TAVI had a significant Shapiro-Wilk value ($p = 0.014$). Pre and Post RBANS Figure Recall data were transformed using reflection and square root transformation. The pre and post-TAVI Digit Span Backwards distributions were positively skewed, and the post-TAVI Digit Span Backward Shapiro-Wilk was significant ($p = 0.009$). A logarithmic transformation on Digit Span Backward raw score improved normality (Shapiro-Wilk value = 0.95, $p = 0.11$). The pre and post-TAVI Verbal Series Attention Test (VSAT) time also positively skewed. A logarithmic transformation on the VSAT Time improved normality (Shapiro-Wilk $p > 0.05$). The Trailmaking Test (TMT) A and B time for both pre- and post-TAVI were positively skewed. An inverse transformation for the TMT A Time was performed to improve normality (pre-TAVI TMT A Shapiro-Wilk $p = 0.067$, post-TAVI TMT A Shapiro-Wilk $p = 0.58$). A logarithmic transformation on TMT B time raw score improved normality (pre-TAVI Shapiro-Wilk value $p = 0.49$, post-TAVI Shapiro-Wilk value $p = 0.79$). The following variables did not achieve normality after transformations: RBANS Figure Copy, RBANS Line Orientation, RBANS Picture Naming, RBANS List Recognition, TMT A errors, TMT B errors, FAQ, DSRS, PSMS.

Patient Characteristics

Patient characteristics are summarized in Table 2.

Table 2

Sample Baseline Characteristics

Variable	*n*	*Mean±SD*	*Range*
Age	46	79.04±7.79	59-90
Education Level	43	12.51±3.75	6-20
WTAR Standard Score	40	97.23±12.59	81-123
Gender			
Male	29	--	--
Female	17	--	--
BMI	46	31.15±6.54	21-47
STS Score	45	6.65±3.09	1.47-15.50
EuroScore	19	9.07±5.54	1.06-20.36
Diabetes	18 (39%)	--	--
Type I	2	--	--
Type II	16	--	--
NYHA Class	32	--	--
I	4	--	--
II	8	--	--
III	19	--	--
IV	1	--	--
CKD	16 (35%)	--	--
Hyperlipidemia	33 (72%)	--	--
Hypertension	34 (74%)	--	--
COPD	7 (15%)	--	--

Table 2. cont.

Variable	*n*	*Mean±SD*	*Range*
Mood Disorder	11 (24%)	--	--
Depression	6 (13%)	--	--
Anxiety	2 (4%)	--	--
Mixed Anxiety/ Depression or unspecified	3 (7%)	--	--
Carotid Disease	9 (20%)	--	--
CAD	33 (72%)	--	--
Prior CABG	14 (31%)	--	--

BMI = body mass index; STS = The Society for Thoracic Surgeon's risk score; NYHA = New York Heart Association Functional Classification; CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease; CAD = coronary artery disease

Procedural Characteristics

TAVI procedural characteristic data were collected for 46 participants. Table 3 summarizes these data.

Table 3

TAVI Procedural Data

Variable	*n*	*Mean±SD*
Valve Type	46	--
Edward SAPIEN	34	--
CoreValve	12	--
Valve Size	--	--
23 mm	14	--
26 mm	17	--
29 mm	8	--
31 mm	7	--

Table 3. cont.

Variable	*n*	*Mean±SD*
Procedure Route		
Transfemoral	36	
Transapical	9	
Valve in Valve	2	--
Pre- Mean Gradient	44	46.84±8.28
Post- Mean Gradient	39	11.31±5.10
Procedure Length (minutes)	149.9	98±212
Length of Stay	43	4.05±4.91

Edward SAPIEN = transcatheter heart valve, Edwards Lifesciences device; CoreValve = Medtronic transcatheter aortic valve replacement system

Cognitive Assessment

Dependent *t*-tests were used to compare pre and post-TAVI cognitive measures. Variables not normally distributed were excluded from the analyses.

The results for the RBANS *t*-tests are presented in Table 4. Results of the dependent t-test using the RBANS show that the Language Index significantly differs from baseline (M = 91.42, SD = 9.04) to one month post-TAVI (M = 95.50, SD = 10.86, t = -2.59, df = 37, p = 0.014, d = 0.42). The participants scored, on average, 4.08 points higher at one month than prior to the TAVI procedure.

At the RBANS subtest level, results of the dependent t-test show that the Fluency subtest improved significantly from baseline to one month post-TAVI (*p = 0.023, d =* 0.38). Results also show significant decline on the List Recall subtest from baseline (M = 3.21, SD = 2.22) to one-month post-TAVI (p = 0.001, d = 0.56). On average, participants recalled about one less word (mean difference = 0.90) at one month than baseline. Results

Table 4.

RBANS Dependent t-tests comparing baseline and one month post-TAVI

	Pretest		Posttest			
Variable	*M*	*SD*	*M*	*SD*	*t*	*df*
RBANS Total Index	85.26[d]	14.69	85.74[d]	13.41	-0.33	34
Immediate Memory Index	84.33[d]	15.76	84.46[d]	15.85	-0.055	38
List Learning	19.80	5.49	19.43	5.32	0.43	39
Story Learning	12.97	4.39	13.33	4.80	-0.56	38
Visuospatial/ Constructional Index	92.11[d]	18.90	89.66[d]	17.77	0.96	37
Figure Copy[c]	16.36	2.67	16.41	3.13	--	--
Line Orientation[c]	14.76	4.58	14.03	4.89	--	--
Language Index	91.42[d]	9.04	95.50[d]	10.86	-2.59*	37
Picture Naming[c]	9.36	0.84	9.46	0.72	--	--
Fluency	14.59	3.57	16.10	4.35	-2.36*	38
Attention Index	87.25[d]	15.74	86.89[d]	14.50	0.18	35
Digit Span	8.92	2.07	8.67	2.11	0.79	38
Coding	29.58	9.42	29.89	9.53	-0.37	35
Delayed Index	85.63[d]	16.42	87.55[d]	15.81	-0.87	37
List Recall[a]	3.21	2.22	2.31	2.23	-3.44*	37
List Recognition[c]	17.55	1.95	17.45	2.18	--	--
Story Recall	6.44	2.81	6.64	2.93	-0.48	38
Figure Recall[b]	9.51	5.62	10.85	5.31	2.31*	37

Table 4. cont.

M = mean, SD = standard deviation, df = degrees of freedom,

[a] t-test completed with inverse transformation data to achieve normality

[b] t-test completed with reflected a square root transformation to achieve normality

[c] t-test not completed due to failure to meet assumptions

[d] standard scores derived from raw score transformations using RBANS Manual

* $p < 0.05$

show significant improvement on the Figure Recall subtest from baseline to one month post-TAVI ($p = 0.027$, $d = 0.37$). No other significant differences were observed between baseline and at one month on RBANS measures.

Dependent *t*-tests comparing baseline to one month post-TAVI were completed for the following cognitive measures: Trailmaking Test A and B, Verbal Series Attention Test, WAIS-IV Digit Span Backward, Letter Fluency, Stroop Color-Word Interference Test, Mini-Mental State Examination. Results are presented in Table 5. No significant differences were observed.

Table 5.

Dependent t-tests comparing baseline and one month post-TAVI on cognitive measures

	Pretest		Posttest			
Variable	*M*	*SD*	*M*	*SD*	*t*	*df*
MMSE	25.88	2.81	25.75	3.17	0.321	39
VSAT Time[a]	130.50	41.22	130.20	46.33	0.23	34
Trail Making Test	--	--	--	--	--	--
A: Time (sec)[a]	51.44	25.45	56.38	32.88	-1.62	33
A: Error[b]	0.05	0.22	0.18	0.46	--	--
B: Time (sec)[a]	139.28	61.48	151.96	80.86	-1.31	24
B: Error[b]	0.53	0.80	0.93	1.04	--	--

Table 5. cont.

	Pretest		Posttest			
Variable	*M*	*SD*	*M*	*SD*	*t*	*df*
Digit Span Backward[a]	7.26	1.83	8.67	2.11	0.27	34
Stroop	--	--	--	--	--	--
Word	72.72	15.27	73.52	15.41	-0.41	32
Color	49.31	10.54	49.28	12.57	0.02	31
Word-Color	22.25	7.06	24.53	8.53	-1.94	31
Letter Fluency	25.51	11.83	27.43	11.01	-0.73	34

[a] t-test completed with logarithmic transformation data to achieve normality
[b] t-test not completed due to failure to meet assumptions

A standard multiple regression was conducted to determine if the independent variables procedure length, difference in mean gradient, and STS score predict the change in RBANS Total Index Score. Procedure length is an indirect measure of the operation complexity. The mean gradient is a measure of valve efficiency, and is routinely used to measure the severity of aortic stenosis. The STS score represents an estimated mortality percentage that is obtained using an algorithm that combines multiple chronic medical conditions and previous cardiovascular risk factors. Regression results indicate that the overall model does not significantly predict the change in RBANS Total Index scores ($R^2_{\text{adj}} = 0.008$, $F(3,27) = 0.946$, $p = 0.375$). The model accounts for 10.6% of the variance in the change in RBANS Total Index score in the sample. The regression coefficients are presented in Table 6.

The regression was repeated with the same independent variables to predict change in scores that showed significant change on previous t-tests: RBANS Language

Table 6.

Regression coefficients for model predicting change in RBANS Total Index score

	ß	*t*	*p*	Partial *r*
Procedure Length (minutes)	-0.167	1.754	0.091	-0.160
STS score	0.523	-0.316	0.754	-0.61
Change in mean gradient	0.211	-0.842	0.407	0.320

STS = The Society for Thoracic Surgeon's risk score

Index, RBANS Fluency, List Recall, and Figure Recall. In predicting RBANS Language Index change, regression results indicate that the overall model does not significantly predict the change in RBANS Language Index scores ($R^2_{adj} = -0.050$, $F(3,28) = 0.504$, $p = 0.682$). The model accounts for 5.1% of the variance in the change in RBANS Langauge Index score in the sample. In predicting RBANS Fluency change, regression results indicate that the overall model does not significantly predict the change in RBANS Fluency scores ($R^2_{adj} = -0.076$, $F(3,29) = 0.244$, $p = 0.865$). The model accounts for 2.46% of the variance in the change in RBANS Fluency subtest score in the sample. In predicting RBANS List Recall subtest raw score change, regression results indicate that the overall model does not significantly predict the difference ($R^2_{adj} = 0.126$, $F(3,28) = 2.468$, $p = 0.081$). The model accounts for 2.1% of the variance in the change in RBANS List Recall subtest score in the sample. In predicting RBANS Figure Recall subtest raw score change, regression results indicate that the overall model does not significantly predict change ($R^2_{adj} = -0.016$, $F(3,28) = 0.836$, $p = 0.485$). The model accounts for 8.2% of the variance in the change in RBANS Figure recall subtest score in the sample.

Mood, Quality of Life, and Frailty Assessment

Dependent *t*-tests were used to compare pre and post-TAVI quality of life measures. Variables not normally distributed were excluded from the *t*-test analyses. Results are summarized in Table 7.

Results of the GDS dependent t-test revealed a significant decrease from baseline to one month post-TAVI *(*p = 0.018, *d* = 0.41). The participants endorsed on average 1.50 less depressive symptoms at one month than prior to the TAVI procedure. Results also show significant increase on the KCCQ from baseline to one-month post-TAVI (*p* < 0.001, *d* = 1.08).

Table 7.

Dependent t-tests comparing baseline and one month post-TAVI on quality of life measures

	Pretest		Posttest			
Variable	*M*	*SD*	*M*	*SD*	*t*	*df*
KCCQ	38.93	9.81	51.55	9.99	-6.80**	39
GDS	7.33	4.78	5.83	4.09	2.47*	35
Gait Speed	5.77	1.59	5.32	1.56	1.56	34
FAQ	7.00	10.27	6.69	10.10	--	--
DSRS	3.81	4.67	3.48	5.75	--	--
PSMS	7.26	1.90	7.42	2.06	--	--

KCCQ = Kansas City Cardiomyopathy Questionnaire; GDS = Geriatric Depression Scale; FAQ = Functional Activities Questionnaire; DSRS = Dementia Severity Rating Scale; PSMS = Physical Self Maintenance Scale

* $p < 0.05$

** $p < 0.001$

Participants were defined as "frail" when gait speed for 5 meter walk exceeded 6 seconds and at least one CES-D question was endorsed (see "Frailty" in literature review for detailed description). Seven participants (7 of 37, 19%) met frailty criteria at baseline. Two participants (2 of 34, 6%) met frailty criteria at one month. Five participants that were frail at baseline were no longer frail at one month, and two participants maintained frailty status at one month. A summary of the frailty characteristics is presented in Table 8. No statistical analyses were conducted on the frailty data.

Table 8

Summary of group data for participants meeting frailty criteria

	n	MMSE	RBANS	GDS
Frail at baseline	7	27.4	73.9	10.7
Frail at one month	2	24.5	78	9

RBANS = Repeatable Battery for the Assessment of Neuropsychological Status Total Index Score mean; Frail = gait speed >6 seconds/5meters and endorsement on at least one CES-D question for frailty; MMSE = Mini-Mental State Examination mean; GDS = Geriatric Depression Scale

Neuroimaging and Cognitive Performance

Thirty-five baseline and 22 one-month follow-up MRI protocols were completed. Six participants (27.2%) evidenced new ischemic lesions at one month. Characteristics and cognitive performances for participants with evidence of new ischemia are presented in Table 9.

A series of Mann-Whitney *U* tests were computed to compare cognitive performance in participants with new lesions ($n = 6$) to those without ($n = 16$). Participants with new ischemia were not significantly different than those without ischemia on post-TAVI RBANS Total Index ($U = 37$, $z = -0.81$, $p = 0.45$). Participants with new ischemia did not significantly differ from participants without new ischemia on RBANS Index scores (Immediate Memory Index, $U = 40$, $z = -0.59$, $p = 0.59$;

Table 9

Characteristics of participants with new ischemia evidenced on MRI at one month

	Baseline		Follow-up		
Participant	RBANS	MMSE	RBANS	MMSE	Change
1	110	27	103	29	-7
2	82	23	82	23	0
3	91	28	68	28	-23*
4	70	26	76	22	+6
5	70	23	73	26	+3
6	97	30	101	28	+4

RBANS = Repeatable Battery for the Assessment of Neuropsychological Status Total Index Score; MMSE = Mini Mental State Examination; Change = Post RBANS Total Index - Pre RBANS Total Index
*significant change based on reliable change index (1.96*Standard Error of Measurement)

Visuospatial/Constructional Index, $U = 45.5$, $z = -0.19$, $p = 0.86$; Language Index, $U = 44$, $z = -0.30$, $p = 0.80$; Attention Index, $U = 50$, $z = 0.15$, $p = 0.91$; Delayed Memory Index, $U = 34.5$, $z = -1.00$, $p = 0.33$).

Wilcoxon Signed Rank tests were used to compare pre and post-TAVI performance in participants with new ischemic lesions. The Wilcoxon Signed Rank tests results are summarized in Table 10. The Wilcoxon Signed Rank tests demonstrated no significant differences between pre and post-TAVI cognitive measures. The Wilcoxon Signed Rank test revealed a significant difference between and pre and post-TAVI mean gradient scores.

Table 10

Wilcoxon Signed Rank Tests results in participants (n = 6) with new ischemic lesions

Variable	*z*-score	*p*
MMSE	0.00	1.00
RBANS Total Score	-0.41	0.69
RBANS Immediate Memory Index	-0.14	0.89
RBANS Visuospatial/Constructional Index	-1.47	0.14
RBANS Language Index	-0.42	0.67
RBANS Attention Index	0.00	1.00
RBANS Delayed Memory Index	-0.67	0.50
RBANS Fluency Subtest	-0.63	0.53
RBANS List Recall Subtest	-0.54	0.59
RBANS Figure Recall	-0.42	0.67
DSB	0.00	1.00
Stroop Word-Color Test	-0.27	0.79
KCCQ	-1.75	0.08
GDS	-0.41	0.68
Mean Gradient	-2.02	0.043*

Stroop Word-Color = third trial of the Stroop Word-Color Test; KCCQ = Kansas City Cardiomyopathy Questionnaire
* = $p < 0.05$

CHAPTER IV

DISCUSSION

The TAVI patient population is older adults (*M* = 79.04 years old*, SD* = 7.79) with multiple medical conditions (see Table 2). The patient population has high rates for chronic medical conditions (i.e., chronic kidney disease, chronic obstructive pulmonary disease, coronary artery disease, etc.) that potentially contribute to changes in functional abilities and cognitive functioning. Therefore, the TAVI population has unique cognitive concerns. The present study's sample had an education level slightly above high school (*M* = 12.51, *SD* = 3.75, range 6 to 20) and an estimated premorbid cognitive ability in the average range (WTAR Standard Score, *M* = 97.23, *SD* = 12.59). Despite estimated average cognitive functioning, when compared to similar aged adults at baseline, some areas of cognitive functioning fell into low average range (Standard Score (SS) = 80-89): RBANS Total Index, Immediate Memory Index, Attention Index, Delayed Index Standard Scores. On the RBANS, language and visuospatial/constructional abilities were within the average range (SS = 90-109). Mild decline in attention and verbal memory are consistent with the cognitive sequalae of cardiovascular diseases, and consistent with previous research of pre-cardiac surgery patients (Silbert, Scott, Evered, Lewis, Maruff, 2007).

In TAVI patients, the overall cognitive functioning appears stable one month following the procedure. Of the 23 cognitive measures compared (pre versus post-TAVI) only 4 showed significant change (three measures improved and one declined). The observed significant changes are likely not clinically significant (see below), and without a control group comparison we cannot conclude that these changes exist beyond those expected through practice effects. There were statistically significant improvements in the RBANS Language Index, the RBANS Fluency subtest, and the RBANS Figure Recall subtest. The mild improvements are consistent with previous studies; Ghanem and colleagues (2013) also found a significant improvement on the RBANS Language Index at a 3-month post-TAVI evaluation. At the subtest level, a significant improvement was observed on the Fluency subtest of the Language Index. The Picture Naming subtest was not analyzed because it failed normality assumptions. Ghanem et al. (2013) did not analyze results at the subtest level, so it is unknown if an increase in Fluency was also consistent with their results. Letter fluency was also examined in the present study, which requires participants to give words beginning with a certain letter rather than words within a semantic category (as in the RBANS). When participants were given the phonemic cues (Letter Fluency) no significant improvement was observed. There are several reasons why RBANS Fluency and Letter Fluency produced different results. First, RBANS Fluency is based on one trial while Letter Fluency scores are comprised of three trials. Second, the RBANS Fluency was introduced before Letter Fluency, so task familiarity and practice effects may have influenced Letter Fluency performance. Third, semantic and phonemic fluency tasks likely engage different brain areas, with phonemic fluency being more sensitive to frontal lobe dysfunction (Strauss, Sherman, & Spreen, 2006). Although Fluency loads the Language Index on the RBANS, semantic fluency is often considered an executive or frontal lobe function (Butler, Rorsman, Hill & Tuma, 1993). Other measures of executive function did not significantly change (Trailmaking B, VSAT, Digit Span Backward). However, Stroop Word-Color Interference (i.e., trial three) was near significance (p = 0.06). The improvement on RBANS Fluency exists without generalized executive function improvement.

The significant improvement of RBANS Figure Recall and significant decline on RBANS Delayed List Recall may have nullified any changes in overall memory performance. The present study's results are consistent with Ghanem and colleagues (2013) who also did not find a significant change in delayed memory. However, Alassar and colleagues (2015) did find an improvement in memory performance using a complex figure test and auditory verbal learning test. The complex figure and auditory verbal learning test may be more sensitive to changes in delayed memory than the RBANS. The improvement in visual memory (Figure Recall) and decline in verbal memory (List Recall) could be unique to our sample or could be representative of trends in the population. Future research examining memory performance in the TAVI population may benefit from differentiating language and visual memory tasks.

The present study failed to find significant change in mental control and processing speed, as predicted. Knipp and colleagues (2013) found significant improvement in TA-TAVI participants on MMSE and Digit Span Backwards between the postoperative evaluation and at the three month follow-up. The improvement at three months was not significantly different from baseline (Knipp et al., 2013). The present study included other measures of mental control (e.g., VSAT, Trailmaking Test, Stroop Word-Color) with Digit Span Backward in an effort to observe nuanced changes in complex attention. The lack of significance at follow-up supports that previously observed changes in mental control are transient in nature.

No significant changes were found in processing speed measures (RBANS Coding, Stroop Word, Stroop Color, Trailmaking Test A). Prior to the present study's outset, no previous TAVI cognitive studies included measures of processing speed. As processing speed influences performance across cognitive measures, it was important to rule out changes in processing speed as the underlying mechanism for changes in complex mental processes. Specifically, given the time limits in fluency tests, improved processing speed would help account for significant improvement in RBANS Fluency. The present study's results are consistent with a recent publication in TAVI cognitive research: Alassar et al. (2015) also failed to find significant improvement in processing speed following the TAVI and in AVR patients.

Ghanem and colleagues (2013) found a significant improvement on the RBANS Immediate Memory Index three days postoperative. The improvement did not persist at the three-month follow-up (Ghanem et al., 2013). The lack of significance on the RBANS Immediate Memory Index supports the transient nature of improvements found by Ghanem et al. (2013).

Despite statistically significant changes, the clinical relevance is important to examine. Using the reliable change index (Jacobson & Truax, 1991), two scores are determined as significantly different when obtaining the scores by chance (based on a measure's error) has a less than 5% probability. Reliable change index scores were calculated for RBANS Language Index, RBANS Fluency, and RBANS Figure Recall using the following formula: RCI = 1.96(Standard Error of Measurement). The RCI's were calculated using standard error of measurement scores for ages 80-89 (Randolf, 2012), because the age group was most representative of the present study's sample. An RCI was not calculated for List Recall because Randolf (2012) did not provide a standard error of measurement. No observed changes in RBANS met criteria for a reliable change. The difference in pre-post RBANS Language Index was 4.08 points, which fell below the RCI threshold (RCI = 12.11). On average, the difference in RBANS Fluency was 1.51 words, which fell below the RCI threshold of 4.08. The participants mean score for Figure Recall was 1.34 points higher after the TAVI, which falls below the RCI threshold for significant change (RCI = 3.94). Failing to exceed the RCI indicates that the difference between pre and posttest scores could not be reliably measured based on the psychometric properties of the RBANS index and subtest scores. The group difference scores (i.e., RBANS Language Index, Fluency, and Figure Recall) are statistically significant, but the ability to consistently measure these changes on an individual basis are unlikely.

The lack of significant cognitive changes is still clinically relevant. Postoperative cognitive decline (POCD) is a common concern, especially following cardiac surgery. POCD prevalence rates have varied from 10-60% of patients following CABG, and rates are typically higher following valve surgery due to increased micro-emboli (Lombard & Mathew, 2010). The high ischemic injury rates in previous TAVI studies (Arnold et al., 2010; Rodes-Cabau et al, 2011; Kahlert et al., 2010; Samim et al., 2015) have brought cognitive implications and functional changes to the forefront of TAVI-related outcome research.

Previous studies have shown ischemic injury rates post-TAVI in as high as 90% of patients (Samim et al., 2015). However, high incidence of ischemia may have been inflated by follow-up neuroimaging timing with higher rates within one week post procedure. Alassar and colleagues (2015) found that approximately 1/3 of patients with initial ischemia resolved at 3 months. Similarly, Kahlert and colleagues (2010) found 80% of acute restricted diffusion detected by DW-MRI following the procedure resolved at 3 months. The present study found 27% (6 of 22) had ischemic lesions that persisted at one month. The lesions were generally small and dispersed throughout the brain. No participants were diagnosed with a stroke following the TAVI; therefore, all lesions were assumed as clinically silent. However, two participants in the study may have had neurological changes, which suggests clinically apparent stroke or transient ischemic attack (TIA). One participant excluded from the MRI protocol, reported transient unilateral hearing loss that resolved at one month. Another participant that withdrew from the study before the one month follow-up had a major stroke: occlusion of the middle cerebral artery (MCA). No other neurological symptoms were reported; however, a neurological examination was not included in the present study.

Of the six participants with new lesions, only one participant evidenced a clinically significant decline in overall cognitive function (RBANS Total difference = 23, RBANS Total score RCI = 7.19). Based on Ghanem and colleagues' (2013) results, group differences in cognitive performance between participants that experienced new lesions compared to those without were not anticipated. No significant differences were observed between persons with lesions and those without, supporting the notion that the majority of ischemic lesions following TAVI are likely clinically silent. However, only 6 participants evidenced new ischemia, which likely resulted in insufficient power to detect even medium to large effect sizes.

Numerous factors potentially influence cognitive function following cardiac procedures beyond direct cerebral injury. The change in RBANS Total score from pre to post-TAVI was not significantly predicted using the independent variables procedural length, STS score, and postoperative mean gradient. Procedure length is an indirect measure of surgery complexity and previous research indicated longer procedure length in patients with postoperative cognitive decline (Ghanem, 2013). The STS score, a routinely used algorithm to predict mortality, represents a summation of medical conditions and cardiac risk factors. Mean gradient is used to grade the severity of aortic stenosis (Otto, 2006), and a lower post-TAVI mean gradient represents improved functioning and blood flow through the aortic valve. Procedure length, mean gradient, and STS were not predictive of changes in RBANS Total score. Similarly, procedure length, mean gradient, and STS score failed to significantly predict changes in RBANS Language Index, RBANS Fluency subtest, RBANS List Recall, and RBANS Figure Recall.

Quality of life improves following the TAVI procedure. A significant improvement was observed in the KCCQ, which is consistent with previous TAVI studies. The KCCQ includes aspects of cardiac symptom severity and activity level. Improved quality of life may be related to reduced aortic stenosis symptoms (e.g., angina, shortness of breath, etc.) resulting from successful aortic valve implantation. In addition to improved KCCQ scores, participants had significantly improved GDS scores. The improved mood can be attributed to multiple factors. First, as evidenced in the KCCQ, reduced symptom severity and improved activity may improve mood. Second, the pre-TAVI GDS was administered a day before the procedure and temporary distress may have inflated baseline GDS scores. Some GDS questions relate to future worries (e.g., "Are you afraid that something bad is going to happen to you?") and a major medical procedure may induce distress. Third, a complex relationship exists between cardiovascular disease, cardiac surgeries, and depression. Depression can increase incidence for cardiovascular disease (Lett et al., 2004) and stroke (Pan et al., 2011). Depression with onset later in life may result from the interrelationships between cardiovascular disease, cerebral injury, and cognitive function (Taylor, Aizenstein, & Alexopoulos, 2013). White matter hyperintensities (i.e., bright areas on MRIs in the white matter tracts, as opposed to the cortical gray matter, resulting from neuronal damage, such as ischemia) are associated with cognitive deficits and onset of late-life depression (Taylor, Aizenstein, & Alexopoulos, 2013). As the present study's participants' had mild cognitive decline, as evidenced by actual performance falling below predicted (WTAR), and multiple vascular risk factors (e.g., coronary artery disease, hypertension, hyperlipidemia, etc.) a "vascular depression" may have resulted. Increased perfusion to the brain from improved aortic valve function potentially influences depressive symptoms. However, future research is needed examining depression in TAVI patients before making any conclusions.

Prior to the TAVI, seven participants met criteria for frailty and two met criteria at follow-up. The low prevalence of frailty within the sample limited statistical analyses. However, patterns in the characteristics of frail participants may inform future research. The pre-TAVI Total RBANS score for frail participants fell below the overall sample's mean RBANS Total score, and the GDS scores appear higher. In future research, use of cognitive measures and mood symptoms may help further define frailty. In the present study, two questions from the CES-D were used in meeting criteria for frailty. A relationship between endorsement on the CES-D questions and higher GDS scores is anticipated, as both are measures of depression. Lower Total RBANS scores in frail individuals could be bidirectional. Frail individuals may have a lowered ability to engage in cognitively demanding tasks. Additionally, cognitive decline may be related to increased incidence of frailty. Examining cognitive changes in frail TAVI patients in future research could help further our understanding of the frailty construct and how frail individuals differ from non-frail patients.

Limitations

A limitation in the present study is high family-wise error rate. Controlling for family-wise error using Bonferroni or a less conservative Holm step-down procedure for the dependent t-tests results in only two significant differences (KCCQ, $p < .001$; RBANS List Recall, $p = 0.001$). Given the potential for Type I errors, replication of the study's results are needed.

Another limitation is low *n* for both ischemic lesions and frailty. Low *n* prohibited using MRI data in regression analyses. Additionally, nonparametric analyses, the Mann-Whitney *U,* were used to compare group differences using the neuroimaging data. Nonparametric tests tend to have lower power than parametric (Howell, 2010). Using parametric analyses, a larger *n* would increase the likelihood of meeting a test's assumptions (e.g., normal distribution).

Another limitation is the complex medical conditions present in most TAVI candidates. Multiple chronic medical conditions make distinguishing and isolating relevant variables difficult. Future studies will likely have similar sample characteristics because the TAVI remains an alternative procedure for high-risk patients; however, healthy control group comparisons are needed in future research.

Future Directions

The risk of cerebral injury following TAVI remains a major concern in the TAVI community, because in recent years many studies published support higher ischemic injury rates in TAVI patients (Kahlert et al., 2010; Samim et al., 2015). However, a link between silent ischemia and decreased cognitive or functional ability remains unsubstantiated (Alassar et al., 2015; Ghanem et al., 2013). Randomized controlled trials are needed to understand the relationship between TAVI and cognitive performance.

Additionally, using DW-MRI may not provide the best measure of neuronal injury. Many ischemic lesions resolve on the imaging (Kahert et al., 2010; Alassar et al., 2015), suggesting that higher rates of ischemia may not result in permanent neuronal damage. Additionally, baseline MRI brain classification may predict cognitive decline better than postoperative ischemia lesions (Lund et al., 2005). In the present study, no significant differences were found between those with new lesions and those without on cognitive measures using Mann-Whitney *U,* and that Ghanem and colleagues (2013) failed to find differences between the groups. Therefore, future research may find other markers of brain health more useful than new ischemic lesions.

Since the present study found a significant improvement in mood, further research is needed to explain the change. Specifically, are external factors (i.e., improved quality of life, decreased effects of aortic stenosis in daily life, postoperative decreased stress after surviving a cardiac procedure etc.) or physiological changes (i.e., increased perfusion to the brain) accounting for the observed mood changes?

Finally, future research may extend the patient selection criteria beyond the current population (i.e., ineligible for AVR). Given the generally stable cognitive performance following TAVI (present study; Alassar et al., 2015; Ghenam et al., 2013), patient's with pre-existing cognitive or neurological disorders that otherwise qualify for AVR, may have better long term cognitive results with an alternative TAVI procedure.

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