A BIOPSYCHOSOCIAL EXAMINATION OF TRANSCATHETER AORTIC VALVE REPLACEMENT HEALTH OUTCOMES

by

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June, 2015

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Cardiovascular disease (CVD) is the leading cause of death in the world accounting for 17.3 million deaths annually. Transcatheter aortic valve replacement (TAVR) was developed 13 years ago to treat people suffering from one of the most common manifestations of CVD, valve disease. While preliminary research has indicated that physiological benefits of TAVR are favorable, psychosocial benefits and psychosocial predictors for physical and psychological outcomes have received less attention. In the current study, TAVR patients (N = 34) were queried on a number of biopsychosocial factors at baseline and three months post-op. Results revealed substantial improvement in both general and disease specific QOL post-TAVR as measured by the SF-12 PCS (z = -2.84, p = .004, r = .69) and KCCQ (z = -3.36, p = .001, r = .84). There was also a decrease in anxiety as measured by the HADS (z = -2.47, p = .014, r = .58) and dyspnea as measured by selected items of the UCSD-SOBQ (z = -3.01, p = .003, r = .71). Biopsychosocial factors that were most strongly associated with the greatest improvement in disease specific QOL post-TAVR were low baseline scores on the KCCQ (r = -.811, p < .01), low levels of physical activity (r = -.625, p < .05), and worse dyspnea (r = .620, p < .05). Contrary to hypothesis, there was

no significant association between baseline levels of positive expectations, satisfaction with life, or psychological distress, with post-op QOL improvement. Overall, results suggest that patients may experience meaningful gains in QOL post-TAVR and, in fact, those patients who report the worst biopsychosocial health at baseline may likely experience the most substantial QOL improvements.

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A Dissertation

Presented to the Faculty of the Department of Psychology

East Carolina University

In Partial Fulfillment of the Requirements for the Degree

Doctor of Philosophy in Health Psychology

by

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Acknowledgements

I would like to offer my sincere thanks to Dr. Sam Sears, who directed this dissertation and served as my graduate mentor. I would also like to thank Dr. Karl L. Wuensch, Dr. Lesley Lutes, Dr. John Cahill, and Dr. Matt Whited for the invaluable time, assistance, and insight that each contributed to this project and my graduate training. Finally, special thanks to my wonderful wife, Vickie and my three awesome children, Kevin, Jake, and Lawson for providing their unconditional love and support over the past five years of my doctoral training.

TABLE OF CONTENTS

LIST OF TABLES

CHAPTER 1: INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the world accounting for 17.3 million deaths annually, with an expected increase to 23.3 million by 2030 (World Health Organization, 2011). CVD manifests in a variety of ways including myocardial infarction, stroke, heart failure, arrhythmia, and heart valve disease. Valve disease has traditionally been treated with surgical aortic valve replacement (SAVR), an invasive, open-heart procedure with high mortality risk for many elderly patients (Brennan et al., 2012). Transcatheter aortic valve replacement (TAVR) was developed 13 years ago as an alternative procedure with an important benefit of much lower mortality risk (Cribier et al., 2002). The quality of life (QOL) benefits of TAVR have been established as desirable, but psychosocial benefits and predictors for physical and psychological functioning outcomes have not been examined. The current biopsychosocial investigation gathered and analyzed information from patients undergoing TAVR by using a self-report survey. The first aim of the study was to describe the characteristics of a population of TAVR patients who were contraindicated for SAVR, across the following areas: demographics, physical activity, medication adherence, QOL, anxiety, depression, life satisfaction, positive health expectations, dyspnea, and will-to-live. The second aim was to examine changes in TAVR patients from pre-surgery baseline to 3-months post-surgery in several of the same areas including: physical activity, QOL, anxiety, depression, dyspnea, and will-to-live. The third aim was to investigate possible predictors of change in QOL in TAVR. Predictors that were analyzed independently were baseline levels of QOL, anxiety, depression, satisfaction with life, positive health expectations, dyspnea, and will-to-live.

The current study provides information that will educate valve patients, health care providers, and family members of the potential benefits of TAVR versus the unique risks. It is also hoped that this information will help patients reap the full benefit of TAVR by increasing their knowledge and encouraging them to pursue personal change to reduce risk and improve broad health outcomes.

CHAPTER II: LITERATURE REVIEW

Cardiovascular Disease

Cardiovascular disease (CVD) is a broad term that includes all diseases of the heart and blood vessels that collectively represent a worldwide epidemic. Not only is CVD the leading cause of death in the world (WHO, 2011), it is also the leading cause of death in the United States with approximately 600,000 Americans dying of CVD annually (Roger et al., 2011). In terms of financial cost, CVD accounts for expenditures of $108.9 billion annually in the US alone (Heindenrich et al., 2011), an amount that is increasing annually (Kochanek**,** Xu, Murphy, Miniño, & Kung, 2009; WHO, 2011).

Heart Valve Disease

About 5 million Americans are diagnosed with valve disease each year (American Heart Association, 2013) with the disease affecting 25% of people over 65 and 48% of those over 84 (Stewart et al., 1997). Heart valves function by opening and closing with each heartbeat to properly direct blood flow. Diagnosis of valve disease is made when one of the four valves in the heart (tricuspid, pulmonary, mitral, and aortic) ceases to function properly. Aortic stenosis is the most frequently diagnosed valve disease among people over the age of 75 in the Western World with a prevalence of 2.5% at 75 years of age, and 8.1% at age 85 (Nkomo et al., 2006). Aortic stenosis is a condition in which the valve between the left ventricle and the aorta narrows, thus obstructing blood flow onward to the rest of the body (Bonow et al., 2008). This condition demands that the heart regularly pump harder, weakening the heart muscle, and leading to symptoms such as angina, fatigue, shortness of breath, heart palpitations, heart murmur, and dizziness. Common causes of aortic stenosis include

congenital heart defects, calcium buildup on the valve, and rheumatic fever, and if unresolved, these conditions may lead to heart failure (Bonow et al., 2008; Goncalves et al., 2013). Risk factors include old age, personal history of rheumatic fever, and family history of congenital aortic valve defects. Symptomatic aortic stenosis is responsible for problems that range in severity from restrictions in normal daily living to serious disability and reduced life expectancy (Bouma et al., 1999). Unfortunately, aortic valve stenosis is not considered a preventable condition.

Traditionally, surgical aortic valve replacement (SAVR) has been the best treatment option for severe aortic stenosis. SAVR is an invasive procedure that requires making a 6-8 inch incision along the center of the sternum in order to gain access to the heart and aortic valve, and then repairing or replacing the valve depending on condition (Otto & Bonow, 2007). After valve replacement, hospital stays are typically 5-10 days followed by a 6-8 week recovery period. Studies of SAVR have shown improvements in QOL among elderly patients (>80) comparable to that of younger patients (Heijmeriks, Pourrier, Dassen, Prenger, & Wellens, 1999; Olsson, Janfjäll, Orth-Gomér, Undén, & Rosenqvist, 1996; Sedrakyan et al., 2003). However, SAVR is also associated with higher mortality rates in elderly populations. Brennan et al. (2012) examined data from a large sample of valve patients *(N* = 145,911) and found that the one-year mortality rate of low-risk, younger SAVR patients (< 70) was significantly better than in older patients (> 80) (5.7% vs.10.8%, $p < 0.0001$). Because of co-morbidities, surgical risk, or short life expectancy, almost a third of patients >75 are not candidates for traditional surgery (Iung et al., 2003).

Transcatheter Aortic Valve Replacement (TAVR)

Many frail patients are unable to undergo SAVR due to surgical risk (Cribier et al., 2002) and TAVR has emerged as a viable alternative. TAVR involves displacing and functionally replacing the patient's native valve with a bioprosthetic valve that is delivered by a transvenous catheter, rather than through invasive, open-heart surgery. The two most common methods of delivery are via the femoral artery (transfemoral placement) or the left ventricular apex (transapical placement) (Smith et al., 2011). Other less common methods of valve delivery are subclavian, transaortic, and transcarotid implantation (Tang et al., 2013). The first human percutaneous transcatheter implantation of an aortic valve prosthesis was performed in 2002 (Cribier et al., 2002) and by 2008 about 1000 valve replacements had been completed worldwide (Vahanian et al., 2008). The number of TAVR procedures has increased dramatically in recent years and by 2013 over 50,000 had been completed (Tang et el., 2013).

Surgical Outcomes of TAVR vs. SAVR and Standard Therapy

One of the first large studies of TAVR *(N* = 699) was the Placement of Aortic Transcatheter Valves (PARTNER) trial (Smith et al., 2011). PARTNER sought to determine the safety and effectiveness of TAVR in high risk, symptomatic patients with severe aortic stenosis. Patients were recruited from 22 centers in the United States, 2 centers in Canada, and 1 center in Germany. Smith and colleagues compared high-risk patients randomized to undergo SAVR or TAVR. At 30 days post-op, the all-cause mortality rate for TAVR patients was approximately half that of the SAVR group (3.4% vs. 6.5%, $p = 0.07$). The TAVR group also had less frequent major bleeding (9.3% vs.

19.5%, $p < 0.001$), less frequent new-onset atrial fibrillation (8.6% vs. 16.0%, $p = 0.006$), and greater New York Heart Association (NYHA) Class III or IV cardiac symptom improvement ($p < 0.001$). NYHA is the most commonly used classification system for describing patient symptoms of heart failure (AHA, 2013) (see Table 1).

Table 1

NYHA Functional Classification (AHA, 2013)

Class	**Functional Capacity: How a patient with cardiac disease feels during physical activity**
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Additionally, TAVR patients had shorter stays in intensive care (3 vs. 5 days, $p < 0.001$), as well as in overall hospital stay (8 vs. 12 days, $p < 0.001$). However, TAVR patients were more likely to have a major stroke (3.8% vs. 2.1%, $p = 0.20$) or major vascular complications (11.0% vs. 3.2%, $p = 0.001$). All-cause mortality differences between TAVR and SAVR patients were relatively equal at one year (24.2% vs. 26.8%, $p = 0.44$), while rates of major stroke continued to be greater for the TAVR group (5.1% vs. 2.4%, $p = 0.07$). There were no significant differences in symptom improvements at one year. Overall, these results indicated that while one-year mortality rates in both procedures were roughly equivalent, specific morbidity risks varied based on procedure.

A subsequent PARTNER trial was conducted to compare TAVR with standard therapy (e.g., balloon aortic valvuloplasty) in high-risk patients with severe aortic stenosis (Leon et al., 2010). Leon and associates reported on patients *(N* = 358) unsuited for SAVR, who had been randomized to TAVR or standard therapy. At 30 days, TAVR patients experienced greater incidence of all-cause mortality (5.0% vs. 2.8%, $p = 0.41$), major stroke (5.0% vs. 1.1%, $p = 0.06$), and major vascular complications (16.2% vs. 1.1%, $p < 0.001$). TAVR patients also experienced reduced rate of NYHA Class III or IV cardiac symptoms ($p < 0.001$). At one year, however, all-cause mortality in TAVR patients was much improved compared to standard therapy (30.7% vs. 50.7%, $p < 0.001$) as was rate of cardiac symptoms (25.2% vs. 58.0%, $p < 0.001$) and re-hospitalization (22.3% vs. 44.1%, $p < 0.001$). Rates of stroke (10.6% vs. 4.5%, $p < 0.04$) and major bleeding (22.3 vs. 11.2%, $p = 0.007$) were higher in TAVR patients. These results indicate that while TAVR resulted in worse outcomes immediately following the procedure, it was superior to standard therapy in reducing the rate of mortality and re-hospitalization at one year, even in light of higher specific, acute procedural risks. At two years, results revealed that TAVR patients had decreased rates of mortality (43.3% vs. 68.0%, $p < 0.001$), death due to all cardiac causes (31.0% vs. 62.4%, $p < 0.001$), lower re-hospitalization rates (35.0% vs. 72.5%, $p < 0.001$) and fewer NYHA class III or IV symptoms (16.8% vs. 57.5%, $p < 0.001$) (Makker et al., 2012). However, there continued to be higher rates of stroke (13.8% vs. 5.5%, $p = 0.01$) and major bleeding (28.9% vs. 20.1%, $p < 0.09$). These results indicate that while the mortality benefit to TAVR over standard therapy is markedly better, there continues to be higher procedural risks for morbidity outcomes.

While some of the differences noted above from the PARTNER trials fall short of reaching statistical significance, they establish trends concerning the relative differences between TAVR and other medical or surgical procedures used to address aortic stenosis. Similar results have been found in non-PARTNER studies.

Genereux and associates (2012) conducted a meta-analysis of outcomes of 3519 TAVR patients from 16 studies completed between January 1, 2011 and December 10, 2011. Estimated mean 30-day and 1-year mortality rates were 7.8% (range 1.7–14.3%) and 22.1% (15.3–30.7%) respectively, and rate of major stroke was 3.2% (0.8–9.0%). Major bleeding rate was 15.6% (7.0% - 25.9%) and vascular complications rate was 11.9% (5.0–23.3%).

Patients who have undergone TAVR commonly have ongoing issues including: paravalvular leak, heart block, stroke, vascular complications, atrial fibrillation, concurrent coronary artery disease (CAD), LV dysfunction, prosthesis-patient mismatch, and problematic heart valve structural integrity and durability (Tang et al., 2013). Paravalvular leak is a side effect of the inability to ensure that the surface of the heart where the valve will be implanted is free of irregular surfaces. Thus, the seal between the heart surface and the valve is sometimes inadequate. Heart block (disruption of the heart's electrical system) may possibly be exacerbated by the pressure of the valve on the His bundle or by other effects of the procedure that are yet not fully understood. These complications are carefully attended to by medical teams but are often irreversible.

With regard to the financial cost, the total one-year cost of TAVR is approximately $67,000 while the one-year cost of SAVR is approximately $53,000

(Osnabrugge et al., 2013). The increased expense of TAVR is primarily due to higher procedural costs, specifically operating room use and materials. While the expense of TAVR exceeds that of SAVR, for inoperable patients Makker et al. (2012) noted that TAVR was cost-effective due to the reduced rehospitalization rates compared to standard therapy (e.g., balloon aortic valvuloplasty).

Research Guidelines for TAVR

Because of the recent emergence of the TAVR procedure, empirical research is needed to determine guidelines for patient selection beyond clinical judgment. Vahanian et al. (2008) recommended four steps of patient selection: 1) confirmation of the severity of aortic stenosis, 2) evaluation of symptoms, 3) analysis of the risk of surgery and evaluation of life expectancy and quality of life, and 4) assessment of the feasibility and exclusion of contraindications for TAVR. Vahanian et al. also recommended that QOL data be captured using standardized metrics, and that comparison groups should include patients who received SAVR.

The Valve Academic Research Consortium (VARC-1), consisting of international experts in TAVR, was organized in 2009. VARC-1 met twice that year to define and establish appropriate clinical endpoints for TAVR in order to standardize clinical research (Leon et al., 2011). While the endpoints defined by VARC-1 were primarily physiological in nature, they also noted the value of assessing clinical benefit endpoints. The use of the NYHA ratings was offered as one acceptable way to rate the clinical benefits of TAVR as they concern functional status. VARC-1 also suggested the use of the Kansas City Cardiomyopathy Questionnaire (KCCQ) to assess health-related QOL. The KCCQ is a 23-item measure commonly used to evaluate the health status of heart

failure patients (Creber, Polomano, Farrar, & Riegel, 2012). The five domains addressed by the KCCQ are: symptoms, physical limitation, social limitation, self-efficacy, and quality of life with higher scores indicating fewer symptoms and better QOL (Green, Porter, Bresnahan, & Spertus, 2000). The importance of assessing frailty as a clinical endpoint was also articulated. While no fixed method of evaluating frailty was established, VARC-1 did articulate the patient characteristics of mobility, strength, endurance, activities of daily living, cognitive impairment, and nutritional status as important criteria of frailty.

Recommended VARC guidelines were further revised and published in 2012 (Kappetein et al., 2012) (VARC-2). VARC-2 noted that improvements needed to be made in current predictive models for operative mortality in TAVR patients. Risk scoring commonly used to stratify patients has been done using the Society of Thoracic Surgeon (STS) risk score and the logistic EuroSCORE (EuroSCORE) with the STS having been found to be more accurate. The STS predicts risk of mortality in patients considered for cardiac surgery (Ad, Barnett, & Speir, 2007) and is calculated using an algorithm considering over 40 clinical parameters including patient demographics and various risk factors such as height/weight, diabetes, renal failure, hypertension, chronic lung disease, peripheral arterial disease, cerebrovascular disease, previous cardiac interventions, preoperative cardiac status, ejection fraction, and aortic stenosis. The EuroSCORE considers 17 parameters grouped into three areas: patient related risk factors (e.g., age, history of cardiac surgery), cardiac factors (e.g., reduced left ventricular ejection fraction [LVEF], recent myocardial infarction), and operation related factors (e.g., emergency operation, other than isolated coronary surgery). The

EuroSCORE is also used to predict outcomes of patients undergoing cardiac surgery (Nashef et al., 1999). VARC-2 noted limitations in the predictive ability of STS scores in high-risk patients with valve disease, however.

In the most recent review of TAVR research literature, Tang and colleagues (2013) also recommended developing better risk scoring and frailty assessment to determine especially high-risk patients. Patient selection criteria continue to be clarified and physical frailty, malnutrition, chronic kidney disease, history of lung, liver, and kidney malignancy, and neurological disorders (e.g., dementia, stroke) were highlighted for continued examination to help determine outcomes and the likelihood of patient return to a semi-independent daily living status.

Tang et al. (2013) and VARC-2 recommended a “heart-team” patient-centered approach to design an individualized optimal management strategy for TAVR candidates (Kappetein et al., 2012). VARC-2 recommended a “dynamic” team including interventional cardiologists, cardiovascular surgeons, imaging specialists, anesthesiologists, geriatricians, and neurologists. A main goal of this team is to evaluate patient risk-benefit ratio to identify “treatment responders vs. non-responders” (Kappetein et al., 2012, p. 1441). Evaluation criteria to make this evaluation includes risk of irreversible morbidity, mortality, and expected improvement in QOL.

Of note, Vahanian et al. (2008), VARC-1, VARC-2 and Tang et al. (2013) did not discuss assessment of mental health for either evaluating outcomes or predicting patient benefit, nor was the inclusion of a mental health provider mentioned as a member of a heart-team. In the years since Vahanian et al. made their recommendations, TAVR procedures have increased 50 fold and have been conducted

in over 40 countries (Tang et al., 2013). The use and adherence to the recommendations by Vahanian et al., VARC-1, VARC-2, or Tang et al. nationally is unknown and the inclusion of psychological factors in research has been extremely limited.

Biopsychosocial Model and TAVR

The biopsychosocial model emphasizes the way in which psychological and social processes interact with biological processes as a way to more completely understand illness (Engel, 1977). In this model, an illness may have initial medical causation, the symptoms and trajectory of which may be exacerbated by social factors (e.g., family conflict, loneliness) and/or by psychological factors (e.g., depression, anxiety). Medical illness may also have psychological or social precipitants, as when anxiety triggers physiological responses (e.g., cortisol release) that suppress the immune system, leading to contracting medical disease that would have otherwise been defeated by natural antibodies. The usefulness of the biopsychosocial model of illness in general, and in heart disease in particular, has been supported by an abundance of studies since Engel first proposed the model in 1977 (Biderman, Yeheshkel, & Herman, 2005; Marušič, Gudjonsson, Eysenck, & Starc, 1999).

The TAVR procedure attempts to return patients to a relatively normal functioning but does not always succeed. The physical reasons for poor outcomes have received much attention but it is also possible that poor outcomes may have a psychological component. For example, in some cases, people with heart disease who inordinately experience negative emotions and social inhibition may fare worse (Pedersen & Denollet, 2006). In other cases, recovery may be hindered by a patient's

psychological state such as clinical depression or anxiety (Foxwell, Morley, & Frizelle, 2013). Even as patient outcomes may be impacted by psychological factors, it is has also been shown that psychological factors can have a role in predicting patient outcome. For example, depression has been found to predict adherence in weight loss programs with more severely depressed individuals having a greater likelihood of either dropping out or maintaining static weight (Somerset, Graham, & Markwell, 2011). A meta-anaylsis by Rugulies (2002) found that depression predicted the development of coronary heart disease (CHD) among those who were initially healthy. A better understanding of biopsychosocial factors will better inform prospective patients and health providers of the pros and cons of TAVR. Psychological predictors, if found, may inform patients to consider psychological intervention that may result in improved physical gains. Improvements in outcomes provided by psychosocial care will not only provide better patient satisfaction and health, but will also reduce medical costs through increased patient engagement in relationships and life activities that help to strengthen both body and mind.

The following is a chronological review of select QOL research related to TAVR. Brief descriptions of the measures used are included within this review, with more complete descriptions and psychometric data provided at Appendix B.

Psychosocial and QOL Data for TAVR Patients

In the first study examining QOL in TAVR patients, Ussia et al. (2009) administered the Short Form-12 Health Survey (SF-12) to consecutive patients (*N* = 30) at both pre-op and at 5 months post-op. The SF-12 is a twelve-question survey that measures functional health and well-being from the patient's perspective (Ware et al.,

1996). The average age of the sample was 81.7 years, 43% male, 93% were NYHA Class II or III, and they had markedly worse QOL at pre-op as measured by the SF-12 than an age-matched general population. Post-op results demonstrated a significant improvement in the mean physical component score (28.5 vs. 41.3, $p < 0.001$) and mental component score (37.8 vs. 48.3, $p < 0.001$). There was also marked improvement in physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health scores. In addition, there was significant improvement in NYHA class (2.7+0.6 vs. 1.8+0.5, $p < 0.001$). None of these patients reported worse QOL after the TAVR procedure.

In the first of only two randomized studies examining QOL in TAVR patients, Reynolds et al. (2011) compared two groups of patients ($N = 358$) who either underwent TAVR or standard therapy. The TAVR group scored significantly higher on QOL than the standard therapy group at all time points after baseline with mean between-group differences ranging from 13 to 26 points ($p < 0.001$) as assessed with the KCCQ. The TAVR group also scored significantly higher on the physical and mental health scores of the SF-12 at each time point (5.7 and 6.4 points, respectively; $p < 0.001$). The gains experienced by TAVR patients compared to standard therapy demonstrate significant patient benefit to QOL. In addition, within-group differences in the TAVR group were significant on both measures at each time point (see Table 2). This magnitude of difference can also be considered clinically significant.

In a second randomized study, Reynolds et al. (2012) evaluated QOL at multiple time points in two groups of high-risk patients ($N = 628$) with severe aortic stenosis who underwent either TAVR or SAVR. Within-group differences for the group randomized to

transfemoral TAVR (*n* = 230) are displayed at Table 2 and show significant improvement on all measures. Participants randomized to transapical TAVR demonstrated many of the same benefits as the transfemoral TAVR group although generally to less degree. Baseline characteristics of both groups were similar and while the researchers suggested several possible reasons for the differences, they admitted that an explanation for the differences was unclear. They found that patients who underwent transfemoral TAVR demonstrated substantially more health benefits at one month post-op than those who underwent SAVR as measured by the KCCQ (difference, 9.9 points; 95% CI: 4.9 to 14.9; $p < 0.001$), SF-12 (difference on PCS, 2.0 points; 95% CI: 0.1 to 3.9; $p = 0.04$; MCS, 5.4 points; 95% CI: 3.1 to 7.7; $p < 0.001$), and Euroqol-5D (EQ-5D) (difference, 0.06 points; 95% CI: 0.02 to 0.01; $p = 0.008$). The EQ-5D is a preference/utility-based measure that describes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman et al., 2011). There were no significant differences between TAVR or SAVR groups on either the KCCQ, SF-12, or EQ-5D at 6 or 12 months. These results suggest there are likely immediate QOL benefits from the less-invasive procedure but once physical recovery is complete, TAVR and SAVR patients seem to share equivalent QOL benefits over time.

Fairbairn and colleagues (2012) assessed the benefits of TAVR and also examined predictors of outcomes at multiple time points. The SF-12 and EQ-5D was administered to TAVR patients (*N* = 102) at pre-op and three subsequent times post-op, to evaluate the benefits to health related QOL and to find predictors of patient benefit. Results from the SF-12 demonstrated significant patient improvement at six months on the PCS (29.5 vs. 38.3, $p < .001$) but not on MCS (45.4 vs. 47.4, $p = 0.71$). The

researchers also calculated disease burden from participant responses to the SF-12 by using the Short Form-6D (SF-6D) to measure quality-adjusted life years (QALYs) (Phillips, 2009). QALYs are established by considering the quality and quantity of life gained by medical interventions, as well as the financial cost of the intervention. EQ-5D, VAS and SF-6D scores all significantly improved (54 vs. 65, $p < 0.001$; 51.1 vs. 68.2, $p = 0.008$; 0.60 vs. 0.69, $p = 0.001$, respectively). The results from the SF-12 indicated that the benefits of TAVR were experienced in the physical realm more than the mental realm in this sample.

Fairbairn et al. (2012) also assessed predictors of change using a general linear model. Male sex, patients younger than 80, and patients operated on by a more experienced surgeon had significantly greater improvement than the other groups, while patients with higher baseline NYHA functional class reported less improvement. The largest improvements in QOL happened at the 30-day post-op measures compared to subsequent time points. Baseline assessment found that these TAVR patients had worse scores on all of their measures compared with age-matched, general U.S. population norms. At the 6-month assessment, however, the results of the TAVR group were better than the same aged US norms on the EQ-5D, VAS, and the physical component score of the SF-12, with similar scores on the SF-6D and the mental component score of the SF-12.

Krane et al. (2012) reported on TAVR patients ($N = 106$) who completed the SF-36 at baseline, 3 months post-op, and one year post-op. At three months, the physical component scores improved from 31.8 to 37.8 ($p < .001$), while mental component scores remained approximately the same (48.6 vs. 47.9, $p = 0.67$). At one year, there

were similar results on the physical component scores (31.8 vs. 36.9, $p < 0.001$) and mental component scores (48.6 vs. 49.6, $p = 0.18$). Of note, their overall SF-36 scores were similar to age-matched norms for the standard population at both three months and one year. The NYHA class improved significantly at both three month and 12-month follow-up as well (3.1 vs. 1.9/2.0, $p < 0.001$). Krane et al. also assessed patient-related and non-patient, procedure-related factors predictive of improvement. More severe STS risk score was associated with lower QOL benefits at three months, but there were no associations with QOL found for a host of other examined factors including height, weight, EF, comorbidities, and COPD. The majority of patients reaffirmed their decision to undergo TAVR at both 3 months and 12 months (86.2% and 88.6% respectively).

Only one study to date has examined anxiety or depression in TAVR patients with a measure specifically designed for that purpose. Amonn et al. (2013) assessed QOL and psychosocial well-being in high-risk valve patients ($N = 144$) using the SF-36 and Hospital Anxiety and Depression Scale (HADS) at 15 ± 10 months post-op. The HADS is a 14-item measure that assesses depression and anxiety in hospital settings (Zigmond & Snaith, 1983). No baseline assessment was done with these measures. Fifty-one patients underwent transapical TAVR and 93 underwent SAVR. Notably, the TAVR group had a much higher logistic mean EuroSCORE (26.5 vs. 12.1), higher NYHA class (67% vs. 47% were in NYHA Class III or IV) and lower LVEF (mean of 49.6 vs. 58.1) at baseline suggesting worse disease severity. The rate of mortality was similar 30 days post-op but was lower for the SAVR group at final follow-up.

Scores were not significantly different between groups on the HADS with mean scores on the anxiety subscale of 4 for each group, and 4 and 5 for depression in the

TAVR and SAVR groups respectively. The only score that was significantly different on the SF-36 was that of the general health subscale (52.4 vs. 64.1, $p < .005$), on which the TAVR patients had much lower scores. The only statistically significant predictor was that higher STS scores predicted lower post-operative SF-36 scores ($p < 0.007$). Over 80% of both groups reported substantial improvement in general health as a result of their procedure and 87.1% of TAVR patients and 94.3% of SAVR patients reaffirmed their decision for surgery at post-op assessment. While important, this study is unable to draw conclusions about the effects of TAVR on symptoms of anxiety or depression because the researchers did not administer the HADS pre-operatively and thus cannot compare baseline scores to post-op scores to assess change. Moreover, while the absolute percentages of post-operative distress are generally consistent with other areas of cardiac psychology, the conclusions that can be drawn based on this single study are limited.

Summary of Previous TAVR Psychosocial and QOL Research

Table 2

Summary of studies assessing QOL in TAVR patients

Author	N	Lost to mortality n (%)	Age, year	Female, n (%)	Time-points, months	Measure	QOL change	NYHA change	Patients reaffirming TAVR -%	Country of study (# of sites)
Ussia et al. (2009)	30	8 (27)	81.7 ± 4.7	17 (57)	5	SF-12v2	PCS: 28.5 to 41.3 (p < .001) MCS: 37.8 to 48.3 (p < .001)	2.7 vs. 1.8 (p < .001)	***	Italy (1)
Gotzmann et al. (2010)	54	6 (11)	79.1 ± 7	22 (50)	1	MLHFQ	44 vs. 28 (p < .001)	3.0 vs.1.9 (p < .001)	***	Germany (1)
Krane et al. (2010)	99	20 (20)	81 ± 6	58 (58.6)	3	SF-36	PSS: 31.2 to 38.6 (p < .001) MSS: 48.5 to 47.3 (p = .5)	3.1 vs. 1.9 (p < .001)	85	Germany (1)
Bekeredjian et al. (2010)	87	7 (8)	86 ± 2.9	47 (59)	6	SF-36	PSS: 28.4 to 46.8 (p < .001) MSS: 37.3 vs. 50.6 (p < .001)	3.1 vs. 1.4 (p < .001)	***	Germany (1)
Georgiadou et al. (2011)	36	6 (17)	80.5 ± 5.9	15 (42)	11.3 ± 4.9	SF-36 SF-12v2	PSS: 21.6 vs. 46.7 (p < .001) MSS: 42.9 vs. 55.2 (p < .001) MCS: 22 vs. 48.9 (p < .001) PCS: 43.3 vs. 52.2 (p < .001)	3.0 to 1.2 (p < .001)	***	Greece (1)
Gotzmann et al. (2011)	70	14 (20)	78 ± 6.6	26 (51)	12 ± 1	MLHFQ	39.6 vs. 26.1 (p < .001)	***	***	Germany (1)
Ussia et al. (2011)	143	***	81 ± 4.6	85 (59)	5 12	SF-12v2	PCS: 28.3 vs. 44.0 (p < .001) MCS 38.0 vs. 47.3 (p < .001) PCS: 28.3 vs. 42.4 (p < .001) MCS 38.0 vs. 48.2 (p < .001)	***	***	Italy (1)

Reynolds et al. (2011)	179	55 (31)	83 ± 9	97 (54)	1 6 12	KCCQ SF-12 KCCQ SF-12 KCCQ SF-12	36.2 vs. 61.6 PCS: 28.2 vs. 34.6 (p < .001) MCS: 44.5 vs. 47.9 (p < .03) 36.2 vs. 70.7 PCS: 28.2 vs. 36.0 (p < .001) MCS: 44.5 vs. 51.0 (p < .001) 36.2 vs. 69.4 PCS: 28.2 vs. 34.9 (p < .001) MCS: 44.5 vs. 53.3 (p < .001)	***	***	USA (21)
Fairbairn et al. (2012)	99	20 (20)	80 ± 6	51 (51)	1 6 12	SF-12v2 EQ-5D SF-12v2 EQ-5D SF-12v2 EQ-5D	PCS: 29.5 vs. 36.3 (p < .001) MCS: 45.4 vs. 46.4 (p = .47) 54 vs. 65 (p < .001) PCS: 29.5 vs. 38.3 (p < .001) MCS:45.4 vs. 47.4 (p = .71) 54 vs. 68 (p = .006) PCS: 29.5 vs. 34.4 (p < .02) MCS: 45.4 vs. 46.9 (p = .58) 54 vs. 65 (p = .001)	***	***	UK (1)
Krane et al. (2012)	186*	37 (21)	80.8 ± 6.8	118 (63)	3 12	SF-36	PSS: 31.8 vs. 37.8 (p < .001) MSS: 48.6 vs. 47.9 (p = .67) PSS: 31.8 vs. 36.9 (p < .001) MSS: 48.6 vs. 49.6 (p = .18)	3.1 vs. 1.9 (p < .001) 3.1 vs. 2.0 (p < .001)	86.2 88.6	Germany (1)
Tarmasso et al. (2012)	100	***	79.7 ± 6.1	46 (46)	24	SF-36v2 MLHFQ	PSS: 31.9 vs. 51.5 (p < .0001) MSS: 44.7 vs. 49.5 (p = .0002) 41.5 vs. 15.9 (p < .0001)	***	***	Italy (1)
Reynolds et al. (2012)**	348	84 (24)	83.6 ± 6.8	147 (42.2)	1 6 12	KCCQ SF-12 EQ-5D KCCQ SF-12 EQ-5D KCCQ SF-12 EQ-5D	39.3 vs. 63.0 (p < .001) PSS: 29.7 vs. 34.7 (p < .001) MSS: 47.0 vs. 51.3 (p < .001) .66 vs. .74 (p < .001) 39.3 vs. 69.1 (p < .001) PSS: 29.7 vs. 36.4 (p < .001) MSS: 47.0 vs. 52.1 (p < .001) .66 vs. .76 (p < .001) 39.7 vs.68.4 (p < .001) PSS: 29.7 vs. 36.0 (p < .001) MSS: 47.0 vs. 52.0 (p < .001) .66 vs. .75 (p < .001)	***	***	USA (22), Canada, (2) Germany (1)
Kala et al. (2013)	30	***	***	***	1, 3, 12	EQ-5D	50 vs. 67 (p < .001) ****	***	***	Czech. (1)
Goncalves et al. (2013)	74	15 (20)	82 ± 8	40 (54.1)	6.5	MLHFQ	PD: 23.2 vs. 8.6 (p < .001) ED: 5.4 vs. 2.6 (p < .0001)	2.9 vs. 1.4 (p < .001)	94.3	Spain (1)
Amonn et al. (2013)	51	16 (31)	79.7 ± 9.2	25 (49)	15 ± 10	SF-36 HADS	*****	***	87.1	Switzer-land (1)
Elmalem et al. (2014)	73	17 (19)	82.3 ± 7.3	32 (43.8)	1 6	EQ-5D EQ-5D	.66 vs. .73 (p < .001) .66 vs. .73 (p < .0001)	3.2 vs. 2.0 p < .001 3.2 vs. 1.9 p < .001	***	France (1)

** 43 refused follow-up assessment*
*** Data for transfemoral TAVR group only*
**** Insufficient data*
***** 12 month data only*
****** Measures only assessed at follow-up*

PCS: physical component score
MCS: mental component score
PSS: physical summary score
MSS: mental summary score
PD: physical dimension
ED: emotional dimension

A summary of the results from all TAVR studies that have examined QOL is provided in Table 2. These studies have consistently and uniformly shown that TAVR patients report improved QOL concerning physical health post operatively as measured by the SF-36 family of assessments (Amonn et al., 2013; Bekeredjian et al., 2010;

Fairbairn et al., 2012; Georgiadou et al., 2011; Krane et al., 2010; Krane et al., 2012; Ussia et al., 2009; Ussia et al., 2011; Reynolds et al., 2011; Reynolds et al., 2012; Tarmasso et al., 2012). All but three studies (Fairbairn et al., 2012; Krane et al., 2010; Krane et al., 2012) have also shown significant improvement in mental QOL. Studies have also uniformly demonstrated improved QOL as measured by disease specific measures of QOL including the MLHFQ (Goncalves et al., 2013; Gotzmann et al., 2009; Gotzmann, 2011; Tarmasso et al., 2012), and the KCCQ (Reynolds et al., 2011; Reynolds et al., 2012), as well as a general measure of QOL, the EQ-5D (Elmalem et al., 2014; Fairbairn et al., 2012; Kala et al., 2013; Reynolds et al., 2012). In at least two studies, these gains were so substantial that TAVR patients reported QOL as good or better than norms for their age (Fairbairn et al., 2012; Krane et al., 2012). They also provide evidence that many patients experience improvements in QOL within the first month after TAVR (Fairbairn et al., 2012; Gotzmann et al., 2009; Reynolds et al., 2011; Reynolds et al., 2012). Several studies showed reported reduction in NYHA class (Bekeredjian et al., 2010; Georgiadou et al., 2011; Goncalves et al., 2013; Gotzmann et al., 2009; Krane et al., 2010; Krane et al., 2012; Ussia et al., 2009). Several studies also found that a very large percentage (85 – 94%) of TAVR patients were satisfied with their decision to undergo TAVR (Amonn et al., 2013; Goncalves et al., 2013; Krane et al., 2010; Krane et al., 2012). These findings begin to establish a trend that TAVR patients are experiencing QOL benefits in more than one domain. However, the exact nature of those benefits is less clear. Many are physical and/or mental in nature, but it is also likely that some are psychological. While one study used a measure that specifically measured emotional health (Amonn et al., 2013), the measure was not administered at

baseline and was used primarily to compare differences between SAVR and TAVR groups post-operatively with no differences found.

While this body of literature is significant, as with any study, there are limitations in the findings and conclusions that can be drawn. First, all but the two studies by Reynolds are single-center studies done in European countries with relatively small sample sizes. Second, the ability to generalize results to US and other populations may be limited. Third, in all of these studies for which there is mortality data, a substantial number of patients died before completion of follow-up creating the potential of selection bias. Fourth, time of follow-up was limited to one year in all but one study (Amonn et al. 2013) and that study was cross-sectional with a wide variability in time of assessment since surgery. Extended time points would be more meaningful in ascertaining the long term effects of TAVR on QOL. Fifth, only four studies had comparison groups (Amonn et al., 2013; Kala et al., 2013; Reynolds et al., 2011; Reynolds et al., 2012). No studies had control or placebo groups for understandable reasons. While that would have provided the strongest test of the specific effects of TAVR, because of the disease state of these patients it would be unethical to conduct such studies. Only two of the four studies with comparison groups were randomized (Reynolds et al., 2011; Reynolds et al., 2012) so differences in between-group results in Kala et al. and Amonn et al. and within-group differences in the other studies may be influenced by differences in baseline characteristics of the study population. Lastly, while predictors of outcomes were examined by a few of these studies (Amonn et al., 2013; Bekeredjian et al., 2010; Fairbairn et al., 2012; Krane et al., 2012), the factors that were considered varied and, therefore, there is no consensus on what predicts positive or negative health outcomes.

Patient Characteristics for Future Research

While several studies have examined QOL in TAVR research, many other important patient characteristics have received little attention. The following is a brief summation of information concerning important patient characteristics that merit investigation in this patient population.

Psychological distress. Psychological distress is a general term that can be used to describe the unpleasant symptoms of the two most common psychological disorders, anxiety and depression (Poole et al., 2015).

Anxiety. Anxiety disorders are the most common psychological disorders, affecting 30% of the general population (Kessler, Chiu, Demler, & Walters, 2005). The presence of an anxiety disorder has been associated with increased prevalence of a variety of physical ailments including hypertension (Johannessen, Strudsholm, Foldager, & Munk-Jørgensen, 2006), diabetes (Atlantis, Vogelzangs, Cashman, & Penninx, 2012), and peptic ulcer disease (Goodwin & Stein, 2002). Elevated levels of anxiety in cardiac patients have been found in numerous studies (Fan, Strine, Jiles, & Mokdad, 2008; Kawachi et al., 1994; Kubzansky, Cole, Kawachi, Vokonas, & Sparrow, 2006; Rozanski, Blumenthal, Davidson, Saab, & Kubzansky , 2005). Anxiety is believed to affect the function of the heart by exacerbating electrical instability (Rozanski, Blumenthal, & Kaplan, 1999) and contributing to atherogenesis (Kubzansky & Kawachi, 2000; Manuck and Krantz, 1986). Shen et al. (2008) used four scales of the MMPI to assess anxiety in men (N = 635) over an average of 12.4 years. They created an overall index scale of anxiety using factor analysis and found that anxiety-prone dispositions were a strong risk factor for MI. Fan et al. (2008) examined measures of anxiety,

depression, and other behavioral risk factors on a large national sample *(N* = 129,499) of people over the age of 44 and found that participants who had a lifetime history of anxiety disorders were more likely than others to have either angina, coronary heart disease, MI, or stroke (16.6% vs. 10%). Existing research implicates anxiety as playing a potentially significant role in cardiac disease and the possibility that anxiety level may be a predictor of health outcome in TAVR patients warrants investigation.

Depression. There is broad evidence that depression is associated with increased risk of adverse cardiovascular events and mortality (Barth, Schumacher, & Hermann-Lingen, 2004; Blumenthal et al., 2003; Carney, Freedland & Shepps, 2004; Frasure-Smith, Lesperance, & Talajic, 1995). Major depressive disorder is also prevalent in patients with CVD with estimates ranging from 15-40% (Office of Disease Prevention and Health Promotion, 1998). Depression is also associated with health behaviors that increase the risk of CVD including smoking, poor dietary habits, non-adherence to medication regimen, and sedentary lifestyle (Kop & Plumhoff, 2012). Depression has been found to be a significant predictor of morbidity, mortality, and low QOL in patients with severe heart disease (Mallik et al., 2005). Mallik et al. assessed patients who underwent CABG *(N* = 963) using the Geriatric Depression Scale (GDS) and the physical component scale of the SF-36. Patients with a GDS score of < 5 experienced a mean improvement of 60.1% on physical function, patients with a score between 5 and 9 experienced an improvement of 49.8%, while patients with a GDS score of > 9 experienced an improvement of 39.7% (p = 0.002). The authors found that an elevated score on the GDS (> 9) was a stronger predictor of poor physical well-being than other measures of disease severity such as previous MI, heart failure on

admission, history of diabetes, and LVEF. In a recent meta-analysis, Lueng et al. (2012) reported that both pre-morbid and post-morbid depression was associated with worse outcomes in patients with coronary heart disease. Based on studies such as these, depression appears to be associated with worse outcomes in patients with heart disease. Therefore, examining the effects of depression in TAVR patients is particularly warranted.

Positive Psychology/Resilience Factors. Patient factors that fall within the realm of both positive psychology and resilience have been found to be associated with health outcomes. These factors include such components as satisfaction with life, will to live, and positive health expectations.

Satisfaction with life. Satisfaction with life as a whole is considered an important component of subjective well-being (Pavot & Diener, 1993; Lyubomirsky, King, & Diener, 2005) and has been found to be associated with improved physical health outcomes such as reduced risk of aortic calcification (Matthews, Owens, Edmundowicz, Lee, & Kuller, 2006), fewer emergency room and hospital visits (Gil et al., 2004), fewer illnesses (Goldman, Kraemer, & Salovey, 1996), and longevity (Levy, Slade, Kunkel, & Kasl, 2002). Life satisfaction has also been found to be associated with improved outcomes such as academic success (Borello, 2005) reduced suicide risk (Koivumaa- Honkanen, et al. 2001), and expectation for success (Wright & Mischel, 1982). While this construct has yet to be included in any previous investigations of TAVR, given the rising importance and role that both positive and negative affect can play, assessment of this construct was included in the current study to determine if it was associated with post-op quality of life gains .

Will to live. Clinical lore among surgeons has long speculated about the role will to live may play in patient outcomes and, in fact, research suggests that patient will to live may play a crucial role in mortality (Levy, Slade, Kunkel, & Kasl, 2002; Phillips & Feldman, 1973; Ray, 2004; Shimizu & Pelham, 2008). Shimizu and Pelham (2008) replicated previous studies that had suggested that people were able to defer death until after meaningful events (e.g., holidays, birthdays) by analyzing a database of over 30 million decedents and found that people were more likely to die on days following an event like Christmas, than on the days preceding. Levy et al. (2002) analyzed a database of 660 individuals aged 50 and older and found that those with positive self-perceptions of aging lived 7.5 years longer than those with less positive self-perceptions ($p < 0.001$). They assessed will to live with three items asking patients to rate the degree to which their life was empty-full, hopeless-hopeful, and worthless-worthy with one item of each pair on the opposite ends of a seven point scale. They found that a patient's will to live partially mediated the relationship between positive self-perceptions of aging and longer life. Further, Martickainen & Valkonenen (1996) studied married couples ages 35 to 84 *(N* = 1.5 million) and found they were more likely than normal to die within the six months after their spouse had died, suggesting an increased vulnerability to disease. Reasons for this vary but one hypothesis is that having a spouse may help keep people engaged in healthy behaviors and thus, the loss of one's spouse decreases such behaviors, hastening mortality. Alternatively, the loss of a spouse may result in weakening the survivor's will to live as part of the grieving process. Further, since almost all TAVR patients are quite elderly and face multiple health issues,

it may be that a patient's will to live may waver in light of heightened perceptions of the inevitability of death.

***Positive health expectations*.** Positive expectations about the future have been found to be associated with better mental and physical health by a number of studies (Peterson & Bossio, 2001; Scheier et al., 1989; Taylor & Brown, 1988). Optimistic outlook may increase the likelihood one will adopt adaptive coping strategies like problem-solving rather than avoidance (Nes & Segerstrom, 2006) and may also result in better response to stressors (Aspinwall & Taylor, 1997). Leedham, Meyerowitz,Muirhead & Frist (1995) examined the relationship between positive expectations and health in heart transplant patients and found they were associated with patient adjustment and QOL. Sears et al. (2004) found that cardiac patients with high health expectations reported better general health at follow-up after controlling for important baseline cardiac health factors. Therefore, results from studies examining the effects of health expectations in a group of elderly, frail TAVR patients may provide evidence for the need to develop interventions to improve QOL in this population.

Behavioral factors. Important behavioral factors that merit investigation in TAVR patients include physical activity, shortness of breath, and medication adherence. The relevance of these factors concerning this patient population is described in detail below.

Physical activity. The benefits of physical activity and the consequences of the lack of physical activity have been documented in an abundance of literature (Physical Activity Guidelines Advisory Committee, 2008). While the elderly are one of the least active population groups, there are a variety of benefits they may gain from improved

physical activity including less depression, improved independence, better cognitive functioning, and better overall QOL (Nelson et al., 2007). However, to date we have no understanding about the activity patterns of TAVR patients and how they may play a role in treatment outcomes. Therefore, obtaining information about self-reported physical activity levels at baseline and post-TAVR may help increase understanding of the physical benefits of TAVR and whether pre-TAVR physical activity levels may be a predictor of other health outcomes.

Shortness of breath. Shortness of breath, also known as dyspnea, is one of the most prominent symptoms of aortic valve disease (Carabello, 2013). Worsening dyspnea often means a worsening prognosis in valve disease. Dyspnea is one of several symptoms, that when occurring alone in the presence of severe aortic stenosis, may result in recommendation for valve replacement (Shah, 2012). Dyspnea is one factor that inhibits people with valve disease from living a full and active life and improvement in dyspnea may be expected after TAVR. As such, patient self-report of symptoms of dyspnea provides one measure of improvement post-TAVR and may also be found to be a predictor of QOL as well.

Medication adherence. Non-adherence to medication protocol has been defined as taking medications as prescribed only 75% of the time or less (Gehi, Ali, Na & Whooley, 2007). The estimated average adherence rates to medication instructions in cardiac patients has been found to be between 51% to 79%, depending on the number of daily doses (Horwitz et al., 1990). Therefore, better understanding the extent to which patients adhere to their medication regimen would certainly impact the benefits they could gain from TAVR.

Summary

TAVR has been found to be an extremely beneficial surgical procedure for treating patients contraindicated for SAVR. The effects of TAVR in improving QOL have consistently been demonstrated in the past 12 years. TAVR is a relatively new medical procedure and research to date has provided a starting point for gaining an understanding of the outcomes of TAVR and for examining possible predictors of outcomes. However, several important factors have not been examined to date that could play a significant role in treatment outcome and have significant implications for patient care. As emphasized in this literature review, almost all patient characteristics that are psychological in nature have been neglected in TAVR research. In addition, important physiological characteristics and health behaviors in patients with valve disease have been unaddressed. The overarching aim of this proposed research is to provide a better understanding of the psychological and physiological benefits of TAVR and to gain a better understanding of patient characteristics associated with desirable health outcomes.

Study Aims

Aim 1. The first aim of this study was to describe the characteristics of a population of TAVR patients (who were contraindicated for SAVR) on the demographic data and measures described above. Baseline data on physical activity, anxiety, depression, life satisfaction, positive health expectations, dyspnea, and will-to-live have not previously been gathered on TAVR patients. This data provides information to future TAVR patients and health care providers on the preoperational biopsychosocial

condition of valve patients. The first aim was accomplished by gathering baseline characteristics by counts, percentages, and mean ± SD where appropriate.

Aim 2. The second aim of this study was to describe changes in TAVR patients on physical activity, generic and disease-specific, anxiety, depression, dyspnea, and will-to-live between baseline and 3-months post-op. The advantage of testing each patient against his or her baseline value is that it corrects for any potential survivor bias due to participant mortality. Based on the non-normal distribution of scores, the second aim was accomplished by determining differences in the results of each measure from baseline to 3-months by using the Wilcoxon Signed Rank Test.

Based on previously described research, it was expected that physical activity, QOL, and dyspnea would demonstrate significant improvement as a result of TAVR. It was not expected that anxiety, depression, or will-to-live would change significantly as those states are generally a result of many more factors than TAVR would directly impact.

Aim 3. The third aim of this study was to analyze possible predictors of change in QOL in TAVR patients as measured by the SF-12v2 and KCCQ at 3-months post-op. Predictors that were analyzed independently included baseline measures of QOL, anxiety, depression, life satisfaction, positive health expectations, dyspnea, and will-to-live. The expectation was that participants with lower baseline QOL and higher dyspnea would experience greater increases on QOL as a result of TAVR alleviating problematic cardiac symptoms that were negatively impacting QOL. The hypothesis was that higher scores on anxiety and depression would be associated with decreased change in QOL. Higher scores on positive health expectations, life satisfaction, and will-to-live were

expected to be associated with increased improvement in QOL because higher scores are associated with greater propensity for positive experiences. Due to the non-normal distribution of scores, a regression analysis was conducted to determine the relationship between each predictor and change in QOL post-TAVR using Spearman's Rho.

The information gathered from this aim may help health care providers better identify patients who may and may not benefit from TAVR. In some cases, early identification may allow for treatment (e.g., pharmacologic or psychological therapy in the case of depression) that may increase the likelihood of positive outcomes of surgery. These psychosocial and physiological predictors have not yet been assessed in TAVR research.

Chapter III: Method

Participants

This study was conducted with patients who had been indicated for TAVR and contraindicated for SAVR, after receiving care at the East Carolina Heart Institute Outpatient Clinic in Greenville, NC or the St. Thomas Research Institute, Nashville, TN. Patients were required to speak and read English, be 18 or older, and be able to cognitively complete questionnaires with assistance from research assistants. The initial expectation was that recruiting 30 patients for the study by May 2014 would be possible based on past history of the number of TAVR procedures performed at this site. That did not prove possible and only 15 were recruited with one of those dying within one week of recruitment and another declining in mental capacity to the point where her ability to complete the questionnaire with meaningful data was compromised. Therefore, the study opened another site in Nashville, TN and from that site 21 participants were successfully recruited for a total of 34 participants.

This study received IRB approvals for East Carolina University (ECU) (Appendix A) and the IRB board at ECU also provided oversight for the St. Thomas site. No subjects were compensated financially or otherwise for participation in this study.

Measures

Participants completed a short questionnaire consisting of questions about demographics, generic QOL, disease-specific QOL, psychological distress, and positive psychology/resilience factors. A description of each section of the survey is provided below.

Demographics. Demographic questions include one question each about marital status, education, employment status, race/ethnicity, and living situation.

Generic QOL. The SF-12v2 is a 12-item revision of the SF-36 (Ware et al., 1996) and provided a general health measure of QOL for this study. The SF-12 maintains 90% of the variance of the mental and physical health scales of the SF-36, although it has less accurate reproduction of the eight scales of the SF-36. Administration time is lowered from five minutes for the SF-36 to two minutes for the SF-12. The SF-12v2 is an updated version of the SF-12 that adjusted some of the response options. A recent review of the SF-12v2 using a large, adult patient population *(N* = 2,410) found that the mental and physical health scales explained over 80% of the total variances of the SF-36v2 (Lam, Lam, Fong & Huang, 2013). The SF-12v2 is scored by computer and provides a *T*-score based on a representative US population sample. Recently evaluated Cronbach's alpha on the physical component scale has been found to range from 0.81 - 0.90 (*M* = 0.87) in various population groups (DeSmedt et al., 2013). Cronbach's alpha on the mental component scale ranged from 0.74 – 0.89 (mean = 0.84). Due to the complexity of the computerized scoring algorthim used to calculate both scale scores of the SF-12, a reliability estimate was unable to be computed for the current study. However, both baseline and post-op Cronbach alpha coefficients were .82 for the measure as a whole.

Disease-specific QOL. The KCCQ is a 23-item measure commonly used to evaluate the health status of heart failure patients (Creber et al., 2012). The five domains addressed by the KCCQ are: symptoms, physical limitation, social limitation, self-efficacy, and quality of life and yield nine subscale scores with scores from 0 – 100;

higher scores are indicative of fewer symptoms and higher QOL (Green et al., 2000). The individual scale scores are combined into an overall summary scale. A change in score of 5, 10, and 20 points on any subscale or the overall summary score represents a small, moderate, and large change respectively (Reynolds et al., 2012). The KCCQ overall summary score has been found to correlate with NYHA functional class as follows: Class I is roughly equal to KCCQ summary score of 75 to 100; Class II, to a score of 60 to 74; Class III, to a score of 45 to 59; and Class IV, to a score of 0 to 44 (Spertus et al., 2005). Arnold et al. (2013) evaluated the psychometric properties of the KCCQ in patients with severe aortic stenosis and found good construct validity when comparing each domain of the KCCQ against a reference measure. In an evaluation by Creber et al., the Cronbach's alpha was 0.92 indicating excellent internal consistency. In the current study, the baseline Cronbach alpha coefficient was .93 and the post-op Cronbach alpha coefficient was .96.

Psychological distress (HADS). The HADS is a 14-item measure that assesses depression and anxiety and is used primarily in hospital settings (Zigmond & Snaith, 1983). All somatic symptoms related to depression and anxiety are excluded from this measure in order to account for the likely experience of such symptoms from known or expected physiological problems in this population. Seven items on the scale assess depression and the other seven items assess anxiety. Each item is scored from 0-3 for a total possible score of 21 on each scale with higher scores representing higher levels of anxiety or depression. The established clinical cutoff for each subscale is eight. A review by Bjelland, Dahl, Haug, and Neckelmann (2002) identified over 700 studies that used the HADS with the majority confirming the two-factor solution in accordance with

the subscales of anxiety (HADS Anxiety) and depression (HADS Depression). Cronbach's alphas for HADS-A varied from .68 to .93 (*M* = .83) and for HADS-D from .67 to .90 (*M* = .82). Mean Cronbach's alpha values indicate good internal consistency for both scales. In the current study, the baseline HADS Anxiety Cronbach alpha coefficient was .82 and the post-op Cronbach alpha coefficient was .55. Question three on the HADS Anxiety scale ("I get a sort of frightened feeling like 'butterflies' in the stomach.") had zero variance in the post-op assessment and was removed for the reliability analysis. The baseline HADS Depression Cronbach alpha coefficient was .73 and the post-op Cronbach alpha coefficient was .80.

Positive psychology/resilience factors. The positive psychology/resilience factors considered in this study are satisfaction with life, will to live, and positive health expectations.

Satisfaction with life scale. This five-question scale developed by Pavot and Diener (1993) assesses satisfaction with life as a whole. Participants rate their satisfaction with different aspects of their life on a 7-point Likert scale. Possible scores range from 5-35 with higher scores indicating greater life satisfaction with a score of 20 representing the neutral point on the scale. Scores between 5 and 9 indicate that the respondent is extremely dissatisfied with life, scores between 10 and 14 indicate moderately dissatisfied, scores between 15 and 19 indicate slightly dissatisfied, scores between 21 and 25 represent slightly satisfied, scores between 26 and 30 indicate moderately satisfied, and scores ranging between 31 and 35 indicate that the respondent is extremely satisfied with life. Cronbach's alpha has been shown to range from .79 - .89 (Pavot & Diener, 1993; Adler & Fagey, 2005). This measure was only

administered at baseline and in the current study the Cronbach alpha coefficient was .89.

Will-to-live scale. Participants rated their will-to-live on a single-item VAS with anchors of “no will to live” and “absolute will to live”. This scale has been used in one other study and had a high correlation with depression, anxiety, desire for death, burden to others, and hopelessness (Chochinov et al., 2005). However, its psychometric properties have not been evaluated. There are no published scales of measures of will to live for which psychometric properties have been evaluated.

Positive health expectations scale. The PHE assesses patient beliefs about the efficacy of their treatment and their future outlook (Leedham et al., 1995). The scale was first used with heart transplant patients and demonstrated good convergent validity with QOL scores, divergent validity with mood disturbances scores, and predictive validity with physical health measures. Sears et al. (2004) used this measure to assess PHE in ICD patients and modified it by adding a question assessing motivation for ICD implantation. The current study has similarly modified the PHE with a question assessing motivation for valve surgery. Respondents rate their health expectations on a 7-point Likert scale. There are eight questions and possible scores range from 8 to 56 with higher scores indicating a more positive outlook. Cronbach’s alpha was 0.81 and 0.88 in the Leedham et al. and Sears et al. studies respectively, indicating good internal consistency. This measure was only administered at baseline. In the current study the Cronbach alpha coefficient was .82.

Behavioral factors. The behavioral factors examined in this study are physical activity, shortness of breath, and medication adherence.

Physical activity scale. Five standardized questions concerning physical activity were used that came from a questionnaire developed for the Heart and Soul Study (Whooley et al., 2008), a large study *(N* = 1,024) of patients with coronary heart disease (CHD). The questions for this study queried participants on the amount of exercise they have conducted over the previous month, including one question asking patients to rate the amount of exercise they get compared to others their age and sex. The range of possible scores was 0-17 with higher scores indicating greater physical activity. In the current study the baseline Cronbach alpha coefficient was .64 and the post-op Cronbach alpha coefficient was .74.

Shortness of breath scale. The SOBQ is a self-report questionnaire in which patients indicate the severity of shortness of breath experienced during 21 activities of daily living that vary in rate of exertion (Eakin, Resnikoff, Prewitt, Ries, & Kaplan,1998). Ratings for each item are on a 6-point scale (e.g., 0 = Not at all, 4 = Severely, 5 = Maximally or unable to do because of breathlessness). An additional three questions inquire about limitations due to shortness of breath, fears about overexertion, and fear of shortness of breath. The maximum score is 120 and a change of 5 points is considered clinically significant (Ries, 2005). Reliability has been found to be superior to other measures of dyspnea including the Baseline Dyspnea Index (BDI), American Thoracic Society Dyspnea Scale and the Oxygen Cost Diagram (Eakin et al., 1998). Validity has been found to be good after examination of variables with which it is believed to be related such as exercise tolerance, health-related QOL, lung function, and depression. The study by Eaken et al. had a Cronbach's alpha value of 0.96 indicating excellent internal consistency. In the current study the baseline Cronbach

alpha coefficient was also .96. The post-op Cronbach alpha coefficient could not be computed because only one participant completed all questions.

In this study, many participants chose not to answer several questions that inquired about activities that they had either not done in too great a time period or currently engaged in too infrequently to feel comfortable assessing (e.g., washing a car, mowing a lawn). Therefore, questions that were answered by fewer than 75% of participants (questions 14 and 17-21) were removed from consideration in this analysis. The highest possible score in this scale, now entitled Geriatric SOBQ, was 90. Participants who answered at least 15 of the 18 questions of the Geriatric SOBQ were assigned a score computed on a 90 point scale. In the current study the baseline Cronbach alpha coefficient of the Geriatric SOBQ was .95 and the post-op Cronbach alpha coefficient was .93.

Medication adherence scale. Five standardized medication adherence questions were used that also came from the Heart and Soul study (Gehi et al., 2007). The questions for this study queried participants on the degree to which they adhered to their medication protocol over the previous month with a possible range of scores from 0-25 with lower scores indicating greater adherence. In the current study, baseline Cronbach alpha coefficient was .67. The post-op Cronbach alpha coefficient could not be computed because four of the five questions had zero variance.

Procedure

Potential participants were identified by their physician upon arrival and check-in at their scheduled TAVR review appointment. Patients indicated for and choosing TAVR were approached by a research assistant and given a brief description of the study and

invited to participate. If they accepted, the informed consent was reviewed and signed. The questionnaire was explained and either self-administered or administered with the assistance of the research assistant. Patients were contacted for the subsequent administration of the measure via phone or mail three months post-TAVR.

Statistical Analyses

Statistical analyses were performed with SPSS® 20.0 (SPSS Inc., Chicago, IL). In all analyses, $p \leq .05$ was considered significant and no adjustments were made for multiple comparisons since the evaluated data were not random and due to concern for Type II Error in this novel population (Rothman, 1990). Effect sizes of .1, .3, or .5 were considered small, medium, or large respectively (Cohen, 1992) and calculated using the convention, $r = z$ / square root of N, where, for between groups comparisons, N = total number of cases, while for within group comparisons N = total number of cases multiplied by the total number of observations (Pallant, 2007).

Baseline population characteristics on demographic data and the measures described previously were calculated by counts, percentages, and mean ± SD where appropriate. Between group comparisons of baseline characteristics were conducted using Mann Whitney U based on the non-normal distribution of scores. Changes in TAVR patients from baseline to 3-months post-op on physical activity, QOL as measured by the KCCQ and SF-12v2, anxiety, depression, dyspnea, and will-to-live were assessed by using the Wilcoxon Signed Rank Test based on the non-normal distribution of scores. Nonparametric tests were conducted using normal approximations (Bellara, Julien, & Hanley, 2010). Possible predictors of change in QOL in TAVR patients (as measured by the SF-12v2 and KCCQ) were analyzed

independently and included baseline measures of QOL, anxiety, depression, life satisfaction, positive health expectations, dyspnea, and will-to-live. A regression analysis was conducted to determine the relationship between each predictor and change in QOL post-TAVR using Spearman's Rho due to the non-normal distribution of scores.

CHAPTER IV: RESULTS

Demographic Data

A total of 39 patients were approached to participate in the study and of these, 36 agreed for a participation rate of 92%. Two patients declined to participate for unknown reasons and one patient declined due to concern that completing the survey would induce anxiety. Of the 36 patients who agreed to participate, one died prior to returning the baseline survey. Another patient who agreed to participate was later deemed ineligible due to cognitive concerns raised by a family member who was also a primary care provider. Of the 34 patients completing the baseline survey, thirteen were recruited from the East Carolina University Heart Institute site and 21 were recruited from the St. Thomas Research Institute site in Nashville, Tennessee. Of the 34 participants,18 completed the post-op survey for a follow-up rate of 53%. Patients ranged in age from 52 to 95 with a mean age of 79.2. Baseline demographic characteristics of the study group are provided at Table 3 and baseline clinical scores are provided at Table 4.

Table 3

Demographic Characteristics

	n (%)
Age (years)	
< 80	17 (50.0%)
80 +	17 (50.0%)
Sex	
Women	16 (47.1%)
Men	18 (52.9%)
Race	
White	32 (94.1%)
Black / African American	2 (5.9%)
Level of education	
Some high school	8 (23.5%)
High school graduate or equivalent	14 (41.2%)
Some college or vocational school	5 (14.7%)
College graduate	1 (2.9%)
Graduate or professional degree	6 (17.6%)

Marital status	
Married	15 (44.1%)
Widowed	13 (38.2%)
Divorced	4 (11.8%)
Never married	2 (5.9%)
Social living status	
Live alone	9 (26.5%)
Live with one or more people	25 (73.5%)

Table 4

Baseline Clinical Scores

Measure	***M***	***SD***	***n***
KCCQ			
Overall Summary Score	54.2	25.9	33
Physical Limitation	53.1	29.4	32
Symptom Stability	43.4	14.2	34
Symptom Frequency	55.7	27.3	34
Symptom Burden	54.2	27.9	34
Total Symptom	54.9	25.2	34
Self-efficacy	92.3	16.3	34
Quality of Life	52.4	29.2	34
Social Limitation	53.5	32.7	32
Clinical Summary	54.7	25.3	33
SF-12			
PCS	28.9	8.8	33
MCS	53.2	10.3	33
HADS Depression	6.7	3.8	34
HADS Anxiety	4.8	4.4	33
Geriatric SOBQ	33.6	21.5	34
Satisfaction with Life Scale	24.8	9.1	24
Positive Health Expectations Scale	46.9	7.9	34
Physical Activity	4.5	3.7	34

Medication Adherence	1.0	1.7	34
Will to Live	9.5	1.8	33

Comparisons of Baseline Scores

Because of the small sample size, the sample was collapsed into no more than two groups for each demographic characteristic and examined for clinically relevant differences for the following measures: all of the KCCQ scales including the overall summary score, SF-12 Physical Component Score, SF-12 Mental Component Score, HADS Depression, HADS Anxiety, Geriatric SOBQ, SWL Scale, PHE Scale, and physical activity. There was insufficient variability on the Will to Live Scale to conduct meaningful analyses. Inspection of data found that they were not normally distributed and therefore within group baseline characteristics were examined using the Mann-Whitney *U* Test. There were significant baseline differences on some measures based on sex, marital status, and age. There were no significant baseline differences based on social living status or education level, however.

Comparisons of Baseline Scores in Men and Women

Results indicated that there was a significant difference in the KCCQ Symptom Burden scores of men (*Mdn* = 62.6, *n* = 18) and women (*Mdn* = 50.0, *n* = 16), *U* = 85, *z* = -2.07, *p* = .038, *r* = .4, with men reporting less difficulty with symptoms. Higher scores on this measure indicate less symptom burden. There was a significant difference in the SF-12 Mental Component Scale scores of men (*Mdn* = 58.6, *n* = 17) and women (*Mdn* = 49.1, *n* = 16), *U* = 66, *z* = -2.52, *p* = .012, *r* = .4, with men reporting better mental functioning scores. Again, higher scores on this measure indicate better mental quality of life. There was also a significant difference in the HADS Anxiety scores of men (*Mdn* = 2.5, *n* = 18) and women (*Mdn* = 5.0, *n* = 15), *U* = 76, *z* = -2.17, *p* = .03, *r* = .4, with

men reporting lower anxiety scores. The KCCQ Total Symptom score of men (*Mdn* = 63.5, *n* = 18) and women (*Mdn* = 44.8, *n* = 16), *U* = 88, *z* = -1.93, *p* = .053, *r* = .3, approached statistical significance. Higher scores indicate greater health quality of life as measured by a combination of symptom frequency and symptom burden scores. No other differences in baseline clinical characteristics for men or women approached statistical significance (Table 5).

Table 5

Sex Comparisons of Baseline Scores

Measure	Sex					
	Men			Women		
	M	***Mdn***	***N***	***M***	***Mdn***	***N***
KCCQ						
Overall Summary	57.7	55.5	18	50.1	48.4	15
Physical Lim	54.6	29.1	18	51.2	46.9	14
Symptom Stab	41.7	50.0	18	45.3	50.0	16
Symptom Freq	62.6	59.4	18	47.9	45.8	16
Symptom Brdn*	64.4	62.6	18	42.7	50.0	16
Total Symptom	63.5	65.2	18	45.3	44.8	16
Self-efficacy	91.7	100.0	18	93.0	100.0	16
Quality of Life	57.7	62.5	18	46.4	41.8	16
Social Limitation	57.0	50.0	17	49.4	50.0	15
Clinical Summary	59.0	60.5	18	49.4	44.8	15
SF-12						
PCS	28.6	31.9	17	29.3	29.2	16
MCS*	57.8	58.6	17	48.3	49.1	16
HADS Depression	6.9	6.5	18	6.5	6.5	16
HADS Anxiety*	3.7	2.5	18	6.0	5.0	15
Geriatric SOBQ	30.9	24.6	18	36.7	33.9	16

SWL	26.9	31.0	13	22.4	25.0	11
PHE	47.3	51.0	18	46.6	47.5	16
Physical Activity	5.2	3.5	18	3.8	3.0	16
Med Adherence	0.7	0.0	18	1.4	0.0	16

* $p < .05$.

Comparisons of Baseline Scores by Age Groups

There were several age differences across the measures. Older patients in this sample appeared to fare better in QOL domains. There was a significant difference in the KCCQ Symptom Frequency scores of patients 80 or older (*Mdn* = 66.7, *n* = 17) and patients under the age of 80 (*Mdn* = 50.0, *n* = 17), *U* = 65.5, *z* = -2.73, *p* = .006, *r* = .5). Higher scores indicate greater health quality of life when measured by heart-related symptom frequency. There was also a significant difference in the SWL scores of patients 80 or older (*Mdn* = 28.7, *n* = 12), and patients under the age of 80 (*Mdn* = 21.0, *n* = 12), *U* = 37, *z* = -2.05, *p* = .04, *r* = .4) with higher scores indicating higher life satisfaction. In addition, there was a significant difference in the physical activity scores of patients 80 or older (*Mdn* = 5.0 , *n* = 17) and patients under the age of 80 (*Mdn* = 3.0, *n* = 17), *U* = 72, *z* = -2.52 , *p* = .012 , *r* = .4) with patients 80 or older reporting greater physical activity.

Table 6

Age Comparisons of Baseline Scores

Measure	**Age**					
	< 80			**80 +**		
	M	***Mdn***	***N***	***M***	***Mdn***	***N***
KCCQ						

Overall Summary	47.9	47.9	16	60.1	58.0	17
Physical Lim	46.0	44.8	16	60.3	60.4	16
Symptom Stab	39.7	50.0	17	47.1	50.0	17
Symptom Freq*	44.3	50.0	17	67.0	66.7	17
Symptom Brdn	49.0	41.8	17	59.3	50.0	17
Total Symptom	46.7	41.8	17	63.2	63.6	17
Self-efficacy	91.2	100.0	17	93.4	100.0	17
Quality of Life	50.3	41.8	17	54.4	58.3	17
Social Limitation	44.8	40.7	16	62.1	50.0	16
Clinical Summary	46.7	42.7	16	62.2	60.5	17
SF-12						
PCS	26.3	28.4	17	31.7	32.7	16
MCS**	50.4	53.7	17	56.1	57.8	16
HADS Depression	7.5	7.0	17	5.9	6.0	17
HADS Anxiety	5.7	3.5	16	3.9	4.0	17
Geriatric SOBQ	38.9	33.0	17	28.4	29.3	17
SWL*	21.0	20.0	12	28.7	31.5	12
PHE	47.8	50.0	17	46.1	45.0	17
Physical Activity**	2.9	3.0	17	6.2	5.0	17
Med Adherence	1.4	0.0	17	0.6	0.0	17

*p < .01, **p < .05

Comparisons of Baseline Scores by Current Marital Status

Comparisons between patients who were currently married and patients who were either widowed, currently divorced, or never married found that married participants reported somewhat less favorable physical health than the other group at baseline. There were significant differences in the SF-12 Physical Component Scale scores of married patients (*Mdn* = 23.1, *n* = 15) and the widowed, currently divorced, or never married group (*Mdn* = 31.7, *n* = 18), *U* = 75, *z* = -2.17, *p* = .03, *r* = .4). Higher

scores indicate better physical quality of life. While not quite reaching statistical significance, there were differences in the Geriatric SOBQ scores of married patients (*Mdn* = 21.2, *n* = 15) and the widowed, currently divorced, or never married group (*Mdn* = 14.6, *n* = 19), *U* = 87, *z* = -1.93, *p* = .54, *r* = .3). Higher scores indicate greater shortness of breath. No other differences in baseline clinical characteristics for current marital status approached statistical significance (Table 7).

Table 7

Marital Status Comparisons of Baseline Scores

Measure	Marital Status					
	Currently Married			Other		
	M	***Mdn***	***N***	***M***	***Mdn***	***N***
KCCQ						
Overall Summary	50.8	46.7	14	56.7	51.6	19
SF-12						
PCS*	24.9	23.1	15	32.3	31.7	18
MCS	54.8	56.7	15	51.9	54.7	18
HADS Depression	7.1	7.0	15	6.5	6.0	19
HADS Anxiety	4.2	4.0	15	5.2	4.0	18
Geriatric SOBQ**	41.8	39.2	15	27.2	22.2	19
SWL	22.4	24.0	10	26.6	29.5	14
PHE	48.5	50.0	15	45.8	44.0	19
Physical Activity	5.1	3.0	15	4.1	3.0	19

* $p < .05$, **$p = .054$

Comparisons of Baseline Scores Based on Level of Survey Completion

Between-group analyses were conducted to identify possible baseline differences between participants who completed the second survey and those who did not because only 18 of the 34 participants completed the post-op survey. Analyses were completed using the Chi-square test for independence for categorical variables and the Mann-Whitney *U* test for continuous variables. Both groups were similar and there were no significant differences on any variables with the exception of study site location. While 100% of the ECU participants completed both surveys, only 24% of the St. Thomas participants did, a difference that was statistically significant, X^2 (1, n = 34) = 15.78, p < .001, phi = -.74.

Comparisons Between Baseline and Post-op Scores

Baseline scores on clinical measures were compared with scores obtained at approximately three months post-TAVR (*M* = 109 days, *SD* = 19.8). Inspection of data found that they were not normally distributed and therefore between groups analyses were conducted using the Wilcoxon Signed Rank Test.

Several statistically significant differences were discovered (Table 8). There was a statistically significant increase in health status post-TAVR as measured by all of the KCCQ subscales except Symptom Stability and Self-efficacy. For example, the KCCQ Overall Summary Score significantly increased, z = -3.36, p = .001, with a large effect size (r = .84). The median score of the KCCQ Overall Summary Score increased from baseline (*Mdn* = 49.8) to post-TAVR (*Mdn* = 85.7). There was a statistically significant increase in physical QOL as measured by the SF-12 from baseline (*Mdn* = 27.9) to post-TAVR (*Mdn* = 40.3), z = -2.84, p = .004, with a large effect size (r = .69). There

was also a statistically significant decrease in anxiety post-TAVR as measured by the HADS, z = -2.47, p = .014, with a large effect size (r = .58). The median score of the HADS Anxiety Score decreased from baseline (*Mdn* = 4.0) to post-TAVR (*Mdn* = 1.5). Finally, there was a statistically significant decrease in shortness of breath as measured by the Geriatric SOBQ. The median score of the Geriatric SOBQ decreased from baseline (*Mdn* = 34.2) to post-TAVR (*Mdn* = 16.0), z = -3.01, p = .003, with a large effect size (r = .71).

Table 8

Baseline and Post-op Comparisons

Measure	Baseline			Post-TAVR			Wilcoxon Signed Ranks		
	M	***SD***	***Mdn***	***M***	***SD***	***Mdn***	***n***	***z***	***p***
KCCQ									
Overall Sum	51.5	21.1	49.8	82.2	13.4	85.7	16	-3.36	**.001**
Physical Lim	51.2	26.0	56.3	70.8	25.6	75.0	16	-2.13	**.033**
Symptom Stab	47.1	12.1	50.0	50.0	8.8	50.0	17	-.82	.414
Symptom Freq	58.7	26.4	60.4	78.6	18.1	75.0	17	-2.51	**.012**
Symptom Brdn	53.5	23.8	50.0	85.3	15.4	83.3	17	-3.36	**.001**
Total Symptom	56.1	23.7	56.3	81.9	15.9	79.2	17	-3.24	**.001**
Self-efficacy	89.0	13.9	100.0	91.9	22.5	100.0	17	-1.03	.303
Quality of Life	48.1	22.1	41.8	89.2	15.3	91.8	17	-3.52	**<.001**
Social Limitation	44.2	27.4	41.8	81.1	22.2	87.5	17	-3.30	**.001**
Clinical Summ	54.3	22.9	57.4	76.6	16.7	76.1	16	-2.84	**.005**
SF-12									
PCS	29.1	8.8	27.9	40.0	9.6	40.3	17	-2.84	**.004**
MCS	56.3	11.1	58.8	57.3	6.6	58.8	17	-.355	.723
HADS Depression	5.8	2.5	6.0	4.7	4.2	3.0	18	-1.48	.139
HADS Anxiety	3.8	2.7	4.0	2.0	2.0	1.5	18	-2.47	**.014**
Geriatric SOBQ	35.1	21.4	34.2	16.4	14.3	16.0	18	-3.01	**.003**
Physical Activity	4.5	3.7	3.0	6.8	4.8	8.0	17	-1.62	.104

Comparisons of QOL Improvement Based on Demographics

As there were some statistically significant baseline differences in scores based on age and sex, comparisons were examined on both those demographic characteristics and changes in QOL. There were no significant differences identified based on either age or sex (Tables 9 and 10).

Table 9

Age Comparisons in QOL Improvement Post-TAVR

Measure	Age					
	< 80			80 +		
	M	***Mdn***	***N***	***M***	***Mdn***	***N***
Change in KCCQ Overall Summary	37.0	48.4	5	31.0	30.8	10
Change in SF-12 PCS	15.2	12.8	6	8.5	8.1	11
Change in SF-12 MCS	1.8	4.7	6	2.2	1.6	11

Table 10

Sex Comparisons in QOL Improvement Post-TAVR

Measure	Sex					
	Men			Women		
	M	***Mdn***	***N***	***M***	***Mdn***	***N***
Change in KCCQ Overall Summary	40.05	42.55	8	24.9	20.1	7
Change in SF-12 PCS	13.4	13.1	10	7.3	8.1	7
Change in SF-12 MCS	-.32	1.8	10	5.5	7.3	7

Comparisons of QOL Improvement Based on Anxiety/Depression

Clinical levels of both anxiety and depression have been associated with poor health outcomes. Because of the small sample size, a new variable was created called "Anxious and/or Depressed" which included participants who had levels of either anxiety or depression that were at clinical cutoff at baseline. Comparisons were made to determine the level of improvement of the anxious/depressed group compared to participants who were neither anxious or depressed (Table 11). A Mann-Whitney *U* test revealed a significant difference in improvement in the SF-12 MCS of participants who were anxious and/or depressed at baseline (*Mdn* = 7.3, *n* = 5) versus those who were not (*Mdn* = -1.8, *n* = 10), *U* = 8.0, *z* = -2.637, *p* = .008, *r* = .68). Higher scores indicate greater improvement in MCS. There were no significant differences on either the KCCQ or the SF-12 PCS (Table 11).

Table 11

Anxious and/or Depressed Comparisons in QOL Improvement

Measure	**Sex**					
	Anxious/Depressed			**Other**		
	M	***Mdn***	***N***	***M***	***Mdn***	***N***
Change in KCCQ Overall Summary	38.2	49.4	5	30.4	30.8	10
Change in SF-12 PCS	9.9	8.8	7	11.6	9.3	10
Change in SF-12 MCS*	8.0	7.3	7	-2.1	-1.8	10

p < .01 (2-tailed)

Correlations Between Baseline Scores and Post-op QOL Increases

Correlations between baseline scores and changes in QOL post-TAVR were investigated using Spearman Rho to identify possible predictors of improvement in QOL (Table 12). The change in KCCQ score for one patient was removed from consideration because the baseline score was so high (97.9) there could only be minimal improvement.

Table 12.

Correlations between Baseline Scores and Increases in QOL

Baseline Measure	Increase in Post-op KCCQ	Increase in Post-op SF-12 PCS	Increase in Post-op SF-12 MCS
KCCQ			
Overall Summary Score	-.811**	-.606*	-.550*
Physical Limitations	-.690**	-.434	-.446
Symptom Stability	-.271	-.071	.003
Symptom Frequency*	-.538*	-.466	-.423
Symptom Burden	-.645**	-.535*	-.465
Total Symptom	-.584*	-.529*	-.431
Self-efficacy	.647**	.385	-.030
Quality of Life	-.635*	-.406	-.563*
Social Limitation	-.744**	-.466	-.354
Clinical Summary	-.751**	-.552*	-.485
SF-12			
Physical Component Score	-.582*	-.522*	-.538*
Mental Component Score	-.086	-.100	-.690**
HADS Depression	.308	.062	.471
HADS Anxiety	-.320	.009	.320

Geriatric SOBQ	.620*	.442	.402
SWL	-.357	-.690*	-.857**
PHE	.287	.140	-.192
Physical Activity	-.625*	-.485	-.616*
Med Adherence	.253	.240	.216

*p < .05 (2-tailed), **p < .01 (2-tailed)

CHAPTER V: DISCUSSION

The current study is the first to examine the inter-relationship between psychological functioning and QOL in TAVR patients in US centers. The primary findings of this study included: 1) TAVR leads to an improvement of QOL, reduction in dyspnea, and reduction in symptoms of anxiety, 2) TAVR patients who demonstrated the greatest gains in QOL were those who reported the lowest levels of QOL prior to the procedure, 3) contrary to hypothesis, psychological factors such as low levels of positive expectations or satisfaction with life were not associated with lower gains in QOL. The following discussion proceeds in the order of the proposed aims of this study.

Baseline Characteristics

Baseline demographic characteristics of this study sample were generally quite similar to that reported from other TAVR studies (see Table 2). One exception was that the baseline mean score on the KCCQ Overall Summary Score of 54.2 was substantially higher than the baseline score of 39.3 reported in the PARTNER trial, a large US study of TAVR patients (Reynolds et al., 2012) and the only other TAVR study that used this measure. There are no TAVR studies with which to compare the HADS, SWL, PHE, dyspnea, or physical activity scores. The men in this sample reported somewhat better psychosocial well-being than women, as demonstrated by statistically significant differences on the KCCQ Symptom Burden scale, SF-12 MCS, and the HADS Anxiety scale. In addition, there was a trend where men reported more favorable QOL on the KCCQ Total Symptom scale (p = .053). Older patients in this sample appeared to fare somewhat better in QOL domains as demonstrated by significantly

better scores on the KCCQ Symptom Frequency scale, SF-12 MCS, SWL scale, and physical activity scale.

Post-op Comparisons

Examination of post-operative changes revealed significant improvement in disease specific QOL post-TAVR on all scales of the KCCQ that are sensitive to disease specific changes in QOL. The only two scales on which there were no significant changes were the symptom stability scale, which reports the degree to which symptoms of heart failure have changed over the previous two weeks, and self-efficacy, which is a measure of the degree to which one feels confident about how to manage symptoms of heart failure. It would not be expected that either of these two scales would be impacted by TAVR. An improvement of 5, 10, and 20 points on any subscale or the overall summary score represents a small, moderate, and large change respectively (Reynolds et al., 2012). In this sample, the mean change for each subscale ranged from 19.6 (Physical Limitation) to 41.1 (QOL). The mean Overall Summary score improved from 51.5 to 82.2 and the post-op score corresponds with NYHA Class I, the least severe of the four functional classes of heart failure. Collectively, these results suggest that the TAVR patients in this study reported significant disease specific QOL benefit from the procedure and highlights the value of the procedure for these selected patients.

An improvement in the SF-12 PCS was similar to results from other trials as well. As previously noted, a change of 2.5 points is considered clinically significant on the SF-12, and the mean change in this sample was 10.9 points. The mean SF-12 MCS demonstrated little change, improving from 56.3 to 57.3. This negligible improvement is

much smaller than in most previous studies. This may be due, in part, to the high baseline MCS of this sample relative to other samples that generally had baseline scores at least 10 points lower than the current sample. In addition, it appears reasonable that the benefits of TAVR would only have an ancillary effect on MCS. Of note, the two largest TAVR studies to date found that TAVR patients demonstrated no gains or only small improvements in MCS scores (Krane et al. 2012; Reynolds et al. 2012) at similar time points post-TAVR. Again, our results suggest that TAVR patients benefitted significantly in generic physical QOL but experienced only limited mental QOL benefit.

Consistent with these results were significant improvements in dyspnea, one of the most common symptoms of heart failure. Mean scores on the Geriatric SOBQ were cut by more than half and indicated dramatic symptomatic improvement. While the mean physical activity score improved, it did not reach statistical significance. Anxiety as measured by the HADS improved significantly as well. The reduction in symptoms of anxiety, while not expected, is not surprising, as some symptoms of anxiety also correlate with symptoms of heart failure that might be expected to improve with gains in cardiac health. Also, since patients completed their baseline survey usually within days of their TAVR, it is possible that anxiety from both their pre-op cardiac health and their pending procedure may have both been reflected in somewhat elevated anxiety scores.

Considered together, the benefits of TAVR on disease-specific and physical QOL in this sample are striking, are consistent with other studies, and add to the growing literature demonstrating gains in these important areas. In addition, improvement in dyspnea, a problematic symptom common in patients considered for TAVR, but not

previously examined with a measure specific to this symptom, also demonstrated substantial improvement. Reduced anxiety was reported as yet, another benefit post-TAVR. These data add to the literature by providing new detail about the psychological and physical experience of patients considering TAVR, and the resultant decline in anxiety-related symptoms post-TAVR that they might experience.

Demographic Differences in Baseline and Post-op Scores

The benefits of TAVR were not statistically different between the younger and older age groups, or between men and women in this study. There are few studies reporting comparisons based on these demographic characteristics post-TAVR. Reynolds et al. (2011) found no significant differences in improvement in QOL at 6 or 12 months based on either age or gender. Krane et al. (2012) found that while female gender was associated with less improvement in QOL at 3 months, there was no statistically significant difference at 12 months. Fairbairn et al. (2012) reported that men reported greater improvement in QOL at 12 months. There were no age differences in changes in QOL found by Fairbairn et al., however. The results of the current study combined with the mixed results from past studies, suggest that age and sex likely have minimal, if any, association with outcome.

Predicting Outcomes

As increasing numbers of TAVR studies have been published and the benefits of TAVR have become more well-defined and accepted, the future of TAVR as a viable procedure for valve disease has become more certain. Accompanying the growth of scientific knowledge has been a greater quest to gain an understanding of predictors of outcomes. There have been a few studies seeking to identify predictors of mortality or

medical complications such as stroke or kidney dysfunction (Gilard et al., 2012; Seiffert et al., 2013; Moat et al., 2011; Rodés-Cabau et al., 2012) but until recently, none have used QOL as an endpoint. Arnold et al. (2014) in using results from the PARTNER trial, published findings examining possible predictors of outcomes in TAVR patients that used both mortality and QOL as endpoints. As they noted, "…the optimal definition for a poor outcome after TAVR should reflect a failure to achieve the goals of the intervention and therefore must include both a mortality and a QoL component" (p. 2687). With a large sample size *(N* = 2137), they were able to use a split-sample design and a multivariable logistic regression model to examine a range of demographic, disease specific, physical, and QOL variables. They found that the most important predictors of poor outcomes were poor functional capacity (as assessed by the distance walked on the 6 Minute Walk Test), lower mean aortic valve gradients, oxygen-dependent lung disease, renal dysfunction, poorer baseline cognitive function, lower BMI, and worse QOL at baseline. While such predictive models cannot guarantee results they do provide important information to patients, family members, and health-care providers to increase understanding of the likelihood of benefit versus the risks involved.

Using improvement in QOL as an outcome, our results were a modest attempt at providing greater understanding of a diverse set of variables that are associated with patient outcome in TAVR. Generally, the results indicated that patients in this sample who reported the worst biopsychosocial health at baseline demonstrated the greatest gains. For example, patients who had the lowest baseline KCCQ Overall Summary scores and/or lowest SF-12 PCS demonstrated the greatest gains post-op on the KCCQ Overall Summary score, the SF-12 PCS, and the SF-12 MCS. Similar correlations were

noted for scores on the Geriatric SOBQ, Satisfaction with Life scale, and the physical activity score such that worse scores in these areas were correlated with greater improvement in QOL. Patients who completed the KCCQ at both pre-op and post-op and who had baseline scores < 50 on their Overall Summary demonstrated gains ranging from 12.4 to 69.8 with a mean improvement of 47.4. To summarize, patients who present with particularly low self-reports of QOL, including low satisfaction with life, and/or who experience problematic dypsnea, and/or low levels of physical activity are likely to experience large and meaningful gains in QOL. Therefore, the substantial QOL benefit that patients eligible for TAVR may likely experience is important to highlight and should be part of the consideration process.

Psychological Distress and TAVR Outcomes

Higher scores on the HADS for either anxiety or depression were not associated with lack of improvement as measured by QOL measures. At baseline, eleven patients met the cut-off for mild depression while seven met the cut-off for mild anxiety. Of those, only five patients meeting cut-off for depression and two meeting cut-off for anxiety completed the post-op survey, precluding meaningful between groups analyses for these factors individually. Instead, one group who met cutoff for anxiety and/or depression was created and compared to the remaining participants on improvement in QOL. Anxiety or depression was not associated with worse outcomes, and in fact, there was statistically greater improvement in MCS among participants with anxiety and/or depression. This suggests that the physiological benefits of TAVR may have been of such magnitude that they were recognized even by those experiencing clinical levels of psychological distress during the timeframe of the procedure.

Medication Adherence

Non-adherence to medication protocol has been defined as taking medications as prescribed only 75% of the time or less (Gehi et al., 2007). Estimated average adherence rates to medication instructions in cardiac patients has been found to be between 51% to 79%, depending on the number of daily doses (Horwitz et al., 1990). The patients in this study demonstrated far higher medication adherence than might be expected, as 100% of participants self-reported taking their medications "nearly every day" for the previous month. Such strong self-reported adherence to medications may be a reflection of both patient specific and situation specific characteristics. For example, excellent adherence may highlight the patient understanding of the severity of their condition. Alternatively, there may have been a high proportion who lived in assisted living situations in which daily support for medication management is the norm. As medication adherence has not been studied in TAVR patients before, it is unknown if these results mirror that of TAVR patients in general or represent a positive report bias.

Will to Live

Responses to the Will to Live measure proved to be generally uniform in our sample. Of all the study measures, this measure anecdotally drew the greatest vocal response from participants who would often respond with something like, "What kind of question is that? Who wouldn't circle a 10 on that?" For example, 29 of 34 participants rated their will to live at baseline as a "10" with 10 being the greatest will to live possible. At post-op, 16 of 18 respondents rated their will to live as a 10 with the other two respondents recording responses of 8 and 9.7. Of note, however, the one mortality identified among participants completing the first survey responded that his will to live

was a 7.5, the second lowest response received among our sample. While it is possible that with a larger sample this measure may be shown to have predictive value concerning outcome, our preliminary results did not indicate that and the measure appears to have limited value from our experience. It is also possible that the way in which we assessed this item, with a single VAS, may not be sensitive enough to adequately capture this construct and again may be subject to a positive response bias in these patients.

Positive Health Expectations

The role of positive health expectations on outcomes had not previously been studied in this population. While positive expectations about the future have been found to be associated with better mental and physical health by a number of studies (Peterson & Bossio, 2001; Scheier et al., 1989; Taylor & Brown, 1988) including in cardiac patients (Leedham et al., 1995; Sears et al., 2004) that was not the case in our sample. This construct was not significantly correlated with baseline QOL in our study. It is possible, since our survey was administered after patients had decided to proceed with the TAVR procedure, that they had essentially become somewhat confident or hopeful that it would be of benefit. Their scores on the PHE scale at baseline might therefore be a reflection of this thought process more than a reflection of their perception of QOL. Positive expectations were not significantly associated with improvement in QOL post-TAVR either. As with psychological distress, this suggests

that the physiological benefits of TAVR may have been of such magnitude that they were recognized by participants regardless of prior level of expectation.

Geriatric SOBQ as an Assessment Tool

As previously described, many participants chose not to answer several questions included in the University of California, San Diego Shortness of Breath Questionnaire (SOBQ) that queried the degree of breathlessness experienced while conducting a variety of activities. If administered in person, they would often respond to the study assistant that they had either not done the activity any time recently, or currently engaged in them too infrequently to feel comfortable assessing (e.g., washing a car, mowing a lawn). This choice was made by participants in spite of instructions stating that "if the activity is one which you do not perform, please give your best estimate of breathlessness." Missing data on this questionnaire was common across both study sites. Therefore, questions that were answered by fewer than 75% of participants (in the current study questions 14 and 17-21) were removed from consideration in this analysis. This revised tool entitled "Geriatric SOBQ" still provided a detailed assessment of a common symptom of valve disease and also had high internal consistency. We suggest that this shorter tool is more appropriate for patient populations marked by greatly reduced physical health and may be a more viable option for future research with similar groups. This abbreviated measure will reduce irrelevant questions, ease patient burden, and likely provide data that is as accurate and possibly more accurate than the complete SOBQ by refraining from inquiring about activities in which participants cannot engage due to their significant physical limitations.

Of note, there was a very strong negative correlation between the baseline Geriatric SOBQ and the baseline KCCQ Overall Summary Score (r = -. 87, n = 34, p < .001) with high levels of dyspnea associated with low levels of cardiac-health related QOL. These results suggest that dyspnea, as measured by the Geriatric SOBQ, may significantly and substantially impact QOL for cardiac patients as assessed by the KCCQ. This also suggests that reduced dyspnea should be an important endpoint for TAVR.

Limitations of the Current Study

There are several important limitations to this study that affect the ability to generalize findings to the TAVR population as a whole. The small sample size is a foremost limitation and inferences derived from these results must be viewed with caution. In addition, there were a high number of participants who were lost to follow-up increasing the possibility of selection bias. While comparisons conducted of baseline measures of patients lost to follow up and those completing the study found no significant differences, the post-op results for patients lost to follow up, of course, remain unknown. The study sample was quite racially homogeneous, a result that was surprising to the investigators considering the racial mix within the general population at the East Carolina site particularly. All but two participants identified as Caucasian and therefore, generalizing these findings to other racial groups must be done with extreme caution.

Limitations of the Study Design

The study was designed recognizing the limited number of prospective TAVR patients available in the geographic area in which it was conducted. For that reason,

statistical analyses were relatively simplistic as did comparisons between groups. Thus, results may be considered most valuable by providing direction for future research. Another limitation is the reliance on self-report and possible response bias. The inclusion of more biomedical data would add to the validity of participant self-report on physical well-being, for example.

Future Implications and Aims

Future studies are necessary to continue to increase the understanding of biopsychosocial predictors of outcomes in the population of those qualifying for TAVR. Psychological factors that have predictive validity are subject to change and the use of interventions to address these factors may lead to improved outcomes. While this small study did not identify such factors, that should not imply that such factors do not exist. A broad and robust literature associated with psychosocial factors in cardiology exists with decades of significant relationships (Rozanski, et al., 2005). Research comparing samples of TAVR patients with poor outcomes with those who experienced desirable outcomes are needed to increase understanding of predictive factors. TAVR will likely continue to expand to increasingly "healthier" groups where psychological factors and motivation are more likely to exert a detectable influence over and above gross physical dysfunction. Arnold et al. (2014) is a recent example of research examining differences between large patient groups based on outcomes. Unfortunately, they did not include psychological factors other than QOL in their design. Frailty has been implicated as a likely predictor of outcomes in TAVR patients (Green et al., 2012; Stortecky et al., 2012). While traditional models of frailty have only included physical factors, future

research should investigate the way in which psychologic factors may also be considered as predictors in a broader, biopsychosocial model of frailty.

Conclusion

The main findings of this study suggest that TAVR leads to an improvement of QOL, reduction in dyspnea, and reduction in symptoms of anxiety. TAVR patients who demonstrate the greatest gains in QOL were those who reported the lowest levels of QOL prior to the procedure. Contrary to hypothesis, there was no significant association between baseline levels of positive expectations, satisfaction with life, or psychological distress, with post-op QOL improvement. These findings suggest that the physiological benefits of TAVR are of such magnitude that they are experienced by patients regardless of less than ideal psychosocial beliefs or distress. In addition, it is reasonable for patients to expect meaningful gains in QOL post-TAVR and, in fact, those patients who report the worst biopsychosocial health at baseline may likely experience the most substantial QOL improvements. However, these findings are preliminary and studies with larger sample sizes are necessary to draw more definitive conclusions. Understanding a biopsychosocial model for TAVR will likely provide comprehensive strategies to optimize clinical outcomes for TAVR patients as the procedure continues to expand to “healthier” populations.

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APPENDIX A - IRB DOCUMENTS

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board Office
4N-70 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office 252-744-2914 · Fax 252-744-2284 · www.ecu.edu/irb

Notification of Initial Approval: Expedited

From: Biomedical IRB
To: Samuel Sears
CC:

Date: 1/2/2013
Re: UMCIRB 12-000766
TAVRS-PPO

I am pleased to inform you that your Expedited Application was approved. Approval of the study and any consent form(s) is for the period of 12/30/2012 to 12/29/2013. The research study is eligible for review under expedited category #5. The Chairperson (or designee) deemed this study no more than minimal risk.

Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a continuing review/closure application to the UMCIRB prior to the date of study expiration. The Investigator must adhere to all reporting requirements for this study.

The approval includes the following items:

Name	Description
Final TAVR Protocol Template for IRB.doc | History	Study Protocol or Grant Application
TAVR Informed Consent including HIPAA.doc | History	Consent Forms
TAVR Recruitment Script.doc | History	Recruitment Documents/Scripts
TAVR Time 1 Questionnaire.doc | History	Surveys and Questionnaires
TAVR Time 2 or 3 Questionnaire.doc | History	Surveys and Questionnaires
TAVR Time2and 3 phonescript.docx | History	Consent Forms

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

Institutional Review Board (IRB)/Independent Ethics Committee (IEC) Authorization Agreement

Name of Institution or Organization Providing IRB Review (Institution/Organization A):
University and Medical Center Institutional Review Board (UMCIRB); East Carolina University ("Designated IRB")

IRB Registration #: IRB00000705 Federalwide Assurance (FWA) #: 00000658

Name of Institution Relying on the Designated IRB (Institution B):
Saint Thomas Health/Saint Thomas West Hospital

FWA #:00003185

The Officials signing below agree that Saint Thomas Health/Saint Thomas West Hospital may rely on the designated IRB for review and continuing oversight of its human subjects research described below: (*check one*)

(___) This agreement applies to all human subjects research covered by Institution B's FWA.

(X) This agreement is limited to the following specific protocol(s):

Name of Research Project: Transcatheter Aortic Valve Replacement Surgery - Predictors of Positive Outcomes – TAVRS – PPO – UMCIRB # 12-000766
Name of Principal Investigator: Samuel Sears, PhD
Sponsor or Funding Agency: N/A **Award Number, if any**: N/A

(___) Other (*describe*):_____

The review performed by the designated IRB will meet the human subject protection requirements of Institution B's OHRP-approved FWA. The IRB at Institution/Organization A will follow written procedures for reporting its findings and actions to appropriate officials at Institution B. Relevant minutes of IRB meetings will be made available to Institution B upon request. Institution B remains responsible for ensuring compliance with the IRB's determinations and with the Terms of its OHRP-approved FWA. This document must be kept on file by both parties and provided to OHRP upon request.

The Office for Human Research Integrity (OHRI) at East Carolina University (ECU) utilizes an electronic IRB submission, review and tracking system (ePIRATE) for all University and Medical Center Institutional Review Board (UMCIRB) submissions. This includes new study submissions, continuing reviews, amendments and reportable events (protocol deviations, violations, and unanticipated events). In addition the minutes of each meeting are also available via ePIRATE. Therefore, there are no handwritten signatures or printed paper approval or acknowledgment letters generated by OHRI regarding decisions/approvals. Any investigator or study team member who is engaged in human research which is reviewed and overseen by the UMCIRB must be a registered user of ePIRATE, including unaffiliated investigators and study team members. As ePIRATE users, these research team members have "real time" access to all submissions and IRB correspondence related to the study on which they serve. In addition, they are copied on all correspondence generated by ePIRATE. All ePIRATE correspondence is sent to the ePIRATE user's email address provided at the time of ePIRATE registration. It is by means of the ePIRATE system that ECU will communicate regularly with St. Thomas Health via the St. Thomas Health local investigators about activity related to this study such as amendments, reportable events, and continuing reviews.

Signature of Signatory Official (Institution/Organization A):

Date: 4/22/2014

Print Full Name: Ronald Mitchelson, Ph.D. Institutional Title: Interim Vice Chancellor for Research & Graduate Studies

NOTE: The IRB of Institution A must be designated on the OHRP-approved FWA for Institution B.

Signature of Signatory Official (Institution B):

Date: 4/21/14

Print Full Name: *Jessica Wells* Institutional Title: *Vice President Education & Research*

APPENDIX B – GLOSSARY OF MEASURES

Euroqol5D (EQ-5D) – The EQ-5D is a preference/utility-based measure that describes five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Herdman et al., 2011). Participants are asked to select one option that best describes their health concerning that dimension from three or five different possibilities depending on version. The question concerning anxiety/depression asks patient's to select one of three responses: I am not anxious or depressed; I am moderately anxious or depressed; I am extremely anxious or depressed. They also rate their overall health on a visual analogue scale (VAS) from 0 to 100. The EQ 5D identifies 243 health states. The EQ 5D has been used in over 500 studies and is used in a variety of ways including monitoring patient health status, assessing health condition severity, evaluating the effectiveness of health procedures and medications, and in economic studies designed to determine resource allocation (Fairbairn et al., 2012; Rabin & Charro, 2001).

Hospital Anxiety and Depression Scale (HADS) - The HADS is a 14-item measure that assesses depression and anxiety and is used primarily in hospital settings (Zigmond & Snaith, 1983). All somatic symptoms related to depression and anxiety are excluded from this measure in order to account for the likely experience of such symptoms from known or expected physiological problems in this population. Seven items on the scale assess depression and the other seven items assess anxiety. Each item is scored from 0-3 and an established clinical cutoff of 8. A review by Bjelland, et al., (2002) identified over 700 studies that used the HADS. They found that most factor analyses confirmed the two-factor solution in accordance with the subscales of anxiety

(HADS-A) and depression (HADS-D) with Cronbach's alphas for HADS-A varying from .68 to .93 (mean .83) and for HADS-D from .67 to .90 (mean .82).

Kansas City Cardiomyopathy Scale (KCCQ) – The KCCQ is a 23-item measure commonly used to evaluate the health status of heart failure patients (Creber et al., 2012). The five domains addressed by the KCCQ are: symptoms, physical limitation, social limitation, self-efficacy, and quality of life (Green et al., 2000). The individual scale scores may be combined into an overall summary scale with scores from 0 to 100; higher scores are indicative of fewer symptoms and higher QOL. The KCCQ summary score has been found to correlate with NYHA functional class as follows: class I is roughly equal to KCCQ summary score of 75 to 100; class II, to a score of 60 to 74; class III, to a score of 45 to 59; and class IV, to a score of 0 to 44 (Spertus et al., 2005). Arnold et al. (2013) evaluated the psychometric properties of the KCCQ in patients with severe aortic stenosis and found good construct validity when comparing each domain of the KCCQ against a reference measure. In the study by Creber et al., the Cronbach's alpha was 0.92 indicating excellent internal consistency.

Logistic EuroSCORE (EuroSCORE) – The EuroSCORE is used to predict outcomes of patients undergoing cardiac surgery. It was developed in 1999 and considers 17 parameters grouped into three areas: patient related risk factors (e.g., age, history of cardiac surgery); cardiac factors (e.g., reduced LVEF, recent myocardial infarction); and operation related factors (e.g., emergency operation, other than isolated coronary surgery) (Nashef et al., 1999). Each of these three areas has a different weight in the scoring algorithm. Studies have criticized the EuroSCORE for overestimating mortality by about twice as much as actual outcome (Siregar et al., 2012).

Minnesota Living with Heart Failure Questionnaire (MLHFQ) - The MLHFQ is a 21-item structured questionnaire that measures patient perceptions about the effects of symptoms, functional limitations and psychological distress of an individual's QOL (Goncalves et al., 2013). Respondents rate the degree that each heart failure related item prevents them from living as they wanted during the previous four weeks using a 6-point Likert Scale . Responses range from 0 (no impact/not applicable) to 5 (severe impact). The MLHFQ produces a total score (21 items, range: 0 to 105), physical score (range: 0 to 40 for 8 items) and emotional dimension score (range: 0 to 25 for 5 items), respectively). Lower scores indicate better HQOL and a change ≥5 points in total score is considered clinically meaningful. The questionnaire can be self-administered or applied in a 5-minute interview. The MLHFQ had been compared to the SF-36 in a sample of valve patients and has been found to have good psychometric properties (Supino et al., 2009).

Patient Health Questionnaire-9 (PHQ-9) – The PHQ-9 is a nine-item measure of depressive symptoms that is commonly used among patients in medical settings (Kroenke, Spitzer & Williams, 2001). There are four possible responses for each item and total scores range from 0 to 27 with higher scores indicating higher levels of depression. Reliability and construct validity has also been found to be excellent. The PHQ-9 has demonstrated sensitivity for major depression of 88% compared with the mental health professional (MHP) interview. Internal consistency has been found to be good with Cronbach's alpha between 0.86 and 0.89.

Positive Health Expectations Scale (PHE) – The PHE assesses patient beliefs about the efficacy of their treatment and their future outlook (Leedham et al., 1995). The scale

was first used with heart transplant patients and demonstrated good convergent validity with QOL scores, divergent validity with mood disturbances scores, and predictive validity with physical health measures. Sears et al. (2004) used this measure to assess PHE in ICD patients and modified it with an added question assessing motivation for ICD implantation. The current study has similarly modified the PHE with a question assessing motivation for valve surgery. Respondents rate their health expectations on a 7-point Likert scale. There are eight questions and possible scores range from 8 to 56 with higher scores indicating a more positive outlook. Cronbach's alpha was 0.81 and 0.88 in the Leedham et al. and Sears et al. studies respectively, indicating good internal consistency.

Short Form 36 Health Survey (SF-36) – The SF-36 survey was developed in 1992 and was constructed to provide a comprehensive yet brief, psychometrically sound measure of health status (Ware & Sherbourne, 1992). The SF-36 assesses eight health concepts: limitations in physical activities because of health problems; 2) limitations in social activities because of physical or emotional problems; 3) limitations in usual role activities because of physical health problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) limitations in usual role activities because of emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. It may be self-administered or administered by a trained interviewer in person or by phone in about five minutes. Dexter, Stump, Tierney & Wolinsky (1996) evaluated the psychometric properties of the SF-36 among 1053 older adults (>50 with severe underlying disease or >75) and found these eight factors explained 65% of the item variance with most items loading on the appropriate factors. Exploratory factor analysis

also found one single underlying health factor as well as a two factor solution for the components of mental and physical health. Falcoz, Chocron, Mercier, Puyraveau, and Etievent (2002) evaluated the SF-36 in cardiac patients and found the psychometric properties to be generally good.

Short Form12 Health Survey (SF-12) – The SF-12v2 is a 12-item revision of the SF-36 (Ware et al., 1996) and will provide one general health measure of QOL for this study. The SF-12 maintains 90% of the variance of the mental and physical health scales of the SF-36, although it has less accurate reproduction of the eight scales of the SF-36. Administration time is lowered from five minutes to two minutes for the SF-12. The SF-12v2 is an updated version of the SF-12 that adjusted some of the response options. A recent review of the SF-12v2 using a large, adult patient population *(N* = 2,410) found that the mental and physical health scales explained over 80% of the total variances of the SF-36v2 (Lam et al., 2013). The SF-12v2 is scored by computer and provides a t-score based on a representative US population sample. Recently evaluated Cronbach's alpha on the physical component scale has been found to range from 0.81 - 0.90 (mean = 0.87) in various population groups (DeSmedt et al., 2013). Cronbach's alpha on the mental component scale ranged from 0.74 – 0.89 (mean = 0.84). The mean Cronbach's alpha values for this review indicate good internal consistency for both scales.

Short Form 6D (SF 6D) – The SF 6D calculates the measure of disease burden in terms of quality-adjusted life years (QALYs) from participant responses to the SF-36 or SF-12 (Phillips & Thompson, 2009). QALYs measure this burden by considering the quality and quantity of life gained by medical interventions and comparing that to the financial cost of the intervention. One QALY is equivalent to one perfect year of life. The

SF 6D reduces the dimensions of the SF-36 to six dimensions: physical functioning, role limitation, social functioning, pain, mental health, and vitality. The SF 6D identifies 18000 health states. (Querecioli et al., 2009). Scores range from 0 (death) to 1 (full health).

Society of Thoracic Surgeon risk score (STS) – The STS predicts risk of mortality in patients considered for cardiac surgery including TAVR. STS is calculated using an algorithm considering over 40 clinical parameters including patient demographics and various risk factors such as height/weight, diabetes, renal failure, hypertension, chronic lung disease, peripheral arterial disease, cerebrovascular disease, previous cardiac interventions, preoperative cardiac status, ejection fraction, and aortic stenosis (Ad et al., 2007). STS score is often used to identify high-risk patients considered for TAVR although it has been found to have limited success in predicting future mortality (Piazza et al., 2010).

The University of California, San Diego Shortness of Breath Questionnaire (SOBQ) – The SOBQ is a self-report questionnaire in which patients indicate the severity of dyspnea experienced during 21 activities of daily living that vary in rate of exertion (Eakin et al., 1998). Ratings for each item are on a 6-point scale (e.g., 0 = Not at all, 4 = Severely, 5 = Maximally or unable to do because of breathlessness). An additional three questions inquire about limitations due to shortness of breath, fears about overexertion, and fear of shortness of breath. Maximum score is 120 and a change of 5 points is considered clinically significant. (Ries, 2005). Reliability has been found to be superior to other measures of dyspnea including the Baseline Dyspnea Index (BDI), American Thoracic Society Dyspnea Scale and the Oxygen Cost Diagram

(Eakin et al., 1998). Validity has been found to be good after examination of variables with which is it believed to be related such as exercise tolerance, health-related QOL, lung function, and depression. The study by Eaken et al. found a Cronbach's alpha value of 0.96 indicating excellent internal consistency.

Will-to-live: The last item in the survey will ask participants to rate their will-to-live on a single-item VAS with anchors of "no will to live" and "absolute will to live". This scale has been used in one other study and had high correlation with depression, anxiety, desire for death, burden to others, and hopelessness (Chochinov et al., 2005). However, its psychometric properties have not been evaluated. There are no published scales of measures of will-to-live for which psychometric properties have been evaluated.