Cardiac biomarkers and health-related quality of life in new hemodialysis patients without symptomatic cardiac disease

By

© Christopher E. Williams

A thesis submitted to the School of Graduate Studies in partial fulfillment of the requirements for the degree of Master of Science.

Faculty of Medicine

Memorial University of Newfoundland

St. John's, Newfoundland & Labrador

May, 2015

TABLE OF CONTENTS

ABSTRACT

Background & Objectives: Quality of life (QOL) is impaired in end-stage renal disease patients, but the cause(s) is uncertain. To determine whether biomarkers of cardiac disease (TNT, NT-proBNP) were associated with change in QOL in the short (24 weeks) and long term (48 & 96 weeks) we studied 596 new hemodialysis patients without symptomatic cardiac disease followed for 2 years.

Design, Setting, Participants & Measurements: Patients were enrolled in a double-blind, randomized controlled trial to assess the impact of anemia correction with erythropoietin. Change in QOL was measured using SF-36, FACIT Fatigue administered at 0, 24, 48 and 96 weeks, with pre-specified domains of interest being SF-36 Physical Functioning, SF-36 Vitality and FACIT Fatigue. In addition to baseline demographic and clinical characteristics, baseline biomarkers of cardiac disease and inflammation were assessed.

Results: The analysis plan pre-specified cut-off for baseline biomarkers as upper quartile. High Trop levels were independently and significantly associated with long term deterioration in all 3 domains. The adjusted B for change in physical function was -6.7 (p=0. 035) at 48 weeks and -7.1(p=0.056) at 96 weeks; for change in vitality -7.1(p=0.036) at 96 weeks; and for change in fatigue-6.2(p=0.035).

Conclusions: In relatively healthy hemodialysis patients, high troponin T levels were associated with deterioration in physical function and vitality as well as increasing fatigue.

ACKNOWLEDGEMENTS

This research project would not have been possible without the support of numerous people. First and foremost, I would like to extend my sincere gratitude to my supervisor, Dr. Patrick Parfrey, who has provided a tremendous amount of support, mentorship, and inspiration throughout the completion of this work. Furthermore, I would like to thank the other members of my supervisory committee, Dr. Bryan Curtis and Dr. Brendan Barrett for their unwavering support and guidance over the course of my project.

In addition, I gratefully acknowledge Dr. Edward Randell, and Dr. Robert Foley, along with my supervisors Dr. Bryan Curtis and Dr. Patrick Parfrey who were instrumental in assisting me to have my research approved for publication in the Canadian Journal of Kidney Health and Disease in July 2014, as well as to deliver a poster presentation during the Canadian Society of Nephrology Conference in Vancouver, B.C. during April 2014.

I would also like to acknowledge Dr. Elizabeth Dicks who provided me with a vast amount of support and advice throughout this entire process. Dr. Dicks was always there to guide me in the right direction and help me in any way that she could and I am extremely grateful for all that she's done.

LIST OF TABLES:

LIST OF FIGURES:

LIST OF ABBREVIATIONS:

CKD – Chronic Kidney Disease

ESRD – End-Stage Renal Disease

KDIGO – Kidney Disease Improving Global Outcomes

GFR – Glomerular Filtration Rate

AER – Albumin Excretion Rate

ACR – Albumin-to-Creatinine Ratio

eGFR – Estimated Glomerular Filtration Rate

HRQOL – Health-Related Quality of Life

SF-36 – Short Form 36

KDQOL – Kidney Disease Quality of Life Questionnaire

FACIT – Functional Assessment of Chronic Illness Therapy

KDOQI – Kidney Disease Outcomes Quality Initiative

MCS – Mental Component Score

PCS – Physical Component Score

CVD – Cardiovascular Disease

BNP – Brian Natriuretic Peptide

NT-proBNP – N-Terminal Pro-Brain Natriuretic Peptide

TNT – Troponin T

ANP – Atrial Natriuretic Peptide

LV – Left Ventricular

CRP – C-Reactive Protein

ES – Effect Size

LVVI – Left Ventricular Volume Index

SPSS – Statistical Package for the Social Sciences

ANOVA – Analysis of Variance

IQR – Interquartile Range

URR – Urea Reduction Ratio

QOL – Quality of Life

LVMI – Left Ventricular Mass Index

Chapter 1: INTRODUCTION

Chronic kidney disease is a global health problem with increasing incidence and prevalence rates being seen worldwide. In Canada between 1.3 million and 2.9 million are estimated to have chronic kidney disease (12.5% of the population) with 730 000 between stages 3-5 (Arora et al., 2013). This is comparable to the estimated prevalence of any stage of CKD in the United States (13.1%) and Australia (11.2%), but significantly higher than Europe (4.7 – 8.1%) and Asia (2.5 – 6.8%; Arora et al., 2013). There are also significant racial differences in the incidence and prevalence rates of chronic kidney disease with African-American and American Indian populations having an incident rate 3.6 and 1.8 times higher, respectively, than Caucasians (Obrador & Pereira, 2014). The increased prevalence of chronic kidney disease worldwide is believed by some to be the result of advancements in treatment for chronic kidney disease that have been made over the last number of decades and the resultant increased survival of patients with end-stage renal disease (Obrador & Pereira, 2014).

Chronic kidney disease is a chronic deterioration of kidney function over time and can be the result of a number of causes. Diabetes and hypertension account for 44% and 27.9% of all causes of incident ESRD, respectively (Obrador & Pereira, 2014; Levey & Coresh, 2012). However other potential causes include glomerulonephritis, polycystic kidney disease, urinary tract obstruction, reflux nephropathy, and drug-induced kidney problems (Kidney Foundation of Canada, 2014). Identifying the cause of CKD is important as it allows for targeted treatment and therapy to prevent and reduce further

kidney damage, as well as awareness of the implications it has on the rate of progression and risk of complications of the disease (Levey & Inker, 2014).

Kidney Disease Improving Global Outcomes defines chronic kidney disease as "abnormalities of kidney structure or function, present for > 3 months, with implications for health." Chronic kidney disease requires the presence of a decreased glomerular filtration rate (GFR) of < 60 mL/min/1.73 m^2, or markers of kidney damage for greater than 3 months. Markers for kidney damage can include albuminuria (AER $\geq$ 30 mg/24 hours; ACR $\geq$ 30 mg/g), urine sediment abnormalities, electrolyte and other abnormalities due to tubular disorders, abnormalities detected by histology, structural abnormalities detected by imagine, or history of kidney transplantation (Kidney Disease Improving Global Outcomes, 2013).

End stage renal disease (ESRD) is defined as eGFR < 15 mL/min per 1.73m^2 (Kidney Disease Improving Global Outcomes, 2013). Dialysis improves blood volume and mineral/electrolyte levels and removes waste products from the blood. There are two types of dialysis used as treatments for kidney disease: hemodialysis and peritoneal dialysis. Hemodialysis functions by taking blood from the patient and passing it through a dialyzer where filtration occurs between the blood and dialysate, separated by an artificial membrane. The "cleansed" blood then passes back into the body's normal circulation. Hemodialysis treatment is effective in relieving some symptoms of uremia. However a new lifestyle is necessary, including adherence to a strict diet, restriction of fluids, and use of a wide variety of medications. Peritoneal dialysis functions on the same principles as hemodialysis, however the blood is filtered by the provision of dialysate inside the

body. The peritoneal cavity is filled with the special dialysis fluid and the blood vessels filter wastes through the peritoneum and into the fluid. The fluid is drained via a catheter and replaced with new dialysis fluid several times daily (Kidney Foundation of Canada, 2013).

Quality of life represents a patient's functioning, well-being and general health in physical, social, and psychological domains (Guyatt et al., 1993), and is a consistent predictor of mortality in patients suffering from ESRD (Lowrie et al., 2003; Lopes et al., 2003; Kalantar-Zadeh et al., 2001). Patients with end-stage renal disease have consistently lower quality of life scores when compared to matched controls without ESRD, with the most significant differences occurring in physical function and vitality domains (Spiegel et al., 2008). A pronounced disparity is also evident in hemodialysis patients without prior symptomatic cardiac disease, who have greater health related quality of life as compared to hemodialysis patients with cardiovascular disease, but whose HRQOL is still impaired when compared to healthy individuals (Foley et al., 2009; Fukuhara et al., 2003). Cardiovascular events, specifically heart failure and atherosclerotic events have a significant impact on quality of life in hemodialysis patients (Briggs et al., 2013).

Health related quality of life for this study was measured and assessed using a number of validated instruments, including the short-form health survey (Ware & Sherbourne, 1992; Fukuhara et al., 2003), the kidney disease quality of life questionnaire (Hays et al., 1994) and the functional assessment of chronic illness therapy measurement system (Webster et al., 2003). These instruments were all developed for self-

administration by patients; however administration of the survey by a trained interviewer can reduce the burden for patients suffering from difficulty reading and severe fatigue. The surveys are scored according to the manuals provided and each raw score is transformed onto a 0 to 100 scale, with a higher value indicating a greater quality of life (Fukuhara et al., 2003; Webster et al., 2003; Hays et al., 1994; Ware & Sherbourne, 1992).

1.1 Study Objectives

The purpose of this study is to assess the predictive value of cardiac biomarkers for quality of life in hemodialysis patients without prior symptomatic cardiovascular disease.

Specifically, the main objective is:

1.) To determine whether the cardiac biomarkers, troponin T and N terminal pro-B type natriuretic peptide, predict deterioration in the physical domains (SF-36 Physical Function, SF-36 Vitality, FACIT Fatigue) of health related quality of life.

Chapter 2: LITERATURE REVIEW

2.1 Search Strategy

A search was conducted through The National Library of Medicine using PubMed, Embase, The Cochrane Library and CINAHL with search terms pertinent to studies on cardiac biomarkers and their predictive value for quality of life in patients with chronic kidney disease. Experts in the field of nephrology known to the author were also asked for their opinions for search directions.

The literature search was limited to English language articles however it was not restricted by date to ensure the information for review would give a complete overview of the history of this illness and the progress made over time; the most recent articles (2000-2014), however, were the main focus for information for this paper.

This literature review will offer background information on chronic kidney disease, specifically end-stage renal disease, as well as cardiac biomarkers and quality of life.

2.2 Chronic Kidney Disease

While it is undisputed that the incidence and prevalence rates of chronic kidney disease are rising globally, it is challenging to determine the precise incidence of new-onset kidney disease. The Framingham Offspring study examined 2585 participants free from pre-existing renal disease over a mean follow-up of 18.5 years and found that 9.4% (244 participants) had developed kidney disease, defined as eGFR $\leq$ 64 and 59 mL/min

per 1.73 m^2 for men and women, respectively (Fox et al., 2004). A retrospective cohort followed over a 5.5 year period, approximated the annual incidence of chronic kidney disease to be 1700 cases per million persons, with CKD defined as serum creatinine $\geq$ 1.7 mg/dL for six months or longer (Drey et al., 2003). It is important to note that the specific measure used to assess the presence of CKD (eGFR, serum creatinine) markedly influences the apparent incidence and prevalence of the disease. In a study by Turin et al., the lifetime risk of progressing to end-stage renal disease was calculated from a cohort of approximately 3 million Canadians. In participants free of ESRD at age 40, the lifetime risk of developing the disease is roughly 1 in 40 for men (2.66%) or 1 in 60 for women (1.76%). However as GFR decreases the risk for progressing to ESRD increases significantly (Turin et al., 2012).

2.2.1 Etiology of Chronic Kidney Disease

Chronic kidney disease is a chronic deterioration of kidney function over time and can be the result of a number of causes. As described by Levey et al. in the "Practice Guidelines for Chronic Kidney Disease", kidney function begins at a "normal" level before increased risk factors lead to kidney damage resulting in a decreased GFR and ultimately kidney failure. While there is no one cause of kidney failure, there are numerous risk factors which can accelerate the damage to the kidneys and subsequent loss in function, which include susceptibility factors, initiation factors, progression factors and end-stage factors. Susceptibility factors increase the susceptibility and likelihood of the kidney being damaged. These factors include increasing age, a family history of renal disease or cardiovascular disease, racial and ethnic status, low birth weight and lower

socioeconomic status. Initiation factors directly damage the kidney and impair function and include diabetes, hypertension, systemic infections, urinary tract infections, obstructions and stones, and drug toxicity. Progression factors worsen an already damaged kidney leading to a greater and accelerated deterioration in function. These factors can include high levels of proteinuria, poor glycemic control for diabetics, smoking and hypertension. End-stage factors are risk factors that increase the risk of death and impaired quality of life for patients in stage 5 CKD. These factors are centralized around dialysis treatment and include lower dialysis dose, vascular access type, anemia, low albumin and late detection and referral (Levey et al., 2003).

2.2.2 Classification of Chronic Kidney Disease

Glomerular filtration rate represents the volume of blood filtered from the glomerular capillaries into Bowman's space per unit time, with a decreasing GFR representing impaired kidney functioning. While normal GFR varies amongst individuals based on age, sex, nutritional status and race, it is still considered the best index of overall kidney function (Levey & Inker., 2014). Albuminuria is most often indicated by an elevated albumin-to-creatinine ratio (ACR), and indicates an increased permeability of the glomerulus to large proteins and macromolecules, resulting from primary or secondary kidney disease (Remuzzi et al., 2006).

Staging of Chronic kidney disease is based on assigning the cause of CKD, assigning the GFR to one of six stages, and classifying albuminuria into one of three categories, which would then serve as a guide for clinical treatment and management. The

cause of CKD is assigned based on the "presence/absence of systemic disease and the location within the kidney of observed or presumed pathologic-anatomic findings" (Kidney Disease Improving Global Outcomes).

The glomerular filtration rate is classified into categories ranging from G1 to G5, reflecting the level of impairment. Stage one (G1) is defined by a normal GFR (>90 mL/min per 1.73 m^2) representing normal or high kidney function, stage two (G2) CKD mildly decreased function with a GFR between 60-89 mL/min per 1.73 m^2, stage three is subdivided into G3a and G3b, with G3a (mildly to moderately decreased) having a GFR between 45-59 mL/min per 1.73 m^2, and G3b (moderately to severely decreased) having a GFR of 30-44 mL/min per 1.73 m^2. This subdivision is intended to outline the relationship between a decreasing GFR and the subsequent increased risk for adverse events and mortality that is associated with it. Stage four (G4) has severely decreased renal function with a GFR between 15-29 mL/min per 1.73 m^2, and stage five (G5) or end-stage renal disease is a GFR less than 15 mL/min per 1.73 m^2 indicating kidney failure (Kidney Disease Improving Global Outcomes).

Since the original KDOQI classification scheme was published in 2002, albuminuria staging has been added to CKD staging based on evidence of an increased risk of mortality or progression to ESRD at high levels of albuminuria, independent of GFR. Stage one of albuminuria (A1) is defined as an ACR< 30 mg/g and is considered normal to mildly increased. Stage two (A2) is moderately increased with an ACR of 30-300 mg/g, with stage three (A3) being an ACR of >300 mg/g or severely increased. If an

albuminuria measurement is unavailable it can be substituted for urine reagent strip results (Kidney Disease Improving Global Outcomes).

2.3 Quality of Life

2.3.1 Short Form-36 (SF-36)

The Short-form health survey was developed as an instrument to assess quality of life in clinical practice and research by examining and assessing eight health concepts. The SF-36 survey is divided into two summary scores, physical component score (PCS) and mental component score (MCS), and comprised of eight sub-scales: PCS – physical functioning, physical role limitations, bodily pain, general health, vitality; MCS – emotional role limitations, emotional well-being, and social functioning (Lopes et al., 2007; Fukuhara et al., 2003).

The usefulness and validity of the SF-36 as a tool for assessing quality of life has been demonstrated and supported by numerous studies. Research by McHorney et al. tested the instruments validity using psychometric and clinical criteria. The results from traditional psychometric and clinical tests of validity were compared and a principal component analysis was used to test the hypothesized domains of physical and mental health. Results from this study supported the validity of using the SF-36 for examining physical health, mental health, social functioning, vitality and general health (McHorney et al., 1993). Other research has confirmed the instruments use and validity specific to the hemodialysis population with a cross sectional study by Wight et al. of 660 end stage renal disease patients concluding that the SF-36 is a practical and consistent questionnaire

and there is evidence supporting its construct validity (Wight et al., 1998). This notion is further supported by Lowrie et al., who collected cross sectional data on 13,952 prevalent dialysis patients to examine whether the physical and mental component summary scores of the SF-36 were predictive for morbidity and mortality. The results of this study indicated that even after adjusting for clinically relevant factors, the PCS and MCS of the SF-36 were powerfully predictive for morbidity and mortality in the dialysis population (Lowrie et al., 2003).

In the SF-36 domain of physical function, the mean score in the general population was 86, for dialysis patients it was 41 (Hopman et al., 2000; Fukuhara et al., 2003), and for the hemodialysis patients without symptomatic cardiac disease it was 67 (Foley et al., 2009). For the vitality domain of SF-36, the score for the general population was 66 (Hopman et al., 2000), for dialysis patients it was 43 (Fukuhara et al., 2003), and for hemodialysis patients without symptomatic cardiac disease 58 (Foley et al., 2009).

2.3.2 Kidney Disease Quality of Life Questionnaire (KDQOL)

The kidney disease quality of life questionnaire is a longer survey that targets health related concerns of patients suffering from kidney disease. The KDQOL is centralized around the SF-36, with 36 generic items, however it also examines 43 kidney disease specific items, producing 11 scales specific for kidney disease including: symptoms, effects of kidney disease on daily life, burden of kidney disease, work status, cognitive function, quality of social interaction, sexual function, sleep, dialysis staff

encouragement, social support and patient satisfaction (Lopes et al., 2007; Hays et al., 1994).

The use of KDQOL as an instrument for examining quality of life has been validated in numerous studies. Research by Hays et al. examined 165 individuals with kidney disease across nine dialysis units in the United States and found internal consistency reliability exceeding 0.75 for every measure except one supporting the reliability and validity of the KDQOL (Hays et al., 2004). A study by Kurella et al. was conducted to validate the cognitive function subscale of the KDQOL. The KDQOL was administered to 157 patients with varying levels of CKD (79 with ESRD) and compared their results in the cognitive function subscale to results obtained from the gold standard test, the Modified Mini-Mental State Exam. Results from this study showed direct correlation between the KDQOL scores and the Mini-Mental State Exam, which led to the conclusion that the KDQOL is a valid instrument for estimating cognitive function in dialysis patients (Kurella et al., 2004).

2.3.3. Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue)

The functional assessment of chronic illness therapy measurement scales are instruments targeted to measuring quality of life in patients suffering from chronic illnesses including cancer, multiple sclerosis, HIV, renal disease, amongst others. There are roughly 50 different generic and targeted questionnaires, including that for fatigue. Raw scores are automatically converted via statistical software packages into scales with higher values indicating a better quality of life (Webster et al., 2003).

While not specifically validated for chronic kidney disease, this instrument has been validated for patients with similar levels of quality of life. Chandran et al. reported the validity of the FACIT-Fatigue questionnaire in psoriatic arthritis patients with an internal consistency score 0.96. Scores were found to be reproducible and correlated with other fatigue instruments that were used (Chandran et al., 2007). This result is consistent with findings from a study be Yellen et al. who measured fatigue and other anemia-related symptoms using the FACT-Fatigue. Yellen et al. demonstrated stable scores (test-re-test r=0.87) and internal consistency (coefficient alpha range = 0.95-0.96) of the FACT-Fatigue instrument when assessing fatigue among cancer patients. Although not specifically validated for chronic kidney disease, this instrument has been demonstrated to be valid and reliable for many other chronic illnesses and has been utilized previously for CKD patients (Parfrey & Wish, 2010).

The FACIT fatigue mean score in the general population was 80 and in diabetic chronic kidney disease patients was 30 (Lewis et al., 2011), as compared to 70 for hemodialysis patients without symptomatic cardiac disease (Foley et al., 2009).

2.4 Cardiac Disease and ESRD

Cardiovascular disease is an important cause of morbidity and mortality in end-stage renal disease patients, accounting for approximately fifty percent of deaths amongst patients on maintenance hemodialysis (Henrich, 2014), and a mortality rate approximated

to be 10 to 100-times higher than age, gender and race matched controls (Wang & Lam, 2012).

Cardiac disease may be caused by vascular disease (atherosclerotic coronary artery disease or microvascular disease), predisposing to myocardial infarction/angina, or by cardiomyopathy (diastolic or systolic dysfunction) predisposing to heart failure (Parfrey et al., 2005).

Cardiovascular disease is the leading cause of death for CKD patients, however the relationship between traditional risk factors (ie: blood pressure, serum LDL cholesterol) and death is complex, with risk at both the highest and lowest levels, potentially indicating confounding by disease severity, malnutrition and inflammation, or unmeasured comorbidities (Levey & Coresh, 2012). According to the National Kidney Foundation practice guidelines, "Cardiovascular disease deserves special consideration as a complication of chronic kidney disease because CVD events are more common than kidney failure in patients with stage G3 (and a small extent stage G4) chronic kidney disease; CKD seems to be a risk factor for cardiovascular disease; and CVD in patients with CKD is treatable and potentially preventable" (Levey et al., 2003). According to Levey & Coresh, several studies have shown that "low GFR and high albuminuria are associated with an increased risk of cardiovascular mortality, de-novo and recurrent cardiovascular events, and subclinical cardiovascular disease." The pathophysiological links between chronic kidney disease and cardiovascular disease include a number of traditional and non-traditional risk factors: hypertension; fluid overload; electrolyte, acid-base and mineral disorders; anemia; dyslipidemia; inflammation; increased oxidative

stress; and prothrombotic stimuli, but could also be the result of reverse causation as CVD is recognized as a risk factor for deteriorating GFR (Levey & Coresh., 2012).

Myocardial dysfunction is common just prior to commencing dialysis and its prevalence increases after treatment onset (Henrich, 2014). A study of 432 patients with chronic kidney disease showed that 31% had evidence of heart failure just prior to beginning dialysis treatment, and once treatment began, an additional 25% developed heart failure at a rate of 7% annually (Harnett et al., 1995). In addition, a study examining 596 incident hemodialysis patients without symptomatic heart disease found that 75% of patients starting hemodialysis had left ventricular hypertrophy, 32% had left ventricular dilatation and 15% had systolic dysfunction (Foley et al., 2009). Cardiovascular events, particularly heart failure and atherosclerotic events have a major impact on HRQOL in ESRD. Hemodialysis patients who have not experienced these events may have elevated troponin T, a marker of myocardial injury, or elevated BNP, a marker of left ventricular wall stress, which may have predictive value for later outcomes (Foley et al., 2010).

2.5 Cardiac Biomarkers

The World Health Organization defines a biomarker as "almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical or biological. The measured response may be functional and physiological, biochemical at the cellular level or a molecular interaction" (Strimbu &

Tavel, 2010). Biomarkers are commonly used now in clinical research and are often the primary end points in clinical trials. More than that, many biomarkers have been validated and characterized as consistent predictors for a variety of clinical outcomes in differing populations. For a biomarker to be clinically useful it has to be: accurate; easily accessible; inexpensive to measure; reproducible; easy to interpret; have a defined "normal" value or range; have high sensitivity and specificity in detecting the condition; and knowledge of the biomarker levels must impact the management of the condition (Wang & Lam, 2012).

Cardiac biomarkers are biomarkers that are specifically used to assess the function and health of the heart, can be used to assess damage and injury, and to stratify patients into risk categories. Troponin T and brain natriuretic peptide are two such commonplace biomarkers, with troponin T functioning as a marker of myocardial injury, and BNP serving as a marker of left ventricular wall stress (Foley et al., 2010). Thus measuring cardiac biomarkers that reflect cardiac injury and dysfunction have clinical value in potentially facilitating the early detection of diseased patients for early treatment (Wang & Lam, 2012).

2.5.1 Troponin T

Troponin is an accessory protein that plays a fundamental role in the contraction of skeletal and cardiac muscle fibres. Troponin is bound to the actin filament of muscle, and in conjunction with tropomyosin, these proteins regulate muscle contraction (Cooper, 2000). Troponin is a complex composed of three components (Troponin C, Troponin I,

Troponin T), each with a unique and specific function. Troponin C is the calcium binding component of the troponin complex, troponin I inhibits the ATPase activity of actomyosin, and troponin T is responsible for the binding of tropomyosin to the troponin complex (Filatov, 1999). The contraction of muscle fibres is triggered by nerve impulses, which subsequently causes the release of calcium into the cytosol from the sarcoplasmic reticulum. When calcium concentrations are high, the binding of calcium with troponin C causes the troponin-tropomyosin complex to shift, relieving the inhibition of troponin I thus allowing the muscle to contract. When calcium concentrations are low, the troponin-tropomyosin complex blocks the interaction of actin and myosin and inhibits the contraction (Cooper, 2000). Approximately 7% of cardiac troponin T exists freely circulating in the myocyte, with the rest remaining bound within the sarcomere. Upon myocardial injury, troponin T is released from the damaged myocardium into the circulation. The degree of cardiac troponin T elevation correlates with the size of the infarct indicating the severity of damage to the myocardium. Cardiac troponin levels are currently the gold standard test for diagnosing acute myocardial infarction, and are important for risk stratification and prognosis (Wang & Lam, 2012).

After an extensive review of the literature examining health databases including PubMed, Embase and The Cochrane Library using the search terms “troponin t”, “quality of life” and “chronic kidney disease”, no literature was found specifically examining troponin T levels and its predictive value for quality of life in patients with chronic kidney disease or ESRD. There is however, a wealth of research that exists examining the

prognostic value of troponin T for cardiac death and all-cause mortality as well as the risk of occurrence of cardiovascular events, some of which is discussed below.

For patients with ESRD, cardiac troponin T is often elevated without the presence of symptomatic cardiac disease or injury, potentially detecting subclinical cell injury due to the stresses invoked by hemodialysis (Khan et al., 2005). Research conducted by Wang et al., 2007 demonstrated that even minimally increased troponin levels have important clinical consequences as dialysis patients with cardiac troponin levels between 0.01 and 0.1 ng/ml have increased risk for mortality and adverse cardiovascular events compared to those with undetectable levels, and those with a troponin T $\geq$0.1 ng/ml are typically the sickest patients with the worst outcomes (Wang et al., 2007). Thus any degree of troponin elevation represents some degree of injury and is associated with increased risk of a cardiovascular event and death.

A systematic review by Khan et al. examined the prognostic value of troponin T and I for patients with end-stage renal disease who were asymptomatic for cardiovascular disease. The meta-analysis selected 28 studies (3931 asymptomatic ESRD patients) that met the explicit inclusion and exclusion criteria and examined whether elevated troponin T levels was predictive for cardiac death. From the pooled analysis specifically examining troponin T and all-cause mortality (17 studies), elevated troponin T was significantly associated with increased all-cause mortality with a relative risk score of 2.64 and a 95% C.I. of 2.17 to 3.20. Khan and colleagues also examined troponin and cardiac death (via 8 studies) and revealed that elevated troponin T was strongly associated with cardiac death over the long-term (RR 2.55, 95% CI 1.93 to 3.37, $p<0.001$). Of the

16 studies that controlled for other prognostic factors (age, diabetes, presence of cardiovascular disease, left ventricular hypertrophy and left ventricular dysfunction), 15 demonstrated an independent association between elevated troponin T and all cause mortality (Khan et al., 2005).

A study conducted by Apple and colleagues, examined the predictive value of troponin T for subsequent death in 733 ESRD patients. Elevated troponin T was defined for the study using the 99th percentile of a healthy reference population (> 0.01 ng/ml). Of the 733 patients, 82% of unselected asymptomatic ESRD patients had a level above this value and it was found that with adjustment for other significant risk factors for mortality (age, history of cardiovascular disease and dialysis duration), elevated troponin T increased the risk of death 2- to 4-fold, and this increased risk of death was maintained over a 1, 2 and 3 year follow-up (Apple et al., 2002).

2.5.2 Brain Natriuretic Peptide

After an extensive review of the literature examining health databases including PubMed, Embase and The Cochrane Library using the search terms “brain natriuretic peptide”, “NT-proBNP”, “quality of life” and “chronic kidney disease”, no literature was found specifically examining NT-proBNP levels and its predictive value for quality of life in patients with chronic kidney disease or ESRD. There is however research that exists examining the prognostic value of BNP for cardiac death and all-cause mortality which will be briefly discussed.

The heart secretes two major hormonal natriuretic peptides to re-establish blood volume homeostasis: atrial natriuretic peptide (ANP) and brain natriuretic peptide. Brain natriuretic peptide is synthesized by the ventricles of the heart and functions in response to myocardial stretch to cause vasodilation, natriuresis and inhibition of the renin-angiotensin system. It is initially synthesized from ventricular myocytes as an amino acid precursor and via intracellular modification, forms a 108-amino acid pro-BNP hormone. This hormone is subsequently cleaved to form a 32-amino acid activated C-terminal fragment (BNP) and an inactive 76-amino acid N-terminal fragment (NT-proBNP). NT-proBNP is largely eliminated by the kidneys and with a half-life of approximately 120 minutes, circulates in concentrations roughly 6 times that of BNP and is cleared by enzymatic degradation with a half life ~ 20 minutes (Wang & Lam, 2012). The precise impact of chronic kidney disease on circulating BNP and NT-proBNP levels is uncertain and continues to be debated, however given that N-terminal fragment is primarily excreted by the kidneys, increased NT-proBNP could potentially be a proxy for residual renal function, a known predictor of morbidity and mortality. These levels are almost invariably elevated in ESRD patients, and increased serum concentrations are highly predictive for cardiac death in many cardiovascular disease states (Tagore et al., 2008).

NT-proBNP elevation in dialysis patients is primarily the result of increased LV systolic and diastolic wall stress, however other mechanisms have been supported as well. Research exists indicating a number of other possible mechanisms for NT-proBNP elevation including: LV end-systolic wall stress; myocardial hypoxia which up-regulates

BNP gene expression; and the high prevalence of LV structural and function abnormalities in dialysis patients (Wang & Lam, 2012).

In a study conducted by Gutierrez et al., NT-proBNP levels were assessed at baseline and serially thereafter in 2990 incident hemodialysis patients. The prognostic value of these NT-proBNP levels for all-cause mortality and cardiovascular mortality was determined. The quartiles of NT-proBNP levels were examined (quartile 3: 5111 – 14,100 ng/L; quartile 4: > 14,100 ng/L), and the one-year mortality rate for the upper quartile was 37.9 deaths per 100 patient-years risk, and 21.2 deaths per 100 patient-years risk in the third quartile. They also reported that increasing quartiles of NT-proBNP was associated with 90 day and 1 year all-cause and cardiovascular mortality and remained significantly independently associated when adjusted for case-mix and laboratory values (Gutierrez et al., 2008).

In a study conducted by Apple et al., 399 end-stage renal disease patients were enrolled to assess the predictive power of hsCRP, cTNT, cTNI and NT-proBNP for all cause mortality. The analysis for NT-proBNP was completed using both the normal cut-off (97.5^{th} percentile – patients aged <75 was 125 ng/L; >75 years was 450 ng/L) and again using tertiles, as 99% of the population had levels greater than the normal cut-off. This finding is likely due to the reliance on renal excretion for NT-proBNP, thus individuals with impaired renal function would have impaired NT-proBNP excretion, and hence the elevated levels. The results from this study showed no significant prognostic value for NT-proBNP and mortality using the normal cut-off (97.5^{th} percentile) for NT-

proBNP levels, however did demonstrate significance using the upper tertiles (Apple et al., 2004).

2.6 Other Factors Influencing Quality of Life in End-Stage Renal Disease

Health related quality of life is impaired in hemodialysis patients, and can be influenced by a number of factors including but not limited to: age, hemoglobin level, socioeconomic status, literacy, dialysis program, ethnic groups, sex, mobility, comorbidities, nutritional status, depression and unsuccessful previous renal transplant (Annees et al., 2014).

After an extensive review of the literature examining health databases including PubMed, Embase and The Cochrane Library using a combination of the search terms "age", "hemoglobin", "demographics", "predictors", "quality of life" and "chronic kidney disease", a variety of literature was found that highlighted several factors and their influences on quality of life in hemodialysis patients.

Morsch et al. conducted a descriptive cohort study on 40 hemodialysis patients to assess the effect of socio-demographic variables, diabetes, and clinical indicators on quality of life as assessed by the SF-36. Morsch and colleagues discovered that being male was significantly associated with improved quality of life in the energy/fatigue domain and that diabetic patients had a significantly worse perception of quality of life than non-diabetic patients in the SF-36 Physical Function domain. Morsch et al. also discovered a correlation between serum albumin ($p<0.05$), end-stage renal disease severity index (used to assess comorbidity aspects: cardiovascular, cerebrovascular,

peripheral vascular disease, peripheral neuropathy, bone disease, respiratory disease, deficient vision, autonomic neuropathy and gastro- intestinal disease, dialytic access and events, diabetes and an open category; $p<0.001$) and hematocrit ($p<0.05$) with physical function. No correlations were found for the energy/fatigue domain (Morsch et al., 2006).

In a study conducted by Bayoumi et al., 100 hemodialysis patients across three hemodialysis units in Saudi Arabia were followed for one year to assess what factors were associated with quality of life using the SF-36 and KDQOL. Researchers found a significant association between employment status and education with quality of life in the univariate analysis but these associations were lost in multivariate modelling. The significant and independent factors associated with worsened quality of life per the multivariate model were increasing age, increasing dialysis duration and being male. While the majority of the literature is in agreement with these findings, there is some debate over the gender impact, with other research indicating that males have a better quality of life in some domains (Morsch et al., 2006). This contradicting result is believed to be the result of the cultural role of the male in Saudi society, and the subsequent increased perception of impairment in daily function thus deteriorating quality of life (Bayoumi et al., 2013).

A systematic review by Spiegel et al. (2008) investigated 47 articles to determine the predictive value of a variety of biomarkers (dialysis adequacy, anemia, nutritional, mineral metabolism, inflammation) for quality of life in hemodialysis patients. Differences in quality of life scores between groups were measured using a scaled effect size (ES), which allowed the researchers to compare quality of life outcomes in different

interventions using the same uniform ES. The range of ES scores was standardized, and each biomarker was stratified as "high" or "low" as defined by the literature. The author's results concluded that patients with end stage renal disease have consistently lower quality of life scores as compared to healthy controls, especially in the physical function and vitality areas, with less impact being detected on mental health. The effect of dialysis adequacy, anemia, nutritional, mineral metabolism and inflammation biomarkers on quality of life was found to be mostly insignificant, with only serum albumin and serum creatinine biomarkers having a significant result, consistently providing the largest change in SF-36 scores, while hematocrit levels were only weakly related (Spiegel et al., 2008).

2.7 Study Rationale

Patients with end-stage renal disease have diminished scores in the physical domains of health related quality of life. Nutritional biomarkers have been shown to be significantly associated with this impairment; however there is a poor association between biomarkers for dialysis adequacy, mineral metabolism and inflammation with changes in quality of life scores (Spiegel et al., 2008).

Cardiovascular disease is the leading cause of death for hemodialysis patients and studies have shown the predictive value of cardiac biomarkers (troponin T and NT-proBNP) for all-cause mortality (Khan et al., 2005; Gutierrez et al., 2008). Despite this known relationship, no research exists that examines the predictive value of elevated cardiac biomarkers for change in the physical domains of quality of life over time.

Hemodialysis patients without prior symptomatic cardiovascular disease may still present with elevated baseline troponin T and BNP levels (Foley et al., 2010). This study examines the association between elevated baseline cardiac biomarkers and change in quality of life over time across the SF-36 Physical Functioning, SF-36 Vitality and FACIT Fatigue domains of health related quality of life.

Chapter 3: RESEARCH METHODS

3.1 Patients and Methods

Incident hemodialysis patients without symptomatic cardiac disease and left ventricular dilation were identified and recruited for participation from one of 95 treatment centers located throughout Canada and Europe to assess the impact of varying degrees of correction of anemia with erythropoietin via a randomized trial. Patients were deemed eligible for participation if they met the following inclusion criteria: (a) predialysis hemoglobin levels between 8 and 12 g/dl, (b) hemodialysis commenced in the preceding 3 to 18 months, (c) 18 years of age or older, (d) left ventricular volume index (LVVI) < 100 ml/m^2 on screening echocardiography (normal < 90 ml/m^2), and (e) predialysis diastolic blood pressure <100 mmHg. Exclusion criteria were as follows: (a) clinical evidence or history of symptomatic cardiac failure or ischemic heart disease, (b) daily prednisone dosages ≥10 mg, (c) medical conditions that are likely to reduce epoetin responsiveness, including uncorrected iron deficiency; concurrent malignancy; blood transfusion in the preceding month; therapy with cytotoxic agents; seizure in the preceding year; hypersensitivity to intravenous iron; and current pregnancy or breastfeeding. Between February 2000 and June 2001, 596 patients enrolled in the study with 30% of participants from Canada, and the remaining 70% from one of nine European countries (Austria, Belgium, France, Germany, Greece, Hungary, Poland, Spain, and United Kingdom). Dr. Patrick S Parfrey centrally monitored the Canadian participants from St. John's, Canada and the European participants were centrally monitored from Manchester, England by Dr. Robert N Foley (Parfrey *et al.*, 2005).

Patients were randomized via an interactive voice randomization telephone system, using permuted blocks and stratifying by gender and epoetin α use, to either the higher hemoglobin target (13.5 to 14.5 g/dl) or lower hemoglobin target (9.5 to 11.5 g/dl). Consequently for the purpose of this thesis all patients were included as one cohort. Patients were masked to treatment assignment, as were their doctors. A 24 week titration period was implemented to achieve appropriate hemoglobin targets followed by a 72 week maintenance period. Hemoglobin levels were achieved and maintained via epoetin α, using a predefined algorithm to calculate the required dosage (150 IU/kg per week for the higher target group). For patients whose hemoglobin levels diverged from the target, epoetin α dosage was modified by 25% (25 IU/kg) of the previous dose to correct for the difference. Epoetin α was administered subcutaneously and intravenously until August 22nd, 2002, at which point a study amendment restricted the administration of the drug to intravenous only. For the duration of the study, a form was faxed weekly to the coordinating centers for each patient detailing hemoglobin levels, epoetin α regimen, blood pressure, and transferrin saturation. In response to the patient information, weekly treatment recommendations were faxed back to treatment centers (Parfrey *et al*., 2005).

Patients were asked to provide a medical history and consent to the collection and administration of tests to obtain baseline evaluations of vital signs, height, weight, blood chemistry, M-mode echocardiography, electrocardiography, and a 6-min walking test. In addition to demographic factors (age, gender, and race), baseline clinical characteristics (diabetes, primary renal disease, dialysis vintage, blood pressure, body mass index, type of vascular access) were recorded, as were conventional laboratory test results (Hb, white

cell count, percentage of iron saturation, urea reduction ratio, and serum albumin) and other serologic tests at baseline. Serum concentrations of BNP and TNT were measured in 2009 using diagnostic kits analyzed on an Elecsys 2010 immunochemistry analyzer (Roche Diagnostics, Montreal, Quebec, Canada). Serum high-sentivity C-reactive protein was measured using CRP reagent and performed on an IMMAGE Immunochemistry system, and Serum IL-6 kits were used with a Unicel DxI 800 Access Immunoassay system to measure serum IL-6 levels (Beckman Coulter, Fullerton, CA). Serum leptin was measured by ELISA technique using kits purchased from Diagnostic Systems Laboratories, Inc (Webster, Tx). Prior to analysis, blood samples were stored securely with researchers at a temperature of minus 80 degrees Celsius (Foley *et al*., 2010).

Quality of life was assessed using two validated instruments, the Medical Outcomes Study Short Form-36 and the functional assessment of chronic illness therapy fatigue scale (Hays *et al*., 1997; McHorney *et al*., 1994; Jhamb *et al*., 2008) with pre-specified domains of interest for analysis: physical function and vitality measured using the SF-36 questionnaire and fatigue using the FACIT fatigue questionnaire. A-priori short-term change in HRQOL was defined as the change from baseline to the assessment at 24 weeks, and long-term change as the change from baseline to the assessment made at 48 and 96 weeks. These tools were administered to patients at weeks 0, 24, 48, and 96.

There was no difference in the clinical or demographic characteristics or in treatment assignment of those who had only one KDQOL assessment (n=12) and those who had serial assessments (n=484). At each assessment, > 90% of patients remaining in the study completed the questionnaire.

Ethics approval for this study was obtained from local research ethics review boards prior to the study being initiated. All patients provided informed consent, and the research was conducted in accordance with Good Clinical Practice guidelines, Declaration of Helsinki and the Tri Council Policy Statements for conducting research on humans. The last patient completed this study in May 2003.

3.2 Statistical Analysis

Data were coded and entered into the Statistical Package for the Social Sciences (SPSS) for analysis (IBM, 2010). Baseline characteristics were described by number (%) or by median with interquartile range. For the cardiac and inflammatory biomarkers, a priori it was specified that high levels were above the 75^{th} percentile.

Univariate linear regression was conducted to assess the association between the baseline variables and baseline health-related quality of life scores and change in scores over time. The independent variables included in the univariate analysis were selected based on potential associations with quality of life after consulting the literature. All clinically significant biomarkers ($p \leq 0.05$) were included in the multivariate models along with all cardiac biomarkers of interests. The change in quality of life over time variable was computed by calculating the difference in quality of life scores for each patient at 24 weeks and baseline, 48 weeks and baseline and 96 weeks and baseline. This change variable was then included in the analysis as the dependent variable. These outcome variables were examined graphically and appeared fairly normally distributed and no further transformation was required prior to statistical analysis. For each analysis missing data was handled using listwise deletion, with checks conducted to ensure that the sample

size was adequate to preserve significance and power for each individual model. Multiple linear regression models were constructed using the enter method and it was pre-specified that these include variables which were associated with the outcome at $p \leq 0.05$ in the univariate analysis. Multivariate models were also created to assess the impact of troponin T and NT-proBNP levels on change in quality of life independent of age, sex, diabetes and baseline HRQOL score. General linear models for repeated measures were also performed to demonstrate the association between elevated troponin T levels and change in quality of life across the three domains.

Repeated measures ANOVA was conducted to supplement and confirm the results obtained from the multivariate regression models. Repeated measures ANOVA is appropriate for analysis when there are repeated measurements that are assumed to be correlated within a subject, in this case quality of life scores over time. This statistical test is similar to multivariate regression models in that it provides the association between the independent variables and the dependent, however the repeated measures ANOVA allows for increased precision since sources of variability between subjects is removed. Repeated measures ANOVA does however require more subjects to maintain power, hence the results can be significantly influenced by missing data (Laerd Statistics, 2013).

Chapter 4: RESULTS

There were a total of 596 new hemodialysis patients without symptomatic cardiovascular disease enrolled in this study across 95 treatment centers in 10 countries between 2000 and 2001 with the last patient completing the study in May 2003. Linear regression and ANOVA models were used to analyze the predictive value of cardiac biomarkers for quality of life over time.

Table 1 shows the baseline characteristics for the study population. The median age was 51.5 years, 39.6% of participants were female, and 10.6% were non-Caucasian. Only 17.8% had diabetes as the cause of end-stage renal disease, and patients with a history of cardiovascular disease were excluded. All patients enrolled had commenced dialysis between 3 and 18 months prior to the start of the study, and the median time on dialysis was 9 months. Of the 596 participants, 502 (84.2%) had a fistula as vascular access. The upper quartile for troponin T was > 0.051 ng/ml (N=118), and for NT-proBNP it was > 651.9 pg/ml (N=120). The median score for SF-36 Physical Functioning was 70, for SF-36 Vitality it was 55 and for FACIT Fatigue it was 73.1.

Table 1:Baseline demographic and clinical characteristics, biomarkers and HRQOL scores

Age (yrs); median (25^{th} to 75^{th} percentiles)	51.5 (39 to 62)
Female; N (%)	236 (39.6)
Non-White Race; N (%)	63 (10.6)
Cause of ESRD:	
Glomerulenephritis; N (%)	171 (28.7)
Diabetic Nephropathy; N (%)	106 (17.8)
Polycistic Kidney Disease; N (%)	54 (9.1)
Hypertension; N (%)	48 (8.1)
Other/Unknown; N (%)	217 (36.4)
Dialysis Duration (mo); median (25^{th} to 75^{th} percentiles)	9 (6 to 14)
Dialysis Access:	
Fistula; N (%)	502 (84.2)
Graft; N (%)	33 (5.5)
Catheter; N (%)	61 (10.2)
Assigned to High Hb Target; N (%)	296 (49.7)
Epoetin Dosage (U/wk); median (25^{th} to 75^{th} percentiles); n=584	6000 (4000 to 8000)
BMI (kg/m^2); median (25^{th} to 75^{th} percentiles)	25.5 (22.6 to 29.3)
Systolic BP (mmHg); median (25^{th} to 75^{th} percentiles); n=595	140 (130 to 158)
Diastolic BP (mmHg); median (25^{th} to 75^{th} percentiles); n=596	80 (71 to 90)
Hemoglobin (g/dl); median (25^{th} to 75^{th} percentiles); n=580	11 (10.2 to 11.7)
Serum Albumin (g/L); median (25^{th} to 75^{th} percentiles); n=588	40 (38 to 41)
Urea Reduction Ratio (%);median (25^{th} to 75^{th} percentiles); n=572	67 (60 to 72.5)
Biomarkers; median (25^{th} to 75^{th} percentiles)	
Cardiac:	
Troponin T (ng/ml); n=481	0.021 (0.009 to 0.051)
NT-proBNP (pg/ml); n=481	289.2 (137.3 to 651.9)
Inflammatory:	
C-Reactive Protein (mg/L); n=481	3.47 (1.47 to 8.13)
IL-6 (pg/ml); n=481	4.39 (2.69 to 8.8)
Leptin (ng/ml); n=481	12.4 (3.7 to 43.8)
Quality of Life Domains; median (25^{th} to 75^{th} percentiles)	
SF-36 Physical functioning; n=457	70 (50 to 85)
SF-36 Vitality; n=457	55 (40 to 75)
FACIT Fatigue; n=572	73.1 (57.7 to 86.3)

Figure 1A and Figure 1B illustrate the distribution of baseline troponin T and NT-proBNP levels. As is demonstrated in Figure 1 A and B, only a small portion of the study

population had elevated cardiac biomarker levels at baseline. The upper quartile for troponin T was > 0.051 ng/ml (N=118) and for NT-proBNP it was >652 pg/ml (N=120).

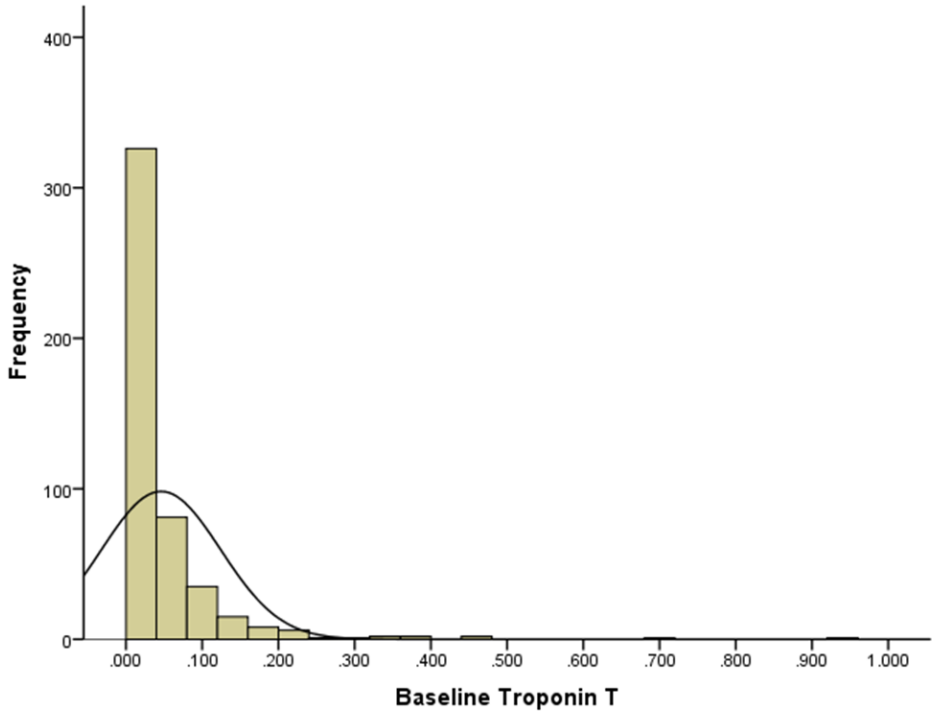

Figure 1A: Distribution of baseline troponin T levels in hemodialysis patients without prior symptomatic cardiac disease. Troponin T levels are expressed in units of ng/mL.

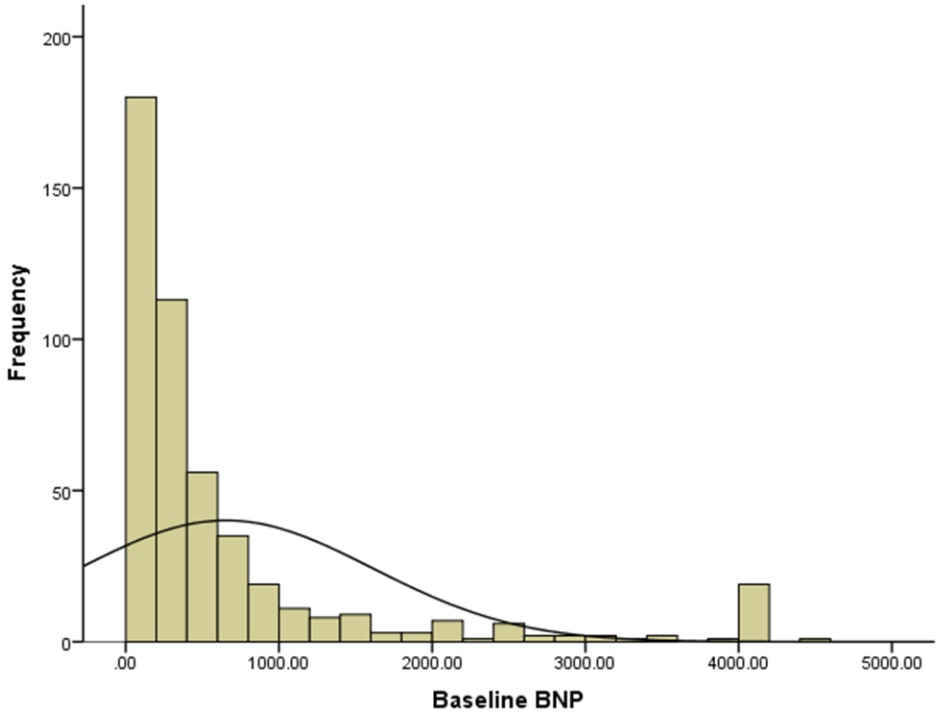

Figure 1B: Distribution of baseline NT-proBNP levels in hemodialysis patients without prior symptomatic cardiac disease. NT-proBNP levels are expressed in units of pg/mL

Figure 2 demonstrates the serial scores for quality of life in SF-36 Physical Function, SF-36 Vitality, and FACIT Fatigue at baseline, 24, 48 and 96 weeks. As signified by the graph, the quality of life scores deteriorated over the course of the 96-week study, however on average the changes were very slight. There was however noteworthy variation in quality of life scores at each time point, which is represented in the interquartile range (IQR). The median score for physical function at baseline was 70 with an interquartile range (IQR) of 50-85, for vitality it was 55 (IQR 40-75) and for fatigue it was 73.1 (IQR 57.7-86.3). At 24 weeks the median score for physical function

was 70 (IQR 50-90), for vitality it was 57.5 (IQR 40-75), and for fatigue it was 75 (IQR 55.8-86.5). At 48 weeks the median score for physical function was 70 (IQR 50-90), for vitality it was 55 (IQR 40-75), and for fatigue it was 73.1 (IQR 55.8-86.5). At 96 weeks the median score for physical function was 70 (IQR 45-90), for vitality it was 55 (IQR 40-75), and for fatigue it was 72.9 (IQR 53.8-88.5).

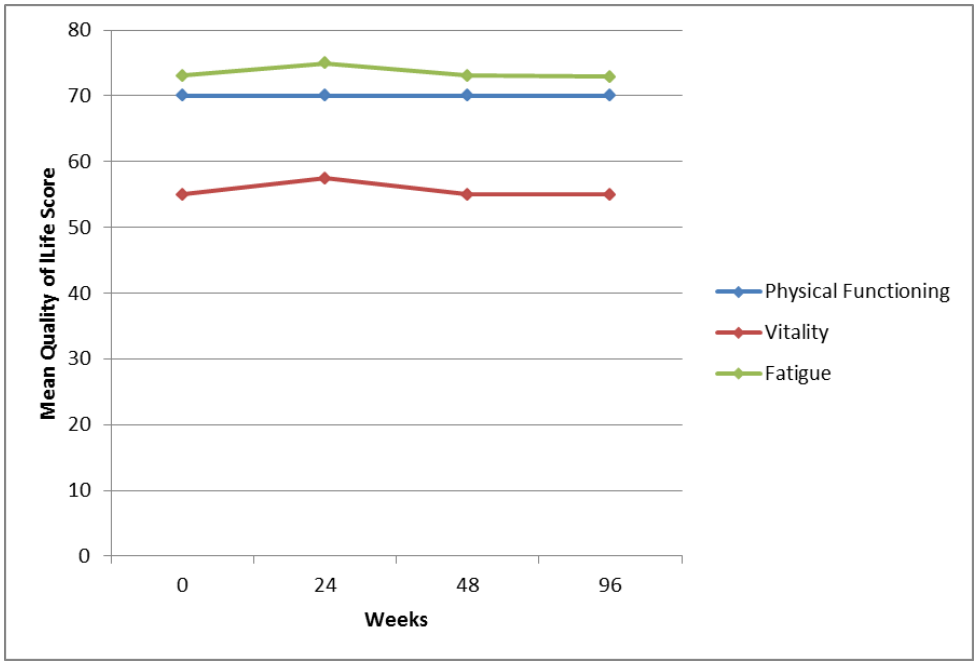

Figure 2: Serial HRQOL scores for SF-36 domains physical function and vitality, and for FACIT fatigue, in hemodialysis patients without symptomatic cardiac disease.

Table 2A and Table 2B show the significant univariate and multivariate associations between high troponin T levels at baseline and baseline clinical characteristics and biomarkers. The independent and significant predictors of elevated troponin levels were male sex ($p \leq 0.001$), older age ($p \leq 0.05$), diabetes ($p \leq 0.001$), high lactate dehydrogenase ($p \leq 0.05$) and high NT-proBNP levels ($p \leq 0.001$).

Table 2A: Significant univariate associations between baseline Troponin T levels and baseline clinical characteristics, using linear regression

Characteristic	Reference	Unadjusted B Coefficient	95% C.I.
Sex	Male	0.52	0.33 to 0.82**
Age	Per 1 year	1.03	1.01 to 1.04**
Diabetes	No Diabetes	4.59	2.81 to 7.48***
LV Mass Index	1 g/m^2	1.01	1.01 to 1.02***
Hb	$\leq$ 11.1 g/dL	0.52	0.33 to 0.80**
Serum Albumin	$\leq$ 40 g/L	0.56	0.36 to 0.88*
Lactate Dehydrogenase	Per 1 U/L	1.02	1.01 to 1.02***
Potassium	Per 1 mmol/L	1.36	1.03 to 1.79*
White Blood Cells	$\leq 8.1 \times 10^9$/L	1.84	1.15 to 2.95*
Platelet Count	$\leq 260 \times 10^9$/L	1.73	1.09 to 2.75*
NT-proBNP	$\leq$ 651.9 pg/ml	4.00	2.55 to 6.28***

p≤0.05;**p≤0.01;p≤0.001.**

Unadjusted B coefficient was calculated using univariate linear regression (column 3 & 4).

Table 2B: Significant multivariate associations between baseline Troponin T levels and baseline clinical characteristics, using linear regression

Characteristic	Reference	Adjusted B Coefficient	95% C.I.
Sex	Male	0.38	0.22 to 0.67***
Age	Per 1 year	1.02	1.00 to 1.04*
Diabetes	No Diabetes	4.62	2.55 to 8.38***
Lactate Dehydrogenase	Per 1 U/L	1.01	1.00 to 1.02*
NT-proBNP	$\leq$ 651.9 pg/ml	3.53	2.04 to 6.13***

p≤0.05;**p≤0.01;p≤0.001.**

Adjusted B coefficient was calculated using multivariate linear regression to identify the significant and independent predictors (column 5 & 6).

Table 3A and Table 3B show the significant univariate and multivariate associations between baseline clinical variables and biomarkers and baseline health-related quality of life scores. The univariate models for SF-36 Physical Functioning show significance for a multitude of factors, however the multivariate model revealed that the

significant, independent variables associated with improved physical functioning scores were younger age ($p \leq 0.01$), presence of a fistula as vascular access ($p \leq 0.01$) and lower NT-proBNP levels ($p \leq 0.05$). For SF-36 Vitality, the multivariate models only showed a significant association for a higher urea reduction ratio ($p \leq 0.05$) with improved vitality. The sole variable with a significant association with improved scores on the FACIT Fatigue scale was a higher URR ($p \leq 0.01$) based on the multivariate models. Model performance was assessed using R^2, which quantifies how much variance in the dependent variable is explained by the independent predictors. For SF-36 Physical Functioning, 21.5% ($R^2 = 0.215$) of the variance in the baseline quality of life can be explained by the multivariate model. When the cardiac biomarkers were removed from the model, the adjusted R^2 value decreased, thus worsening the model. For SF-36 Vitality, $R^2 = 0.066$, meaning a smaller percentage of variation was explained by the model. Neither cardiac biomarker was included in the original multivariate model and when they were added the adjusted R^2 value decreased thus indicating a worse predictive model. The R^2 for FACIT Fatigue was 0.052, indicating 5.2% of the variance in quality of life being explained by the multivariate model. Similarly for Fatigue, the inclusion of the cardiac biomarkers did not improve the adjusted R^2 value.

Table 3A: Significant univariate associations between baseline clinical variables and biomarkers and baseline HRQOL scores using linear regression

Characteristic	Reference	Unadjusted B Coefficient	95% C.I.
SF-36 Physical Functioning			
Female	Male	-7.56	-12.30 to -2.81**
Age	per 1 year	-0.49	-0.63 to -0.35**
Body Mass Index	per 1 kg/m^2	-0.63	-1.05 to -0.20**
Diabetes	No Diabetes	-8.25	-14.27 to -2.23**
Fistula	No Fistula	12.52	6.54 to 18.51**
Serum Albumin	$\leq$ 40 g/L	6.36	1.54 to 11.18**
Serum Creatinine	per 1 umol/L	0.02	0.01 to 0.03**
Sodium	per 1 umol/L	0.76	0.06 to 1.46*
White Blood Cells	$\leq 8.1 \times 10^9$/L	-7.98	-13.60 to -2.37**
Neutrophils	$\leq$ 68%	-7.33	-12.90 to -1.77**
Leptin	per 1 ng/ml	-0.17	-0.26 to -0.08**
Troponin T	$\leq$ 0.051 ng/ml	-9.54	-15.60 to -3.48**
NT-proBNP	$\leq$ 651.9 pg/ml	-6.05	-12.11 to 0.01*
IL-6	per 1 pg/ml	-0.19	-0.38 to -0.01*
SF-36 Vitality			
Female	Male	-5.73	-9.88 to -1.58**
Urea Reduction Ratio	$\leq$ 60%	8.58	3.52 to 13.64**
White Blood Cells	$\leq 8.1 \times 10^9$/L	-6.76	-11.62 to -1.91**
Leptin	per 1 ng/ml	-0.09	-1.17 to -0.01*
C-Reactive Protein	per 1 mg/L	-0.18	-0.35 to -0.00*
FACIT Fatigue			
Female	Male	-5.00	-8.26 to -1.73**
Body Mass Index	per 1 kg/m^2	-0.30	-0.60 to 0.00*
Diabetes	No Diabetes	-5.07	-9.40 to -0.73*
Urea Reduction Ratio	$\leq$ 60%	6.75	3.04 to 10.47**
Leptin	per 1 ng/ml	-0.10	-0.17 to -0.04**

***p≤0.05; **p≤0.01**

Unadjusted B coefficient was calculated using univariate linear regression (column 3 & 4).

Table 3B: Significant multivariate associations between baseline clinical variables and biomarkers and baseline HRQOL scores using linear regression

Characteristic	Reference	Adjusted B Coefficient	95% C.I.
SF-36 Physical Functioning			
Female	Male		
Age	per 1 year	-0.38	-0.56 to -0.20**
Fistula	No Fistula	10.69	3.52 to 17.86**
NT-proBNP	≤ 651.9 pg/ml	-6.33	-12.40 to -0.26*
SF-36 Vitality			
Urea Reduction Ratio	≤ 60%	6.33	0.48 to 12.17*
FACIT Fatigue			
Urea Reduction Ratio	≤ 60%	5.61	1.42 to 9.81**

***p≤0.05; **p≤0.01**
Adjusted B coefficient was calculated using multiple linear regression to identify the significant and independent predictors (column 5 & 6).

Table 4A and Table 4B show the significant univariate and multivariate associations between baseline clinical variables and biomarkers and short-term change (24 weeks) and long-term change (48 & 96 weeks) in HRQOL for the three specified domains.

For the SF-36 Vitality domain, the multivariate model showed significance between being in the higher hemoglobin target group ($p \leq 0.05$) and having a lower platelet count ($p \leq 0.05$) with an improved short term change in quality of life. The multivariate models revealed a significant association between a lower URR ($p \leq 0.01$), a higher serum calcium ($p \leq 0.01$), a lower platelet count ($p \leq 0.05$) and a higher Epo dose ($p \leq 0.01$) with improved quality of life over 48 weeks. These appear to be relatively random associations with little biologic rationale. The multivariate models showed elevated troponin T levels to be significantly associated with worsening vitality over 96 weeks ($p \leq 0.05$). The R^2

value for the multivariate model assessing change at 24 weeks was 0.028, which didn't include the cardiac biomarkers. When the cardiac biomarkers were added to the model, the adjusted R^2 value increased, indicating better model performance, however the individual cardiac biomarkers were not significantly associated with the change in quality of life. This trend was seen in both the change at 48 weeks model, as well as the change at 96 weeks. The R^2 value for multivariate model assessing change at 48 weeks was 0.080, and for change at 96 weeks it was 0.038, thus indicating that a relatively small amount of the variance seen in vitality is explained by the multivariate models.

For SF-36 Physical Functioning, having an elevated platelet count was significantly associated with deterioration in quality of life over 24 weeks ($p \leq 0.01$). The multivariate models for long-term change in quality of life showed higher serum calcium ($p \leq 0.05$) and lower troponin T levels ($p \leq 0.05$) to be significantly associated with improved quality of life over 48 weeks, and the presence of diabetes to be significantly associated with deteriorating physical functioning over 96 weeks ($p \leq 0.05$). It is important to note the potential of confounding for this analysis, as the patients with higher calcium levels will also have higher albumin levels, so although serum calcium was associated with change in quality of life, it is possible that it is masking the true marker, serum albumin. The R^2 value for change at 24 weeks was 0.032, for change at 48 weeks was 0.033 and for change at 96 weeks was 0.061. When the both cardiac biomarkers were included in the model, the adjusted R^2 value increased at 24 weeks and 96 weeks, thus indicating better model performance, despite the individual cardiac biomarkers not be significantly associated. At 48 weeks however, when NT-proBNP was included in the

model the adjusted R^2 value decreased, indicating worsened model performance. Similarly to SF-36 Vitality, only a small proportion of the variance in quality of life scores are explained by the multivariate models.

The multivariate models revealed a significant association between elevated troponin T levels ($p \leq 0.05$) and worsened FACIT Fatigue scores over 24 weeks. Long-term change deterioration in fatigue scores over 48 weeks was significantly associated with lower serum creatinine ($p \leq 0.05$), and an elevated platelet count ($p \leq 0.05$). No significant associations were found over 96 weeks for FACIT Fatigue. The R^2 value for change in fatigue at 24 weeks was 0.028, for change at 48 weeks was 0.028 and for change at 96 weeks was 0.029. When the both cardiac biomarkers were included in the multivariate model, the adjusted R^2 value decreased at 24, 48 and 96 weeks indicating a worsened model performance. Similarly to the other two domains of quality of life, only a small proportion of the variance in fatigue scores are explained by the multivariate models, indicating that other factors are significantly influencing these patient's quality of life.

Table 4A: Significant univariate associations between baseline clinical variables and biomarkers and change in short-term and long-term HRQOL scores, using linear regression

Characteristic	Reference	Unadjusted B Coefficient	95% C.I.
SF-36 Physical Functioning			
Change at 24 wks			
LV Mass Index	per 1 g/m^2	-0.06	-0.12 to -0.00*
Serum Calcium	$\leq$ 2.42 mmol/L	4.25	0.02 to 8.47*
Platelet Count	$\leq$ 260 x 10^9/L	-5.54	-9.95 to -1.13
Change at 48 wks			
Serum Calcium	$\leq$ 2.42 mmol/L	6.63	1.61 to 11.66**
Troponin T	$\leq$ 0.051 ng/ml	-6.40	-12.62 to -0.18*
Change at 96 wks			
Diabetes	No Diabetes	-7.28	-14.07 to -0.49*
Troponin T	$\leq$ 0.051 ng/ml	-9.43	-16.44 to -2.42**
SF-36 Vitality			
Change at 24 wks			
High Hb Group	Low Hb Group	5.09	1.16 to 9.03*
Platelet Count	$\leq$ 260 x 10^9/L	-5.00	-9.63 to -0.38*
Change at 48 wks			
Urea Reduction Ratio	$\leq$ 60%	-6.97	-12.22 to -1.72**
Serum Calcium	$\leq$ 2.42 mmol/L	5.34	0.94 to 9.73*
Platelet Count	$\leq$ 260 x 10^9/L	-5.93	-10.67 to -1.18*
Epo dose	$\leq$ 6000 U/wk	5.25	1.07 to 9.43*
Change at 96 wks			
Fractional shortening	per 1%	-0.32	-0.62 to -0.02*
Troponin T	$\leq$ 0.051 ng/ml	-7.55	-14.18 to -0.91*
FACIT Fatigue			
Change at 24 wks			
Lactate dehydrogenase	per 1 U/L	-0.05	-0.09 to -0.00*
White blood cells	$\leq$ 8.1 x 10^9/L	-4.32	-8.19 to -0.46*
Troponin T	$\leq$ 0.051 ng/ml	-5.38	-9.37 to -1.38**
Change at 48 wks			
Serum Creatinine	per 1 umol/L	0.01	0.00 to 0.02**
Platelet Count	$\leq$ 260 x 10^9/L	-5.06	-9.20 to -0.93*
Change at 96 wks			
Epo Dose	$\leq$ 6000 U/wk	-5.11	-9.92 to -0.31*

***p≤0.05; **p≤0.01**

Unadjusted B coefficient was calculated using univariate linear regression (column 3 & 4).

Table 4B: Significant multivariate associations between baseline clinical variables and biomarkers and change in short-term and long-term HRQOL scores, using linear regression

Characteristic	Reference	Adjusted B Coefficient	95% C.I.
SF-36 Physical Functioning			
Change at 24 wks			
Platelet Count	$\leq 260 \times 10^9$/L	-5.93	-10.37 to -1.50**
Change at 48 wks			
Serum Calcium	$\leq$ 2.42 mmol/L	6.00	0.39 to 11.62*
Troponin T	$\leq$ 0.051 ng/ml	-6.70	-12.93to -0.47*
Change at 96 wks			
Diabetes	No Diabetes	-8.84	-16.61 to -1.07*
SF-36 Vitality			
Change at 24 wks			
High Hb Group	Low Hb Group	5.11	1.07 to 9.14*
Platelet Count	$\leq 260 \times 10^9$/L		-9.58 to -0.40*
Change at 48 wks			
Urea Reduction Ratio	$\leq$ 60%	-7.06	-12.35 to 1.77**
Serum Calcium	$\leq$ 2.42 mmol/L	6.18	1.62 to 10.74**
Platelet Count	$\leq 260 \times 10^9$/L	-5.01	-9.84 to -0.18*
Epo dose	$\leq$ 6000 U/wk	5.73	1.53 to 9.93**
Change at 96 wks			
Troponin T	$\leq$ 0.051 ng/ml	-7.09	-13.73 to -0.46*
FACIT Fatigue			
Change at 24 wks			
Troponin T	$\leq$ 0.051 ng/ml	-4.91	-9.09 to -0.74*
Change at 48 wks			
Serum Creatinine	per 1 umol/L	0.01	0.00 to 0.02*
Platelet Count	$\leq 260 \times 10^9$/L	-4.78	-8.92 to -0.63*
Change at 96 wks			

***p≤0.05; **p≤0.01**
Adjusted B coefficient was calculated using multiple linear regression to identify the significant and independent predictors (column 5 & 6).

Table 5 shows the unadjusted and adjusted B coefficients for baseline troponin T levels and baseline HRQOL scores and change in quality of life over time from the univariate and multivariate analysis. In the unadjusted, univariate models elevated

troponin T is significantly associated with lower physical functioning at baseline, 48 weeks, and 96 weeks, with deteriorating vitality at 96 weeks and deteriorating fatigue at 24 weeks (approaches significance at 96 weeks). In the multivariate model controlling for other significant variables, elevated troponin T levels were significantly associated with deteriorating physical functioning at 48 weeks (approaches significance at 96 weeks), deteriorating vitality at 96 weeks and worsening fatigue at 24 and 96 weeks. When controlling for age, sex, diabetes status and baseline QoL score, high troponin T levels were associated with worsening physical functioning over 24, 48 and 96 weeks, with deteriorating vitality over 96 weeks and with worsening fatigue levels over 24 weeks. Examination of the unadjusted and adjusted B coefficients suggests consistent impact of baseline troponin T levels on change in HRQOL.

Table 5: Summary of the unadjusted and adjusted B coefficients for baseline Troponin T levels and baseline HRQOL scores and change in these scores over time

	Unadjusted B	p value	Adjusted B*	p value*	Adjusted B**	p value**
SF-36 Physical Functioning						
Baseline	-9.54	0.002	-5.92	0.071		
Change at 24 wks	-4.13	0.111			-6.02	0.018
Change at 48 wks	-6.40	0.044	-6.70	0.035	-8.09	0.008
Change at 96 wks	-9.43	0.009	-7.60	0.056	-8.42	0.015
SF-36 Vitality						
Baseline	-1.56	0.571				
Change at 24 wks	-3.46	0.182			-3.23	NS
Change at 48 wks	-1.36	0.633			-1.36	NS
Change at 96 wks	-7.55	0.026	-7.09	0.036	-7.10	0.037
FACIT Fatigue						
Baseline	-1.58	0.465				
Change at 24 wks	-5.38	0.008	-4.91	0.021	-5.95	0.002
Change at 48 wks	-3.89	0.093			-4.22	NS
Change at 96 wks	-5.46	0.057	-6.19	0.035	-4.56	NS

***Adjusted for other variables with p≤0.05.**

****Adjusted for age, sex, diabetes status and baseline QoL score.**

Unadjusted B coefficient was calculated using univariate linear regression.

Adjusted B coefficient was calculated using multivariate linear regression.

Table 6 shows the unadjusted and adjusted B coefficients for baseline NT-proBNP levels and baseline HRQOL scores and change in quality of life over time from the univariate and multivariate analysis. In the unadjusted, univariate models elevated NT-proBNP is significantly associated with less good physical functioning at baseline. The effect persisted in the multivariate model controlling for other significant variables. These are the only significant associations between elevated NT-proBNP and quality of life, indicating no significant relationship or predictive value of deterioration in quality of life over time.

Table 6: Summary of the unadjusted and adjusted B coefficients for baseline NT-proBNP levels and baseline HRQOL scores and change in these scores over time

	Unadjusted B	p value	Adjusted B*	p value*	Adjusted B**	p value**
SF-36 Physical Functioning						
Baseline	-6.05	0.05	-6.33	0.041		
Change at 24 wks	2.09	0.429				
Change at 48 wks	0.57	0.864				
Change at 96 wks	5.18	0.164				
SF-36 Vitality						
Baseline	-1.28	0.641				
Change at 24 wks	0.64	0.810				
Change at 48 wks	4.20	0.157				
Change at 96 wks	-4.08	0.241				
FACIT Fatigue						
Baseline	-2.13	0.318				
Change at 24 wks	-0.76	0.713				
Change at 48 wks	-1.96	0.409				
Change at 96 wks	-3.44	0.242				

***Adjusted for other variables with p≤0.05.**

****Adjusted for age, sex, diabetes status and baseline QoL score.**

Unadjusted B coefficient was calculated using univariate linear regression.

Adjusted B coefficient was calculated using multivariate linear regression.

Table 7 shows the significant associations for the repeated measures ANOVA of the three health-related quality of life domains of interest. For SF-36 Physical Function, age, baseline physical function score, sex, troponin T, the interaction of sex and troponin, and the interaction of diabetes and troponin, were all significantly associated with the repeated measures of physical functioning over time. Of these variables baseline physical function score and troponin T had the highest level of significance with a $p \leq 0.001$. For the SF-36 Vitality domain only baseline vitality score was significantly associated with the repeated measures score however troponin T approaches significance with a $p=0.06$. For the repeated measures of FACIT Fatigue, baseline fatigue score, sex and troponin T

were all significantly associated with the repeated measures score, with baseline fatigue score having the greatest degree of significance ($p \leq 0.001$).

Table 7: Significant associations for repeated measures ANOVA of quality of life scores and baseline clinical characteristics

Characteristic	F	Sig
SF-36 Physical Function		
Age	5.869	0.016
Baseline Physical Function Score	52.358	≤0.001
Sex	4.945	0.027
Troponin T	13.682	≤0.001
Sex * Troponin T	5.420	0.021
Diabetes * Troponin T	5.382	0.022
SF-36 Vitality		
Baseline Vitality Score	34.170	≤0.001
Troponin T	3.580	0.060
FACIT Fatigue		
Baseline Fatigue Score	65.901	≤0.001
Sex	3.923	0.049
Troponin T	4.289	0.040

Chapter 5: Discussion

The current study examined the predictive value of cardiac biomarkers for deteriorating quality of life in new hemodialysis patients without symptomatic cardiovascular disease. The major conclusions from this paper were: that health-related quality of life scores for physical function, vitality and fatigue in this relatively healthy hemodialysis population were closer to the general population scores than unselected hemodialysis patients, and these scores changed minimally over 2 years on average; only a small minority of patients had elevated baseline troponin T levels and these high levels were significantly associated with elevated NT-proBNP independent of age, sex, diabetes; high baseline troponin T levels were significantly associated with a deterioration in quality of life in physical function, vitality and fatigue domains over the short and long term, however NT-proBNP levels were not.

5.1 Health-related quality of life

Patients suffering from end-stage renal disease have consistently lower quality of life scores, particularly in physical function and vitality, when compared to healthy matched controls without end-stage renal disease (Spiegel et al., 2008). In patients with ESRD who are receiving dialysis, the average score for SF-36 physical function is 41 compared to 86 in the general healthy population (Hopman et al., 2000; Fukuhara et al., 2003). This impaired quality of life is maintained for SF-36 vitality, with dialysis patients reporting an average score of 43 (Fukuhara et al., 2003) as compared to 66 in the general population (Hopman et al., 2000), and for FACIT Fatigue as diabetic dialysis patients

report a score of 30 compared to 80 in the general population (Lewis et al., 2011). As indicated, the presence of end-stage renal disease results in severe and drastic declines in patient reported quality of life. The dialysis populations used to generate these statistics are uncontrolled for comorbidities and conditions that may be impacting the patient's quality of life. Patients in these populations may be suffering from cardiovascular disease, diabetes or some other comorbidity that is significantly impacting their day-to-day life resulting in poor self reported health related quality of life.

In this study, the study participants were selected using explicit inclusion and exclusion criteria to ensure a relatively "healthy" hemodialysis population. Participants were all new hemodialysis patients, with no left ventricular dysfunction as indicated by a LV volume index < 100 ml/m^2, and a predialysis diastolic blood pressure < 100 mmHg. Any patients with clinical evidence of symptomatic heart failure or ischemic heart disease or concurrent malignancy were excluded. As a result of these inclusion/exclusion criteria a relatively "healthy" study population was identified with an average quality of life score closer to the general population than to the unselected dialysis population. The "health" status of this population is further confirmed by the observation of an annual mortality of 5%, which is substantially lower than that in unselected hemodialysis patients (Parfrey et al., 2005). The median score for SF-36 physical function for the study population was 67, for SF-36 vitality was 58 and for FACIT Fatigue was 70 (Foley et al., 2009). As previously discussed, the "healthy" study participants more closely resemble the general population, leading to the conclusion that there are comorbidities amongst end-stage renal disease patients that severely deteriorate their quality of life. The presence of

symptomatic cardiovascular disease is one such comorbidity as there is a clear association between the presence of cardiac disease and health-related quality of life in dialysis patients. The presence of cardiovascular disease in end-stage renal disease patients accounts for approximately 50% of deaths amongst patients on maintenance hemodialysis (Henrich, 2014) and leads to a mortality rate that is roughly 10 to 100-times higher than age, gender and race matched controls (Wang & Lam, 2012).

5.2 Baseline elevations in troponin T and NT-proBNP and associations with change in health-related quality of life

Hemodialysis patients who have not experienced cardiovascular events may have elevated cardiac markers (troponin T and NT-proBNP) that may be predictive for later outcomes (Foley et al., 2010). In the study population, there was a substantial minority of participants who had elevated troponin T and NT-proBNP levels at baseline, an expected result given the overall health of the study population.

Troponin T is a biomarker with strong prognostic value for all-cause mortality and cardiovascular outcomes in end-stage renal disease patients (Khan et al., 2005). In a study by Apple et al., elevated cardiac troponin T was defined as greater than the 99th percentile of healthy reference population, > 0.01 ng/ml, with 82% of an unselected hemodialysis population asymptomatic for cardiovascular disease having an elevated level using this cut-off (Apple et al., 2002). A study by Wang et al. demonstrated that even minimally increased troponin T levels (between 0.01-0.1 ng/ml) have increased risk for mortality and adverse cardiovascular events compared to those with undetectable levels (Wang et

al., 2007). Elevated troponin T >0.1 ng/ml typically identifies the sickest patients and those with poor survival and the higher risk of death (Khan et al., 2005; Wang et al., 2007). In a previous study by Foley et al. using the same population of patients as the current study, it was reported that higher troponin T levels were predictive of subsequent cardiovascular events or death in the study cohort, but elevated troponin T levels are not independent of age, diabetes, systolic blood pressure or NT-proBNP (Foley et al., 2010). In our study, the median value for troponin T is 0.021 ng/ml with an interquartile range of 0.009 to 0.051 ng/ml. Elevated troponin T levels for our population were defined by the 75^{th} percentile, > 0.051 ng/ml. Research from Wang & Lam suggests that elevated troponin T levels in hemodialysis patients reflect not only myocardial injury and ischemia but myocardial fibrosis as well (Wang & Lam, 2012). This, coupled with results from the current study, supports the notion that high troponin levels are not innocuous and that they are significantly associated with deterioration in health-related quality of life. It is currently not possible to determine whether this deterioration of quality of life is the result of subsequent cardiac events, or due to a baseline degree of myocardial injury present at the commencement of the study. The latter hypothesis is supported by the fact only 4% of patients proceeded to a cardiovascular event (myocardial infarction, myocardial ischemia, angina pectoris, cardiac failure, pulmonary edema, cerebellar infarction, cerebral haemorrhage, cerebral vascular disorder, or death) by six months (Foley et al., 2010). Furthermore, high troponin T levels were associated with deteriorating quality of life scores at baseline and after short-term follow up across all three domains of interest (Table 4). This lends support to the notion of a baseline level of myocardial injury in hemodialysis patients in the pre-symptomatic phase of cardiac disease, as manifested by

raised serum troponin levels in patients without symptomatic cardiac disease. This may indicate an increased risk of having adverse clinical consequences, revealed by the association with lower quality of life scores in physical domains. More investigation is required however before this hypothesis can be confirmed.

N terminal pro-type B natriuretic peptide is a cardiac biomarker that reflects left ventricular wall stress that can occur secondary to volume expansion, pressure overload and increased wall tension. This biomarker is strongly influenced by renal disease, with increasing concentrations found among dialysis patients with end-stage renal disease (Wang & Lam, 2012). In a study by Apple et al., the normal cutoff for NT-proBNP was the 97.5th percentile, 125 ng/L for patients younger than 75 years, and 450 ng/L for patients older than 75 years (Apple et al., 2004). In our study population the median value for NT-proBNP was 289.2 pg/mL, with an elevated NT-proBNP level being defined as greater than 651.9 pg/mL (75th percentile). Previously in the current study population, it was indicated that NT-proBNP levels were independently predictive for baseline LVMI, of increasing LVMI over time and the resulting occurrence of adverse cardiovascular events, however it was unclear whether the BNP relationship was the result of left ventricular volume overload or underlying cardiac dysfunction (Foley et al., 2010). While elevated NT-proBNP levels may be associated with left ventricular hypertrophy and systolic dysfunction in some populations, in hemodialysis patients who are stable with normal left ventricular function on echocardiography and without a prior history of symptomatic cardiovascular disease, high BNP levels are likely the result of blood volume expansion and require reduction in post dialysis “dry” weight (Parfrey, 2010).

While NT-proBNP is predictive for mortality in hemodialysis patients (Madsen et al., 2007), elevated levels were not consistently associated with a deterioration in health-related quality of life across the three domains of interest at baseline, in the short term or in long term follow-up (Table 5).

5.3 Future Research Directions

The results of this study suggest that further research is required examining markers for cardiovascular disease as predictors for quality of life in hemodialysis patients. Prior research by Foley et al. conducted on the same clinical trial population as this study found an association between BNP and left ventricular mass index (Foley et al., 2010). Given that serial echocardiography data is available from this prior research, and it is believed from this research that troponin T is marking sub-clinical cardiac disease, further analysis could examine whether changes in parameters of left ventricular structure and/or function over time have any association with health-related quality of life.

5.4 Study limitations

This study is a continuation of research published by Parfrey et al. examining the full and partial correction of anemia in hemodialysis patients without symptomatic cardiovascular disease (Parfrey et al., 2005). The original study was a double blind randomized control trial carried out over a 2-year period, during which patients were randomized to a target haemoglobin level that was achieved and maintained by erythropoietin. The measurement of baseline cardiac biomarkers and health-related quality of life scores were a secondary objective. Resultantly, the study from which the

data originated was not designed to properly assess the predictive value of cardiac biomarkers for health related quality of life over time. Cardiac biomarker levels were recorded at baseline and analyzed to assess their association with change in quality of life. Given that quality of life was measured at 0, 24, 48 and 96 weeks, but TNT and NT-proBNP only at baseline, it is not possible to account for the impact that the study procedures and hemoglobin levels had on the cardiac biomarkers and subsequent quality of life scores over the duration of the study.

The patients studied in the original trial were monitored for the duration of the study for adverse cardiovascular events including myocardial infarction, myocardial ischemia, angina pectoris, cardiac failure, pulmonary edema, cerebellar infarction, cerebral haemorrhage, cerebral vascular disorder, or death (Parfrey et al., 2005). It was not possible however to confirm that the deteriorating health-related quality of life scores occurred solely as the result of elevated troponin T, independent of an adverse cardiovascular event, or if the elevated troponin levels were marking for a subsequent adverse event that resulted in the decreased quality of life. The confounding was limited due to the exclusion of patients with prior symptomatic cardiovascular disease and echocardiographic systolic dysfunction, but the potential for a confounding influence still exists, despite best efforts to minimize it's effect.

All study participants received the SF-36, FACIT Fatigue, and KDQOL instruments to asses health-related quality of life at 0, 24, 36, 48, 60, 72, 84 and 96 weeks of the study. At baseline however only 457 patients were included for the SF-36 Physical Functioning & SF-36 Vitality and 572 were included for the FACIT Fatigue (Parfrey et

al., 2005). It is possible that patients who did not have repeat measurements of HRQOL may be systematically different than the measured population. This systematic difference however would likely result in an underestimation of the true association between biomarkers and HRQOL.

The pre-determined statistical plan included dichotomization of both troponin T and BNP levels because they were not normally distributed. Further analysis of these biomarkers as a continuous variable with transformation to tame distributional anomalies could be undertaken to strengthen the validity and significance of the statistical analysis.

Missing data was handled using listwise deletion, a technique with a number of drawbacks including a decreased sample size or loss of data for the statistical analysis, which could impact the power and significance of the results, and the potential of producing bias in the parameters and estimates. It is important to note that the missing value points for this study were assumed to be random and as a result the population included in the analysis is believed to be representative of the study population, however the statistical analysis could have been strengthened if the pattern of missing values was examined and confirmed to be random. This would allow the magnitude and direction of bias introduced by the pattern of missing variables to be assessed, which would have enhanced the power of the analysis. While a number of alternative methods were considered for dealing with the missing values, it was determined that listwise deletion was appropriate given the number of missing cases in the population and the assumption that these missing values were random. The number of subjects included for each analysis was examined for all univariate and multivariate models to ensure adequate sample size

but it is inevitable that power and significance will be negatively impacted by the missing data. This is particularly true for the repeated measures ANOVA, as any missing data point in one of the time intervals would cause the entire subject to be rejected from the analysis, impacting the significance of the findings. There is also the potential for Type 1 error given the number of comparisons that were made in the univariate and multivariate models, which could produce inappropriate and false associations between clinical characteristics and quality of life. It is possible that some of the associations that had little biologic rationale and appeared random could be the result of such an error.

5.5 Conclusion

In conclusion, in a group of incident hemodialysis patients without prior history of symptomatic cardiovascular disease, elevated troponin T levels at baseline were associated with deterioration in SF-36 Physical Function, SF-36 Vitality and FACIT Fatigue over time. In the same group of incident hemodialysis patients there was no detectable association between elevated NT-proBNP levels and deteriorating quality of life in any of three specified domains over time.

References:

Annees, M., Malik, M. R., Abbasi, T., Nasir, Z., Hussain, Y., & Ibrahim, M. (2014). Demographic factors affecting quality of life of hemodialysis patients - Lahore, Pakistan. *Pak J Med Sci, 30*(5), 1123.

Apple, F. S., Murakami, M. M., Pearce, L. A., & Herzog, C. A. (2002). Predictive value of cardiac troponin I and T for subsequent death in end-stage renal disease. *Circulation, 106*, 2941.

Apple, F. S., Murakami, M. M., Pearce, L. A., & Herzog, C. A. (2004). Multi-biomarker risk stratification of N-terminal pro-B-type natriuretic peptide, high-sensitivity C-reactiec protein, and cardiac troponin T and I in end-stage renal disease for all-cause death. *Clin Chem, 50*, 2279.

Arora, P., Vasa, P., Brenner, D., Iglar, K., McFarlane, P., Morrison, H., et al. (2013). Prevalence estimates of chronic kidney disease in Canada: Results of a nationally representative survey. *Cmaj, 185*(9), E417.

Bayoumi, M., Al Harbi, A., Al Suwaida, A., Al Ghanaim, M., Al Wakeel, J., & Mishkiry, A. (2013). Predictors of quality of life in hemodialysis patients. *Saudi J Kidney Dis Transpl, 24*(2), 254.

Briggs, A. H., Parfrey, P. S., Khan, N., Tseng, S., Dehmel, B., Chertow, G. M. et al. (2013). Analyzing health-related quality of life in the EVOLVE trial: The joint impact of treatment and clinical events [Abstract]. *J Am Soc Nephrol, 24* 458A-459B.

Chandran, V., Bhella, S., Schentag, C., & Gladman, D. D. (2007). Functional assessment of chronic illness therapy-fatigue scale is valid in patients with psoriatic arthritis. *Ann Rheum Dis, 66*(7), 936.

Cooper, G. M. (2000). *A molecular approach* (Second Edition ed.). Sunderland, MA: Sinauer Associates.

Drey, N., Roderick, P., Mullee, M., & Rogerson, M. (2003). A population-based study of the incidence and outcomes of diagnosed chronic kidney disease. *Am J Kidney Dis, 42*(4), 677.

Filatov, V. L., Katrukha, A. G., Bulargina, T. V., & Gusev, N. B. (1999). Troponin: Structure, properties, and mechanisms of functioning. *Biochemistry (Moscow), 64*(9), 969.

Foley, R. N., Curtis, B. M., & Parfrey, P. S. (2009). Erythropoietin therapy, hemoglobin targets, and quality of life in healthy hemodialysis patients: A randomized trial. *Clinical Journal of the American Society of Nephrology, 4*, 726.

Foley, R. N., Curtis, B. M., Randell, E. W., & Parfrey, P. S. (2010). Left ventricular hypertrophy in new hemodialysis patients without symptomatic cardiac disease. *Clin J Am Soc Nephrol, 5*, 805.

Fox, C. S., Larson, M. G., Leip, E. P., Culleton, B., Wilson, P. W. F., & Levy, D. (2004). Predictors of new-onset kidney disease in a community based population. *Jama, 291*(7), 844.

Fukuhara, S., Lopes, A. A., Bragg-Gresham, J. L., Kurokawa, K., Mapes, D. L., Akizawa, T., et al. (2003). Health-related quality of life among dialysis patients on three continents - the dialysis outcomes and practice patterns study. *Kidney International, 64*(5), 1903.

Gutierrez, O. M., Tamez, H., Bhan, I., Zazra, J., Tonelli, M., Wolf, M., et al. (2008). N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations in hemodialysis patients: Prognostic value of baseline and follow-up measurements. *Clin Chem, 54*, 1339.

Guyatt, G. H., Feeny, D. H., & Patrick, D. L. (1993). Measuring health-related quality of life. *Annals of Internal Medicine, 118*, 622.

Harnett, J. D., Foley, R. N., Kent, G. M., Barre, P. E., Murray, D., & Parfrey, P. S. (1995). Congestive heart failure in dialysis patients: Prevalence, incidence, prognosis and risk factors. *Kidney Int, 47*, 884.

Hays, R. D., Kallich, J. D., Mapes, D. L., Coons, S. J., & Carter, W. B. (1994). Development of the kidney disease quality of life (KDQOL) instrument. *Quality of Life Research, 3*, 329.

Henrich, W. L. (2014). *Myocardial dysfunction in end-stage renal disease.* Retrieved 03/29, 2014, from http://www.uptodate.com/contents/myocardial-dysfunction-in-end-stage-renal-disease

Hopman, W. M., Towheed, T., Anastassiades, T., Tenenhouse, A., Poliquin, S., Berger, C., et al. (2000). Canadian normative data for the SF-36 healthy survey. *Can Med Assoc J, 163*, 265.

IBM. (2010). *Statistical package for the social sciences (SPSS)* (19th ed.)

Jhamb, M., Weisbord, S. D., Steel, J. L., & Unruh, M. (2008). Fatigue in patients receiving maintenance dialysis: A review of definitions, measures, and contributing factors. *American Journal of Kidney Diseases, 52*(2), 353.

Kalantar-Zadeh, K., Kopple, J. D., Block, G., & Humphreys, M. H. (2001). Association among SF-36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. *J Am Soc Nephrol, 12*, 2797.

Khan, N. A., Hemmelgarn, B. R., Tonelli, M., Thompson, C. R., & Levin, A. (2005). Prognostic value of troponin T and I among asymptomatic patients with end-stage renal disease: A meta-analysis. *Circulation, 112*, 3088.

Kidney Disease Improving Global Outcomes. (2013). KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney International Supplements, 3*(1)

Kidney Foundation of Canada. (2013). *Dialysis.* Retrieved 12/18, 2013, from http://www.kidney.ca/page.aspx?pid=337

Kidney Foundation of Canada. (2014). *Common causes of chronic kidney disease (CKD).* Retrieved 07/15, 2014, from http://www.kidney.ca/page.aspx?pid=321

Kurella, M., Luan, J., Yaffe, K., & Chertow, G. M. (2004). Validation of the kidney disease quality of life (KDQOL) cognitive function subscale. *Kidney Int, 66*(6), 2361.

Laerd Statistics. (2013). *Repeated measures ANOVA.* Retrieved August 15, 2014, from https://statistics.laerd.com/statistical-guides/repeated-measures-anova-statistical-guide.php

Levey, A. S., & Coresh, J. (2012). Chronic kidney disease. *Lancet, 379*, 165.

Levey, A. S., Coresh, J., Balk, E., Kausz, A. T., Levin, A., Steffes, M. W., et al. (2003). National kidney foundation practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *Ann Intern Med, 139*(2), 137.

Levey, A. S., & Inker, L. A. (2014). *Definition and staging of chronic kidney disease in adults.* Retrieved 03/30, 2014, from http://www.uptodate.com/contents/definition-and-staging-of-chronic-kidney-disease-in-adults

Lewis, E. F., Pfeffer, M. A., Feng, A., Uno, H., McMurray, J. J. V., Toto, R., et al. (2011). Darbopoietin alfa impact on health states in diabetes patients with kidney disease: A randomized trial. *Clin J Am Soc Nephrol, 6*, 845.

Lopes, A. A., Bragg-Gresham, J. L., Goodkin, D. A., Fukuhara, S., Mapes, D. L., Young, E. W., et al. (2007). Factors associated with health-related quality of life among hemodialysis patients in the DOPPS. *Qual Life Res, 16*, 545.

Lopes, A. A., Bragg-Gresham, J. L., Satayathum, S., McCullough, K., Pifer, T., Goodkin, D. A., et al. (2003). Worldwide dialysis outcomes and practice patterns study committee: Health-related quality of life and associated outcomes among hemodialysis patients of different ethnicities in the united states: The dialysis outcomes and practice patterns study (DOPPS). *Am J Kidney Dis, 41*, 605.

Lowrie, E. G., Curtin, R. B., LePain, N., & Schatell, D. (2003). Medical outcomes study short form-36: A consistent and powerful predictor of morbidity and mortality in dialysis patients. *Am J Kidney Dis, 41*, 1286.

Madsen, L. H., Ladefoged, S., Correll, P., Schou, M., Hildebrandt, P. R., & Atar, D. (2007). N-terminal pro-brain natriuretic peptide predicts mortality in patients with end-stage renal disease in hemodialysis. *Kidney Int, 71*, 548.

McHorney, C. A., Ware, J. E. J., & Raczek, A. E. (1993). The MOS 36-item short-form health survey (SF-36) : II. psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care, 31*(3), 247.

McHorney, C. A., Ware, J. E., Lu, J. F. R., & Sherbourne, C. D. (1994). The MOS 36-item short-form health survey (SF-36): III. tests of data quality, scaling assumptions, and reliability across diverse patient groups. *Medical Care, 32*(1)

Morsch, C. M., Goncalves, L. F., & Barros, E. (2006). Health-related quality of life among haemodialysis patients - relationship with clinical indicators, morbidity and mortality. *J Clin Nurs, 15*, 498.

National Kidney Foundation. (2002). K/DOQI clinical practice guidelines for chronic kidney disease: Evaluation, classification, and stratification. *American Journal of Kidney Diseases, 39*(S1-S266 (suppl 1))

Obrador, G. T., & Pereira, B. J. G. (2014). *Epidemiology of chronic kidney disease.* Retrieved 07/15, 2014, from http://www.uptodate.com/contents/epidemiology-of-chronic-kidney-disease

Parfrey, P. S. (2010). BNP in hemodialysis patients. *Clin J Am Soc Nephrol, 5*, 954.

Parfrey, P. S., Foley, R. N., Wittreich, B. H., Sullivan, D. J., Zagari, M. J., & Frei, D. (2005). Double-blind comparison of full and partial anemia correction in incident hemodialysis patients without symptomatic heart disease. *Journal of the American Society of Nephrology, 16*, 2180.

Parfrey, P. S., & Wish, T. (2010). Quality of life in CKD patients treated with erythropoiesis-stimulating agents. *Am J Kidney Dis, 55*(3), 423.

Remuzzi, G., Benigni, A., & Remuzzi, A. (2006). Mechanisms of progression and regression of renal lesions of chronic nephropathies and diabetes. *Journal of Clinical Investigation, 116*, 288.

Roberts, M. A., Hare, D. L., Macmillan, N., Ratnaike, S., Sikaris, K., & Ierino, F. L. (2009). Serial increased cardiac troponin T predicts mortality in asymptomatic patients treated with chronic hemodialysis. *Ann Clin Biochem, 46*, 291.

Spiegel, B. M. R., Melmed, G., Robbins, S., & Esrailian, E. (2008). Biomarkers and health-related quality of life in end-stage renal disease: A systematic review. *Clinical Journal of the American Society of Nephrology, 3*, 1759.

Strimbu, K., & Tavel, J. A. (2010). What are biomarkers? *Current Opinion in HIV and AIDS, 5*, 463.

Tagore, R., Ling, L. H., Yang, H., Daw, H., Chan, Y., & Sethi, S. K. (2008). Natriuretic peptides in chronic kidney disease. *Clin J Am Soc Nephrol, 3*(6), 1644.

Turin, T. C., Tonelli, M., Manns, B. J., Ahmed, S. B., Ravani, P., James, M., et al. (2012). Lifetime risk of ESRD. *J Am Soc Nephrol, 23*(9), 1569.

Wang, A. Y., & Lam, C. W. (2012). The diagnostic utility of cardiac biomarkers in dialysis patients. *Seminars in Dialysis, 25*(4), 388.

Wang, A. Y., Lam, C. W., Chan, I. H., Wang, M., Lui, S. F., & Sanderson, J. E. (2010). Sudden cardiac death in end-stage renal disease patients: A 5-year prospective analysis. *Hypertension, 56*, 210.

Wang, A. Y., Lam, C. W., Wang, M., Chan, I. H., Goggins, W. B., Yu, C. M., et al. (2007). Prognostic value of cardiac troponin T is independent of inflammation, residual renal function, and cardiac hypertrophy and dysfunction in peritoneal dialysis patients. *Clinical Chemistry, 53*(5), 882.

Ware, J. E. J., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. conceptual framework and item selection. *Medical Care, 30*(6), 473.

Webster, K., Cella, D., & Yost, K. (2003). The functional assessment of chronic illness therapy (FACIT) measurement system: Properties, applications, and interpretation. *Health and Quality of Life Outcomes, 1*, 79.

Wight, J. P., Edwards, L., Brazier, J. E., Walters, S., Payne, J. N., & Brown, C. B. (1998). The SF-36 as an outcome measure of services for end stage renal failure. *Quality in Health Care, 7*(4), 209.

Yellen, S. B., Cella, D. F., Webster, K., Blendowski, C., & Kaplan, E. (1997). Measuring fatigue and other anemia-related symptoms with the functional assessment of cancer therapy (FACT) measurement system. *J Pain Symptom Manage, 13*(2), 63.