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Investigating the Cardiovascular Effects of 12-months Home Based Nocturnal Haemodialysis versus. Conventional Haemodialysis Treatment: a Non-randomised Controlled Pilot Study.

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PERSPECTIVE

"What matters most to patients?" As a clinician this question is central to the 'why' of the clinical service we provide and how we choose to do deliver it for our chronic kidney disease (CKD) population. Nocturnal haemodialysis is a home-based therapy that offers high-quality, high-value treatment for end stage renal disease (ESRD). The benefits of extended-hours haemodialysis are widely reported, yet currently home dialysis patients account for only 2% of the ESRD renal replacement therapy population in the UK (23rd annual report, UK Renal Registry).

A HomeFirst approach is taken when discussing modality options with advanced CKD patients, yet it is our complex patients who have failed other modalities that we train to undertake nocturnal haemodialysis. The evidence-base for nocturnal haemodialysis is growing and the opportunity to provide individualised, tailored therapy to those that are waiting for or cannot undergo a renal transplant is attractive to both patients and their clinicians.

Having developed an interest in nocturnal dialysis during my nephrology speciality training and seen its life-changing impact on patients with ESRD, I chose to undertake further study looking at the cardiovascular benefits and the impact on oxidative stress and inflammation. This MD became a steppingstone to innovation and brought about a successful Welsh Government Transformation Fund co-productive project in digitalised patient education to improve health literacy, access to and uptake of nocturnal haemodialysis for all kidney patients across Wales. This has since been adopted by the Welsh Renal Clinical Network and upscaled nationally.

SUMMARY

Living with CKD dramatically impacts an individual's quality of life, often mandating frequent life-saving treatment in the form of haemodialysis; with its significant negative impact on cardiovascular morbidity and mortality. The cost to the individual and the NHS is substantial, with the UK ESRD population increasing by 8% year on year.

The overall aim of this research was to examine the effect of nocturnal haemodialysis; an extended-hours therapy on plasma markers of oxidative stress and inflammation and compare cardiovascular outcomes with those attributed to conventional haemodialysis. The primary aim was to compare the effect of nocturnal haemodialysis on myocardial strain, as assessed by LV GLS using STE and cardiac biomarkers. The principal secondary aim was to assess the effect of nocturnal dialysis on the rate of increase of coronary calcification as a marker of coronary disease burden as assessed by CACS. In line with previous research, notably the landmark Alberta trial, FHN and FHNN trials, this thesis demonstrated an improvement in blood pressure control, serum phosphate and reduction in polypharmacy. The nocturnal group saw an improvement in LV GLS ($p=0.04967$) from a more significantly impaired baseline, a non-significant reduction in LVMi and no significant increase in CACS (6%). Contrasted with the conventional group where a 71.2% increase in CACS was observed ($p=0.043$). With regards to changes in systemic inflammation, a reduction in inflammatory marker IL-6 ($p=0.04$) was seen in the nocturnal group. Higher serum hepcidin levels were observed in CAC progressors than those with regression of CAC ($p=0.045$), where significant correlation of baseline hepcidin with relative CACS ($p=0.037$, $r=0.9$) was observed.

This thesis provides new and detailed information on the assessment of cardiovascular disease in dialysis using LV GLS and CACS. Extended hours treatment with nocturnal haemodialysis significantly decreased progression of CAC compared with conventional haemodialysis. Progression appeared to be more dependent on levels of inflammation than deranged bone mineralisation with hepcidin the best predictor of an improvement in GLS and CAC progression. This information will add to the evidence-base and further enable clinicians to make person-centred therapy decisions for their ESRD patients.

DECLARATION AND STATEMENTS

DECLARATION

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

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STATEMENT 1

This thesis is the result of my own investigations, except where otherwise stated. Where correction services have been used, the extent and nature of the correction is clearly marked in a footnote(s).

Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

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LIST OF ABBREVIATIONS

ABTS	2,2-azino-bis-3-ethylbensthiazoline-6-sulfonic acid
ACE	Angiotensin Converting Enzyme
ADH	Antidiuretic Hormone
ADL	Activity of Daily Living
ADMA	Asymmetric Dimethylarginine
ADP	Adenosine Di-phosphate
AE	Adverse Event
AGE	Advanced Glycation End Products
AOPP	Advanced Oxidation Protein Products
AR	Adverse Reaction
ARNI	Angiotensin Receptor Neprilysin Inhibitors
AV	Aortic Valve
AVF	Arteriovenous Fistula
AS	Aortic Stenosis
AT-1	Angiotensin-1
AT-2	Angiotensin-2
ATP	Adenosine Triphosphate
BMP-2	Bone Morphogenetic Protein-2
BMP-6	Bone Morphogenetic Protein-6
BSA	Body Surface Area
CAC	Coronary Artery Calcification
CACS	Coronary Artery Calcification Score
CAD	Coronary Artery Disease
CAPD	Continuous Ambulatory Peritoneal Dialysis
CCL2	Chemokine (C-C motif) Ligand 2
CFM	Colour Flow Mapping
cGMP	Cyclic Guanosine Monophosphate
CKD	Chronic Kidney Disease
CKD-MBD	Chronic Kidney Disease-Mineral Bone Disease
cMR	Cardiac Magnetic Resonance
CO	Cardiac Output
CPP	Calcioprotein Particles

CRIC	Chronic Renal Insufficiency Cohort
CRP	C-Reactive Protein
CSA	Cross Sectional Area
CT	Computerised Tomography
CT-CAC	Computerised Tomography- Coronary Artery Calcification
cTNT	Cardiac Troponin T
CVVHD/F	Continuous Veno-Venous Haemodia(lysis)/ Filtration
CW	Continuous Wave
DBP	Diastolic Blood Pressure
ECHO	Echocardiography
ECG	Electrocardiogram
ECV	Extracellular Volume
EDTA	Ethylenediaminetetraacetic acid
E/e'	Ratio of transmitral doppler early filling velocity to tissue doppler early diastolic mitral annular velocity
ELISA	Enzyme-Linked Immunosorbent Assays
Epo	Erythropoietin
ERI	ESA Resistance Index
ESA	Erythropoietin Stimulating Agent
eNOS	Endothelial Nitric Oxide Synthase
ESRD	End Stage Renal Disease
FGF-23	Fibroblast Growth Factor-23
FGFR4	Fibroblast Growth Factor Receptor 4
FT	Flow Time
FHN	Frequent Haemodialysis Network
FHNN	Frequent Haemodialysis Nocturnal Network
GDF11	Growth Differentiation Factor 11
GDP	Glucose Degradation Products
GLS	Global Longitudinal Strain
HD	Haemodialysis
HFpEF	Heart Failure Preserved Ejection Fraction
HFrEF	Heart Failure Reduced Ejection Fraction
HHD	Home Haemodialysis
HIF	Hypoxia-Inducible Factor

HR	Hazards Ratio
HRA	Health Research Authority
HRQoL	Health-Related Quality Of Life
hsCRP	High Sensitivity C-Reactive Protein
IFN-ɣ	Interferon Gamma
IGF-1	Insulin Growth Factor-1
IL-1	Interleukin-1
IL-6	Interleukin-6
IL-18	Interleukin-18
INHD	In-centre Nocturnal Haemodialysis
IS	Indoxyl Sulfate
IV	Intravenous
IVC	Inferior Vena Cava
IRAS	Integrated Research Application System
JAK/STAT-1	Janus Kinase/Signal Transducer and Activator of Transcription-1
JSRC	Joint Study Review Committee
KDOQI	Kidney Disease Outcomes Quality Initiative
Kt/V	Measure of dialysis adequacy calculated as (K: dialyser clearance of urea, t: dialysis time, V: volume of distribution of urea)
LA	Left Atrium
LASr	Left Atrial Reservoir Strain
LAVI	Left Atrial Volume Index
LMWH	Low Molecular Weight Heparin
LPS	Lipopolysaccharide
LVH	Left Ventricular Hypertrophy
LVM	Left Ventricular Mass
LVMI	Left Ventricular Mass Index
LVSD	Left Ventricular Systolic Dysfunction
MAP	Mean Arterial Pressure
MBD	Mineral Bone Disease
MCP-1	Monocyte Chemoattractant Protein-1
MDA	Malondialdehyde
MV	Mitral Valve

NEP	Neutral Endopeptidase
NF-κβ	Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells
NHD	Nocturnal Haemodialysis
NO	Nitric Oxide
NOX	Nitrogen Oxide
NPRC	Natriuretic Peptide Receptor C
NT-proBNP	N-Terminal pro B-type Natriuretic Peptide
OR	Odds Ratio
PALS	Peak Atrial Longitudinal Strain
PBS	Phosphate Buffer Saline
PCS	P-Cresyl Sulfate
PD	Peritoneal Dialysis
PEW	Protein Energy Wasting
PMP	Per Million Population
POS-S	Palliative care Outcome Scale-Symptoms
PS LAx	Parasternal Long Axis
PTH	Parathyroid Hormone
PVN	Paraventricular Nucleus
PWD	Pulsed Wave Doppler
RAAS	Renin Angiotensin Aldosterone System
REC	Research Ethics Committee
REE	Resting Energy Expenditure
Ret-He	Reticulocyte Haemoglobin Equivalent
ROS	Reactive Oxygen Species
RRF	Residual Renal Function
RRT	Renal Replacement Therapy
RWMA	Regional Wall Motion Abnormalities
SAE	Serious Adverse Event
S Ax	Subcostal Short Axis
SBP	Systolic Blood Pressure
SCFA	Short Chain Fatty Acids
SD	Standard Deviation
SF-36	Short Form-36
STE	Speckle Tracking Echocardiography

SV	Stroke Volume
SVR	Systemic Vascular Resistance
TAOS	Total Antioxidant Status
TBARS	Thiobarbituric Acid Reactive Substances
TGF-β	Transforming Growth Factor Beta
TMAO	Trimethylamine-N-Oxide
TNF-α	Tumour Necrosis Factor Alpha
TREAT	Time to Reconsider Evidence for Anaemia Treatment
TSAT	Transferrin Saturation
TTE	Transthoracic Echocardiography
TV	Tricuspid Valve
UF	Ultrafiltration
UK	United Kingdom
UKRR	United Kingdom Renal Registry
USCOM	Ultrasound Cardiac Output Monitor
VEGF	Vascular Endothelial Growth Factor
VSMC	Vascular Smooth Muscle Cells
VTI	Velocity Time Integral
V2R	Vasopressin-2 Receptor
WHSSC	Welsh Health Specialised Services Committee
WRCN	Welsh Renal Clinical Network

PUBLICATIONS ASSOCIATED WITH THIS RESEARCH

Stephens JW, Brown K, Min T. Chronic kidney disease in type 2 diabetes: Implications for managing glycaemic control, cardiovascular and renal risk. Diabetes, Obesity and Metabolism 2020, 22(S1) 32-45.

Brown K, Bucknall T, Jefferies H, Greene G, Mikhail A, Prior SL, Stephens JW, Obaid D. Progression of coronary artery calcification in unit verses nocturnal haemodialysis patients. ASN 2021, abstract 3608818, poster presentation.

Brown K, Bucknall T, Jefferies H, Greene G, Mikhail A, Prior SL, Stephens JW, Obaid D. Differences in coronary artery calcification scoring (CACS) as a predictor of cardiac events in conventional vs nocturnal haemodialysis patients. UKKW 2021, paper 115 – moderated poster presentation session.

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CHAPTER 1

INTRODUCTION AND REVIEW OF LITERATURE

1.1 Overview

End stage renal disease (ESRD) leads to uraemic complications and associated mortality if renal replacement therapy (RRT) is not initiated. Dialysis-related disease persists despite treatment, with long-term complications and resultant mortality from ensuing cardiovascular events; in particular, sudden cardiac death due to ventricular arrhythmias, myocardial infarction, heart failure and stroke as well as sepsis/ infection.

In addition to traditional cardiovascular risk factors, the uraemic state provides an additional multifaceted dynamic risk, responsible for the increased burden in ESRD. Structural and functional changes including increased sympathetic nerve activity, endothelial dysfunction, oxidative stress and inflammation contribute to the increased morbidity and mortality.

Haemodialysis patient outcomes remain poor for health-related quality of life (HRQoL) when compared to the general population; morbidity and mortality have not improved commensurate with technological advancements or developments in medical therapy. Patient cost is high for conventional in-centre haemodialysis, with travel to and from hospital required for thrice weekly sessions. Frequent patient transport delays and associated job loss heighten the impact. Additional onerous dietary and fluid restrictions, a high medication load and fatigue; both from underlying illness and the treatment required, amplify the haemodialysis patient's burden of disease.

One-year age adjusted survival for prevalent, in-centre haemodialysis patients in the United Kingdom (UK) is 88.3% (Methven S et al., 2017). This is much higher for incident patients at 90.2% (after 90 days survival), many of whom are “crash-landers” and have not previously been seen in clinic by a nephrologist. Among ESRD patients the death rate is highest in the first year of haemodialysis. The cohort aged 35 – 39 years have the highest relative risk of death (RR 22) compared with the general population, this falls to 2.3 as the burden of haemodialysis is reduced by accumulating co-morbidities in those aged ≥85 years. Cardiovascular disease was the highest contributor, accounting for 22% of deaths.

A similar picture exists in the United States, the 5-year survival for haemodialysis patients is 40% compared to 87% for live donor kidney transplant recipients (2008 incident cohort). Dialysis patients aged <80 years can expect to live less than one third as long as non ESRD age-matched peers. Mortality rates are ~4 x higher in >75 years than in the general population with 41% of deaths attributed to cardiovascular disease (United States Renal Data System Annual Data Report, 2015).

The UK ESRD population is increasing by 8% per year. Currently 54% of RRT patients are transplanted, 40% undergo haemodialysis (hospital in-centre 17.5%, satellite unit 20.8%) and 6% peritoneal dialysis. Home haemodialysis (HHD) numbers although small, have increased from 2% over the last 10 years to 4.4% in 2016 (with a larger proportion of patients (6.8%) receiving HHD in Wales (Byrne C et al., 2018).

1.2 Chronic Kidney Disease and Inflammation

The relationship between inflammation and chronic kidney disease (CKD) is multifaceted; an increase in pro-inflammatory cytokines is contributed to by oxidative stress, acidosis, chronic and recurrent infections, altered metabolism of adipose tissue and micro-inflammation as a consequence of gut microbiota dysbiosis (Nallu A et al., 2017) as shown in Figure 1.1.

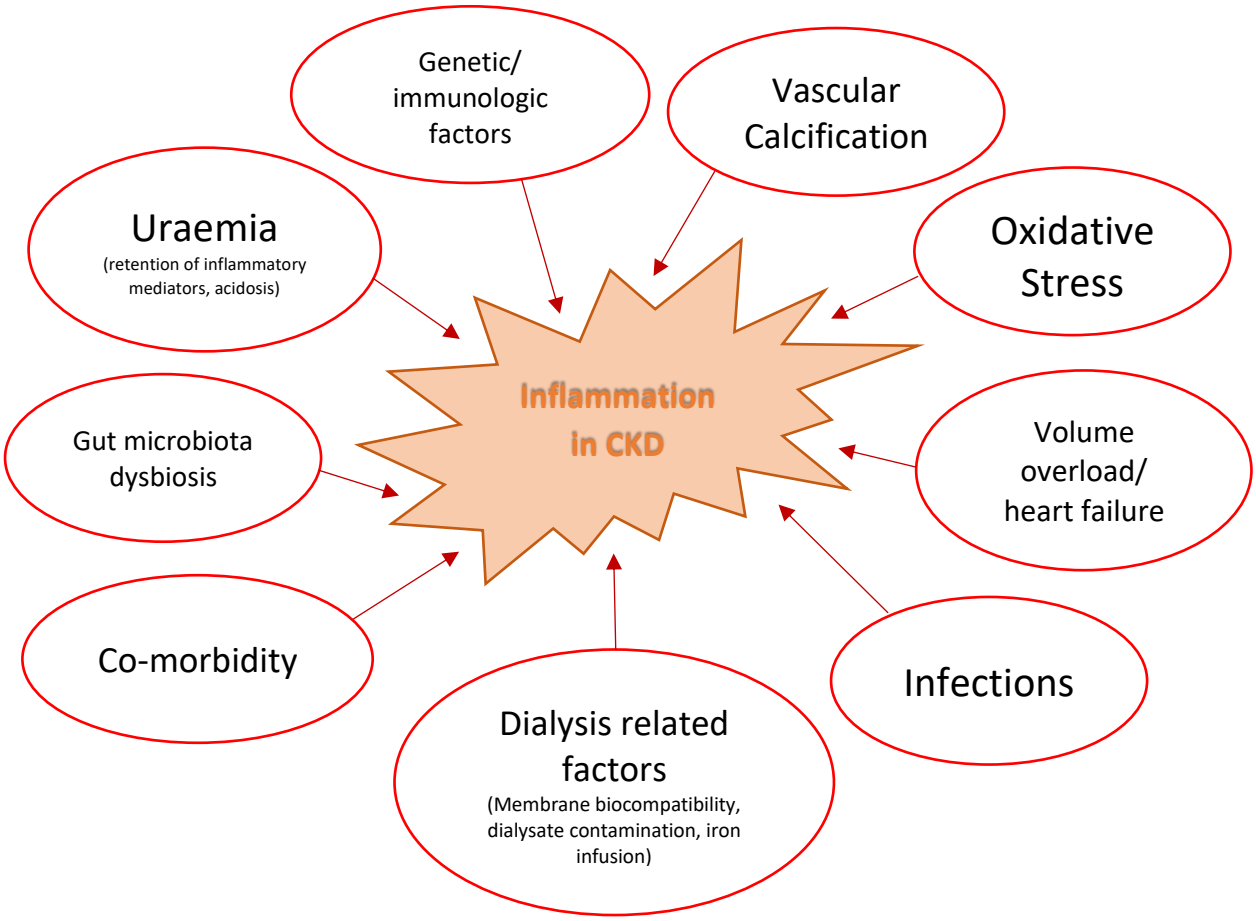


Figure 1.1 Disease and dialysis related factors: multifactorial sources of inflammation in CKD [adapted from Filiopoulos, V. et al., 2009 and Chaykovska et al., 2011].

CKD is characterised by persistent, maladaptive, low-grade inflammation. Systemic and intra-renal inflammation contributes to CKD progression and associated cardiovascular/ mineral bone disease ensue as a result of organ crosstalk as shown in Figure 1.2.

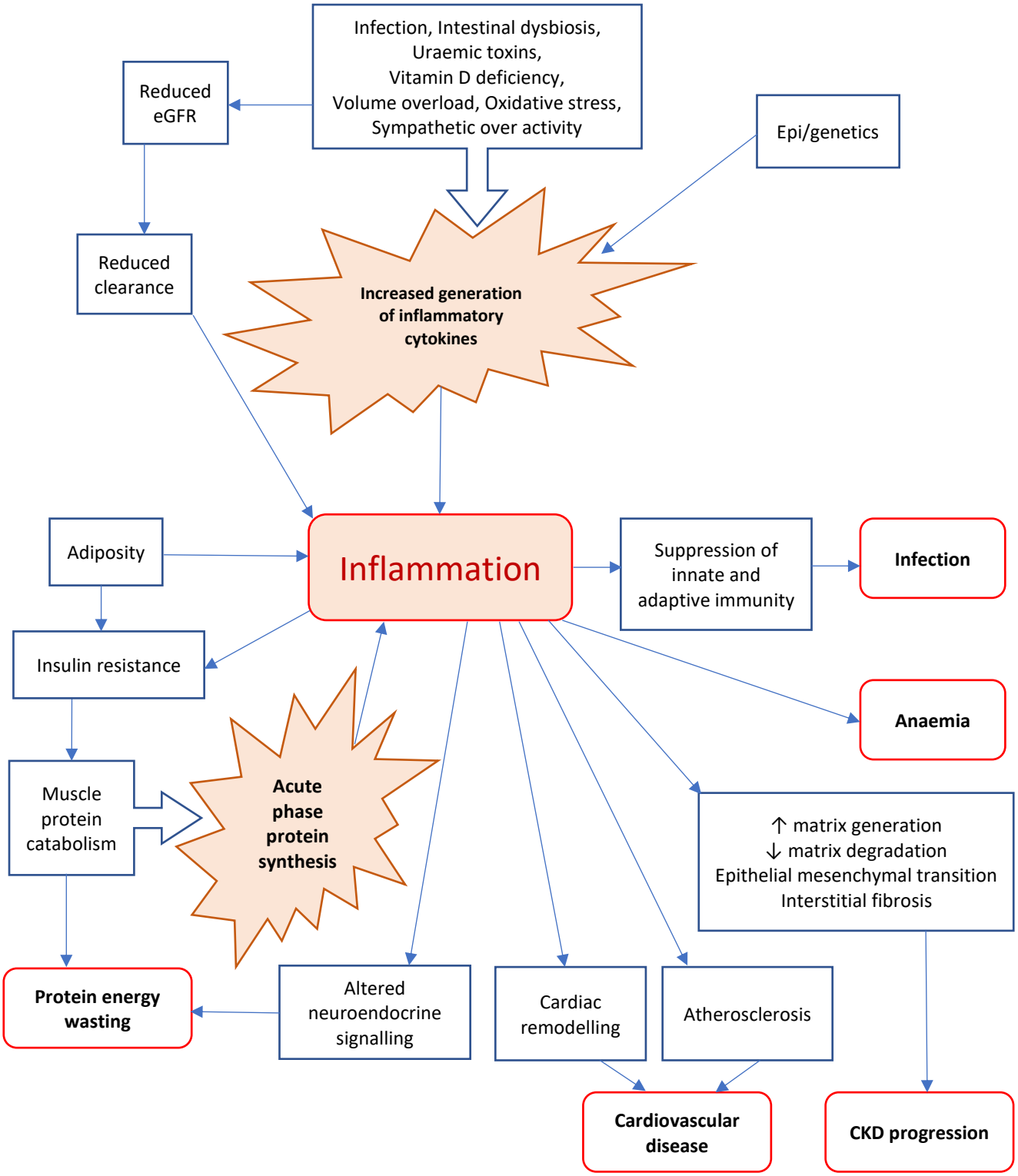


Figure 1.2. Inflammation in CKD [adapted from Raj et al., 2015]

In CKD there is a shift in favour of pro-inflammatory cytokine production; interleukins (IL) IL-1, IL-6, IL-18 and Tumour Necrosis Factor α (TNFα) which regulate the inflammatory response. Some of the downstream effects are mediated and actioned by acute phase reactants such as C-Reactive Protein (CRP), fibrinogen and albumin.

The Chronic Renal Insufficiency Cohort (CRIC) study looked at inflammation and progression of CKD. Elevated plasma levels of fibrinogen and TNFα, plus hypoalbuminaemia were associated with a rapid decline in eGFR and thought to be independent markers of CKD progression (Amdur R.L et al., 2016).

Oxidative stress and inflammation are inexorably linked. Microvascular deregulation and intra-renal production of reactive oxygen species (ROS) cause tubular injury and nephron loss. Pro-inflammatory cytokines activate leukocytes and endothelial cells with local ROS amplification exceeding the antioxidant capacity of the system (Ruiz S et al., 2013) with consequent CKD progression as a result of interstitial fibrosis and tubular atrophy (Mihai S et al., 2018).

1.2.1 Dysbiosis of gut microbiota

The importance of the intestinal microbiome as an organ is increasingly being recognised, and as such the pathophysiology of gut microbiota dysbiosis, cardiovascular risk and CKD progression (Nallu A et al., 2017, Mahmoodpoor F et al., 2017, Chen Y et al., 2017). Elevated urea concentrations in CKD disrupt the normal commensal relationship of gut microbiota with consequent intestinal dysbiosis (Vaziri ND et al., 2013). This shift in gut microbial diversity, results in a reduction in bacteria that produce short-chain fatty acids (SCFA) as nutrition for

colonic enterocytes and an increase in toxins [indoxyl sulfate, p-cresyl sulfate, and trimethylamine-N-oxide (TMAO)] that cause oxidative stress to the kidney (Lau WL et al., 2018), in this way, there is bidirectional interaction and crosstalk amplification of the 'gut-kidney' axis.

Retained uraemic toxins cause intestinal barrier dysfunction (Anders HJ et al., 2013), disrupting the permeability of the intestinal epithelia with the consequence of a "leaky gut". Translocation of these gut-derived toxins to the circulation evokes a systemic inflammatory response. Toxins such as indoxyl sulfate (IS) and p-cresyl sulfate (PCS) circulate bound to albumin (Vanholder R et al., 2014) and therefore are not dialysable. Phenylacetylyglutamine and TMAO, however are not protein bound and can be efficiently removed by dialysis (Xu KY et al., 2017). These toxic gut-metabolites are thought to modulate immunity, blood pressure and lipid metabolism.

Toxins IS and PCS have both been shown to be associated with elevated levels of IL-6 in CKD (Rossi M et al., 2014). Metabolomic studies have shown higher levels of inflammatory biomarkers and uraemic toxins in dialysis compared to non-dialysis patients; IL-6 and monocyte chemoattractant protein-1 (MCP-1) are both positively correlated with IS and PCS (Borges NA et al., 2016). Interestingly the composition of gut microbiota amongst patients with ESRD shows diverse variability, with IS and PCS being associated with contrasting types of gut microbiota (Joosens M et al., 2019).

Fermentation end-products SCFA produced by gut microbes are absorbed into the circulation. Gut dysbiosis has also been demonstrated in patients with systolic

hypertension and CKD (Yang T et al., 2015), where renal juxtaglomerular apparatus secreted renin in response to SCFAs (Wanchai K et al., 2017). Furthermore, SCFAs are thought to have anti-inflammatory properties and are renoprotective against ischaemia-reperfusion injuries (Mafra D et al., 2013).

The ESRD patient is also subject to intestinal oedema and polypharmacy (with the frequent use of antibiotics or oral iron) affecting tight junctions and intestinal permeability (Sabatino A et al., 2014). Dietary restrictions can lead to a prolonged colonic transit time and a further proteolytic shift in microbiota activity (Mihai S et al., 2018).

1.2.2 Oxidative stress and Inflammation

A state of biological oxidative stress exists when ROS outnumber endogenous antioxidant defense systems (Reuter S et al., 2010). In order to stabilise their redox status, ROS or free radicals remove an electron from another molecule.

Inflammation is an adaptive, innate, homeostatic response that occurs as remedy to any physiological change in tissue integrity. States of inflammation and hypoxia stimulate excessive production of ROS, effecting mitochondrial and endoplasmic reticulum function. Inflammatory cytokines also promote ROS imbalance through nitrogen oxide (NOX) enzyme overactivation. ROS are also produced as part of the defensive ‘oxidative-burst’ as activated neutrophils and macrophages resist invading pathogens (Lugrin J et al., 2013).

IL-6 is a multifunctional pro-inflammatory cytokine featuring pleiotropic activity. With a potent ability to immediately induce the acute phase response to environmental stress factors such as infection and tissue injury; regulating inflammation. IL-6 is induced by IL-1, a key-inducer and upstream inflammatory mediator (Dinarello CA, 2011). After local synthesis, IL-6 starts a cascade of signaling events, mainly associated with the JAK/STAT3 pathway (Wang Y et al 2013); releasing C-reactive protein (CRP), serum amyloid A (SAA), fibrinogen and haptoglobin and inhibiting the production of albumin and transferrin. IL-6, along with IL-1 and tumour necrosis factor (TNF)-alpha are considered to be the key cytokines in infection (Dienz O, 2009).

IL-6 is an essential factor in bone homeostasis, its affect causes increased platelet production and reactive thrombocytosis. IL-6 also induces excess production of vascular endothelial growth factor (VEGF) through trans-signaling with TNF, leading to enhanced angiogenesis and increased vascular permeability. IL-6 also plays a pivotal role in iron metabolism by regulating hepcidin expression. The IL-6-hepcidin axis is responsible for anaemia of chronic disease. IL-6 augments transforming growth factor (TGF) β1, a key cytokine involved in the pathogenesis of fibrosis (Zhang XL et al, 2005).

Activation of IL-6 is implicated in renal autoimmune and inflammatory diseases. IL-6 can be produced by podocytes, mesangial, endothelial and tubular epithelial cells. Elevated IL-6 is seen in acute kidney injury (AKI) and chronic kidney disease (CKD). This is due to increased generation from oxidative stress, chronic inflammation and fluid overload and accumulation on account of reduced clearance. A further increase

is seen in end stage renal disease (ESRD) patients, where peritoneal or haemodialysis further stimulate inflammatory responses and increase IL-6 production. IL-6 is therefore both a consequence of CKD as well as a trigger for the progression of and complications related to CKD (Su H, 2017).

The concentration of advanced glycation end products (AGES) rises in association with uraemia of CKD. AGES interact with transcription factors such as the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κβ) pro-inflammatory signaling pathway, thereby stimulating mediators IL-1 and TNFα as shown in Figure 1.3.

IL-6 and high sensitivity CRP (hs-CRP) also increase with progressive CKD. The inflammasome complex releases pro-inflammatory cytokine IL-18, which is thought to be activated by ROS as secondary messengers. IL-18 accelerates vascular calcification alongside the chemokine MCP-1 promotes atherosclerosis and increases the risk of cardiovascular disease.

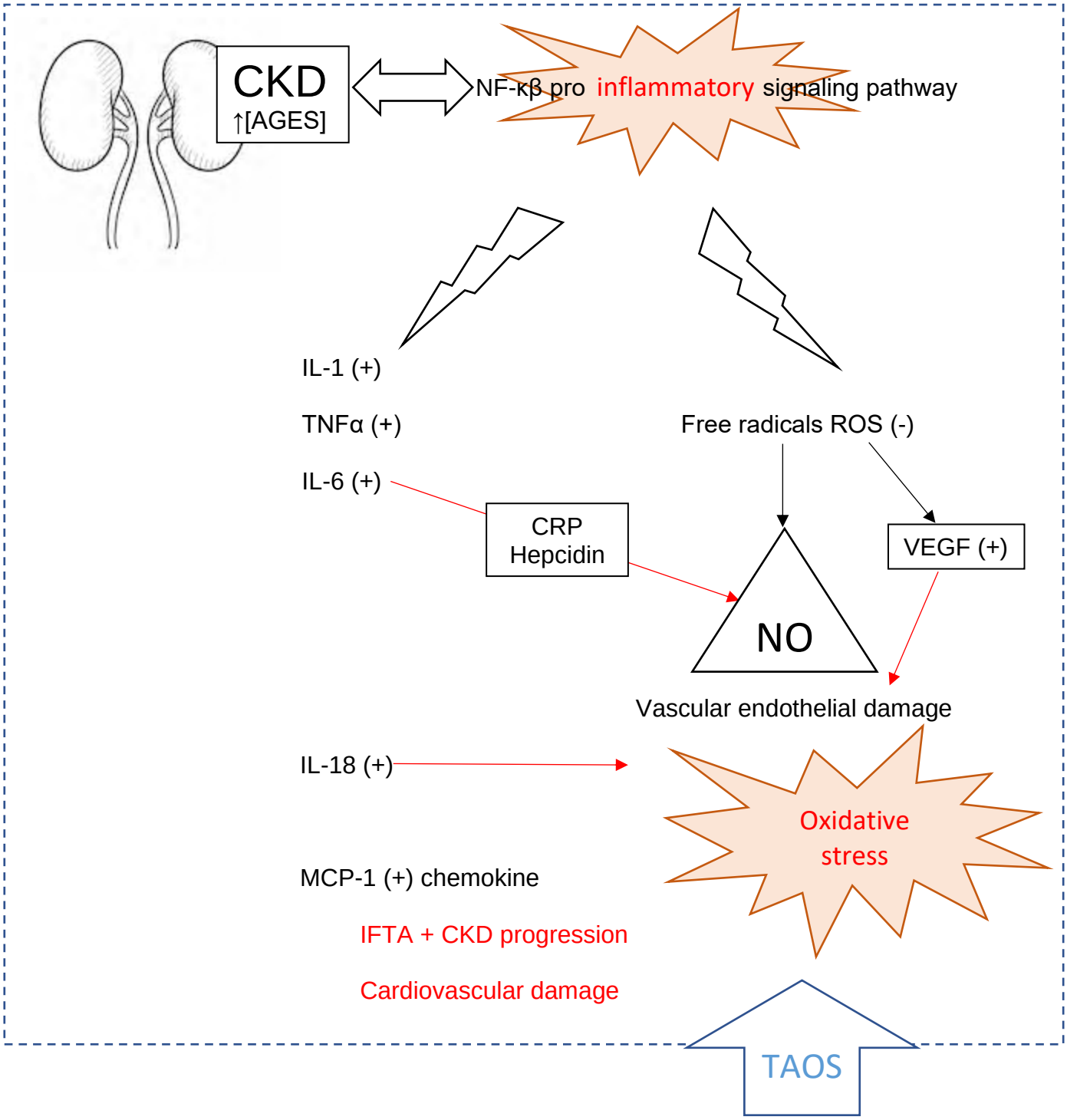


Figure 1.3 Oxidative stress and inflammation in CKD

AGES: Advanced Glycation End products, NF-κβ: Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells, IL-1 Interleukin-1, IL-6 Interleukin-6, IL-18 Interleukin-18, TNFα: Tumour Necrosis Factor Alpha, ROS: Reactive Oxygen Species, CRP: C-Reactive Protein, NO: Nitric Oxide, VEGF: Vascular Endothelial Growth Factor, MCP-1: Monocyte Chemoattractant Protein-1, IFTA: Interstitial Fibrosis and Tubular Atrophy, CKD: Chronic Kidney Disease, TAOS: Total Antioxidant Status.

AGES are formed via the classical Maillard reaction (Singh R et al., 2001) and their presence is closely related to hyperglycaemia. Implicated in atherosclerosis and the accelerated vascular damage of diabetic microvascular disease, AGE interact with the NF-κB pathway and lead to oxidative stress in inflammatory states (Sugiyama S et al., 1996). Hyperglycaemia is not a pre-requisite for accumulation, however and high levels of circulating AGEs are associated with uraemia (Raj DS et al., 2000).

The formation of AGES induces free-radical production and depletes nitric oxide (NO) concentrations, leading to oxidative stress. NO is vasodilatory and has an anti-proliferative effect on smooth muscle cells. AGE accumulation could therefore result in vascular thickening with loss of elasticity, hypertension and endothelial dysfunction. Carbonyl intermediates accumulate due to a reduction in detoxification or renal clearance. They can cause damage themselves as ‘carbonyl stress’ or go on to form AGES. Carbonyl stress has been proposed as a mechanism for accelerated vascular damage causing glomerular insult and ESRD in diabetes (Suzuki D et al., 1999). Molecular weight affects dialysis clearance; therefore, only free (not protein-bound) AGES are removed by peritoneal dialysis and haemodialysis (Miyata T et al., 1997). AGES concentrations fall following renal transplantation; survival improvement may therefore in part be related to a reduction in AGE-induced toxicity (Friedman EA et al., 1999).

Hyperglycaemia-induced oxidative stress and AGES have been suggested to stimulate inflammatory cytokine production. IL-6 is secreted by T-cells and macrophages, its role as a pro-inflammatory cytokine is mediated through its inhibitory effects on pro-inflammatory mediators TNFα and IL-1 with activation of IL-

10. IL-6 mediates the acute phase response and stimulates acute-phase protein synthesis. The degree of IL-6 expression in the kidneys is related to mesangial proliferation and the degree of tubular atrophy; thereby the progression of renal disease (Rivero A et al., 2009).

IL-18 a potent inflammatory cytokine, is secreted by renal tubular epithelia, activated monocytes and macrophages that activate Interferon gamma (IFN-ɣ). It stimulates the production of other cytokines including IL-1, IL-6 and TNFα and may precede their release in the cascade. There is a positive correlation in type 2 diabetes between IL-18 and the level of microalbuminuria. Elevated serum levels of IL-18 may therefore be a useful marker of approaching renal dysfunction in type 2 diabetes (Araki S et al., 2007).

MCP-1 also known as chemokine C-C motif ligand 2 (CCL2) is one of the key chemokines that recruits and activates leucocytes to sites of tissue damage and infection. MCP-1 exhibits a direct pro-atherogenic effect on vascular smooth muscle cells with IL-6 release. As well as being implicated in the pathogenesis of atherosclerosis, MCP-1 can activate tubular epithelial cells, contributing to tubulointerstitial inflammation and ultimately fibrosis associated with loss of renal function (Lloyd CM et al., 1997). MCP-1 also causes glomerular damage and is involved in the primary inflammatory phase of crescentic glomerulonephritis (Viedt C et al., 2002).

Vascular endothelial growth factor (VEGF) and hypoxia-inducible factor (HIF) are the main mediators of oxidative stress-induced angiogenesis. Endogenous ROS

stimulate the induction of VEGF expression in macrophages, smooth muscle and endothelial cells with resultant endothelial dysfunction. VEGF production by foam cells and macrophages may aggravate atherosclerosis (Yang PY et al., 2003).

Hepcidin, a type II acute-phase reactant induced by IL-6, is a key mediator of iron homeostasis. Elevated iron concentrations and inflammation increase hepatocyte hepcidin production, which in turn is suppressed by erythropoietic activity. Extrahepatic sources of hepcidin mRNA include macrophages and to a lesser extent adipocytes. Hepcidin inhibits ferroportin transporter-mediated iron efflux, preventing intestinal absorption by enterocytes, macrophage recycling and release from iron stores. Bone morphogenetic protein-6 (BMP-6) regulates hepcidin transcription (Babitt JL et al., 2006). Hepcidin accumulation occurs in the chronic inflammatory state of CKD due to impaired clearance. It contributes to iron sequestration in macrophages with functional iron deficiency of renal anaemia, oxidative stress and atherosclerosis.

Thiobarbituric acid reactive substances (TBARS) generated during oxidative stress measure malondialdehyde, an end-product of lipid peroxidation that is elevated in association with smoking (Miller ER et al., 1997), atherosclerotic plaque progression (Salonen JT et al., 1997) and cardiovascular disease (Walter MF et al., 2004).

CRP indirectly inhibits production of nitric oxide via endothelial nitric oxide synthase (eNOS) causing endothelial dysfunction. The endothelium produces pro-inflammatory cytokines e.g. IL-6 (which increases CRP production, downregulates eNOS and reduces NO availability) and TNFα which stimulates adhesion molecules

and increases chronic vascular inflammation and cardiovascular risk. Inflammation causes production of ROS, subsequent endothelial dysfunction and impaired vasodilation. TBARs and IL-6 are independently correlated with CRP and strongly predictive of cardiovascular events, independent of traditional risk factors (Nishida H et al., 2011).

TAOS can be calibrated to indicate the degree of oxidative stress or increased susceptibility to oxidative damage. Cytokines and acute phase proteins are key mediators as well as markers of inflammation. Advanced oxidation protein products (AOPP) are biomarkers of damage to proteins by ROS caused by oxidative stress in ESRD (Colombo G et al., 2019).

1.3 Classical markers of cardiovascular dysfunction

1.3.1 B-type natriuretic peptide (BNP)

B-type natriuretic peptide (BNP) is a cardiac hormone, synthesised and released in response to ventricular distension as a result of neurohormonal activation. The main stimulus for BNP release is pressure overload of the heart or cardiac wall stretch, however other stimuli also promote release including hypoxia, ischaemia, angiotensin-II, endothelin I, interleukins and adrenergic agonists.

The precursor proBNP is cleaved in the circulation into the active BNP [32-amino acid, MW 3.5kDa] and biologically inactive N-terminal pro-brain natriuretic peptide (NT-proBNP [76-amino acid, MW 8.5kDa]) which due to its greater stability and longer half-life of 120 minutes lends itself more to analysis (Hall C et al., 2004).

The main physiological function of the bioactive natriuretic peptide is homeostasis and protection from volume overload through renin-angiotensin system inhibition, arterial dilatation, impaired sympathetic nervous system activity, natriuresis and diuresis (Levin ER et al., 1998). Despite the potent natriuretic and diuretic effect of BNP, clinically there is a paradox of sodium retention, pulmonary congestion and peripheral oedema seen in heart failure. This is thought to be due to insufficient maturation of the biosynthetic precursors impeding its homeostatic effect (Goetze JP et al., 2003).

External factors such as age, female gender, renal impairment and systemic bacterial infections can also influence NT-proBNP levels independent of heart failure. NT-proBNP levels are known to be high in patients receiving haemodialysis (Takase H et al., 2014) confounded by comorbid cardiac dysfunction and volume overload with an independent inverse correlation demonstrated between glomerular filtration rate (GFR) and NT-pro BNP (Tagore R et al., 2003, McCullough PA et al., 2008).

Neutral endopeptidases (NEP) degrade circulating BNP (Lainchbury JG et al., 1999). These are expressed in the vascular endothelium, lungs, heart and proximal renal tubules. In disease states where BNP levels are increased, the natriuretic peptide receptor C (NPRC) clearance receptors in the vascular endothelium are saturated and removal is via NEP proteolysis and renal excretion (Maack T et al., 1995, Seymour AA et al., 1995).

The Dallas Heart study found that natriuretic peptide levels were stable whilst estimated glomerular function (eGFR) was within normal range in a healthy

population, yet when eGFR was impaired <90ml/min, levels of BNP and NT-proBNP rose exponentially (Das SR et al., 2008). NT-proBNP levels increase significantly more than BNP in CKD because NT-proBNP is primarily renally excreted.

Studies looking at the fractional excretion of BNP and NT-proBNP in patients with and without renal impairment demonstrated an increase, not only due to reduced clearance but of compromised ventricular function (DeFilippi CR et al., 2007, Goetze JP et al., 2006). Multivariate predictors of NT-proBNP also included β-blocker usage (Davis ME et al., 2006), anaemia (Kanda H et al., 2005, Hogenhuis J et al., 2007) and left ventricular mass (Lukowicz TV et al., 2005). The Cardiovascular Risk Extended Evaluation in Dialysis Patients (CREED) study demonstrated that BNP measurements can reliably be utilised in ESRD to exclude systolic dysfunction and detect LVH, however in this patient population it has a very low negative predictive value (Mallamaci F et al., 2001).

The elevation of serum NT-proBNP is sensitive as a screening, risk stratification and prognostic biomarker in patients with symptoms suggestive of left ventricular systolic dysfunction. Low cut off levels of NT-proBNP (<300 pg/ml in the acute setting, <125 pg/ml outpatient setting) as recommended by the European Society of Cardiology guidelines have a high negative predictive value (Ponikowski P et al., 2016).

BNP and NT-proBNP are strong predictors of cardiac morbidity and mortality in CKD. Moreover, in haemodialysis patients, NT-proBNP was strongly associated with LV systolic dysfunction and cardiovascular death with a greater prognostication than cardiac troponin T (Apple FS et al., 2004). Levels of NT-proBNP fall with

haemodialysis due to clearance (efficiency is further increased with high-flux membranes) and reduced synthesis as a result of the reduction in intravascular volume occurring with ultrafiltration (Madsen LH et al., 2007). However, it is not informative in assessing a patients' dry weight. Investigators have been unable to detect a correlation between volume overload and NT-proBNP with intradialytic changes in preload (Clerico et al., 2001, Madsen LH et al., 2007). Changes in left ventricular mass index (LVMI) over time within the haemodialysis population are closely correlated with variation in the biomarker NT-proBNP (Choi SY et al., 2008). Absolute and longitudinal changes in NT-proBNP concentration in incident dialysis patients are independently associated with an increased risk of 90-day and 1-year mortality (Gutierrez OM et al., 2008).

NT-proBNP levels in the ESRD population are determined by cardiovascular disease; left ventricular hypertrophy (LVH), reduced ejection fraction, residual urine volume and dialysis adequacy (as measured by Kt/V, where K: dialyser clearance of urea, t: dialysis time and V: volume of distribution of urea (Madsen LH et al., 2007).

NT-proBNP levels are decreased by ACE-inhibitors, β-blockers and diuretics. The CARMEN study (Remme WG et al., 2004) looked at the effects of drug therapy on left ventricular (LV) function. It showed that combination therapy with an angiotensin converting enzyme-inhibitor (ACE-I) and a β-blocker had the most pronounced effect. The Cardiac Insufficiency Bisoprolol Study (CIBIS-III) showed initiation of beta-blocker for 6 months followed by dual therapy for 12 months was as effective as 6 months ACE-I therapy, followed by combined therapy. Beta-blockade alone was associated with an increase in NT-proBNP levels and progression of heart failure

(attributed to the rate of β-blocker up titration), however was associated with fewer sudden deaths (Willenheimer R et al., 2005). The most recent European Society of Cardiology guidelines, 2021 recommend the use of angiotensin receptor neprilysin inhibitors (ARNIs) in addition to traditional neurohormonal antagonists (ACE-I, mineralocorticoid receptor antagonists and β-blockers) which are known to improve survival in patients with heart failure with reduced ejection fraction (HFrEF). ARNIs act on the renin-angiotensin-aldosterone system (RAAS) and NEP system. The degradation of natriuretic peptides and bradykinin is slowed as a result of neprilysin inhibition. Diuresis, natriuresis, myocardial relaxation and anti-remodeling effects are enhanced by the augmented generation of cyclic guanosine monophosphate (cGMP) and the physiologic effects of high circulating BNP which inhibit renin and aldosterone secretion (King JB et al., 2015, Mangiafico S et al., 2013).

Vasoconstriction, sodium and water retention and myocardial hypertrophy are reduced by selective angiotensin-1 (AT1) receptor blockade. ARNIs have been shown to be superior to an ACE-I (i.e. enalapril) in reducing the risk of hospitalisation due to heart failure and death (McMurray JJ et al., 2014). The PARADIGM-HF trial was devised to show an advantage with respect to cardiovascular mortality (hazard ratio 0.80 (95% confidence interval, 0.73 - 0.87; $p<0.001$) which was maintained irrespective of background therapy, revascularisation history or β-blocker dose (Okumura N et al., 2016).

1.3.2 Cardiac Troponin T (cTnT)

Cardiac troponin T (cTnT) is a 39kDa protein which forms part of the thin actin filament of cardiac muscle and is a sensitive marker of myocardial necrosis. Serial

measures >20% provide accurate risk stratification for patients presenting clinically with acute coronary syndromes (Ammann P et al., 2004).

Cardiovascular stress and haemodynamic instability are commonplace as evidenced by intradialytic hypotension and cardiac events on dialysis. The Haemodialysis (HEMO) study reported the incidence of sudden cardiac death to be in the region of 22 – 26% of all-cause mortality in ESRD patients (Cheung AK et al., 2004).

Haemodialysis can change the concentration of cardiac enzymes. Studies initially reported an increase in cTnT, seen immediately after conventional in-centre haemodialysis sessions (Mbagaya W et al., 2015, Conway B et al., 2005).
The cause for the reported increase, was thought to be multifaceted and postulated to be a consequence of:-

i) Coexistent subclinical epicardial or microvascular coronary artery disease and heart failure.
ii) Direct myocardial damage from ‘stirring up’ the uraemic milieu and circulating endotoxins (Vaduganathan M et al., 2016).
iii) Intradialytic ‘myocardial stunning’ with regional wall motion abnormalities (RWMAs) due to demand ischaemia from volume shifts and haemodynamic stressors (McIntyre CW et al., 2010).

High ultrafiltration rates are known to be independently associated with abnormal serum troponin levels (Mavrakanas TA et al., 2016). Other studies have reported a reduction in cardiac troponins following haemodialysis, the contrasting results may in part be explained by clearance achieved with low vs high flux membranes (Levi M et al., 2015, Laveborn E et al., 2015).

1.4 Cardiovascular complications of CKD

A complex dynamic interplay exists between CKD and cardiovascular disease, an association first recognised by Lindner et al. in 1974. Uraemic toxins in CKD negatively interact with the inflammatory, fibrogenic and cardiovascular systems. An imbalance exists in favour of pro-inflammatory biomarker production within the cardiovascular-inflammatory axis. Inflammation is known to be associated with coronary artery disease (CAD), diabetes mellitus, the metabolic syndrome and aging.

ESRD confers a 5 – 30 times increased risk of atherosclerotic cardiovascular disease to that of the general population (Longenecker JC et al., 2002). Cerebrovascular, ischaemic heart disease and peripheral vascular disease as co-morbidities are all more prevalent with CKD. Dialysis-related disease complications include hypertension, arrhythmias, coronary artery disease and heart failure.

Traditional Framingham cardiovascular risk factors include hypertension, diabetes, smoking, hypercholesterolaemia, male gender, hyperhomocysteinaemia and age >65 years (Wilson PW et al., 1998). Non-traditional cardiovascular risk factors in CKD patients also include renal anaemia, uraemic toxins including an elevated uric acid concentration (Nakagawa T et al., 2006), proteinuria, abnormal calcium and phosphate metabolism, pro-inflammatory cytokines and oxidative stress.

CKD is a pro-inflammatory state; a cause and consequence of oxidative stress associated with uraemia. Endogenous uraemic toxins and AGE product accumulation are associated with oxidative stress, chronic maladaptive inflammation

and a negative impact upon the cardiovascular system. Adverse manifestations include vascular calcification and atherosclerosis, with resultant arterial stiffness, myocardial fibrosis, cardiomyopathy, arterial thrombosis (Moradi H et al., 2013) and conductive abnormalities (Di Iorio B et al., 2011). A change in cardiac morphology, augmented by mechanical and haemodynamic overload results in LVH and left ventricular dysfunction.

Haemodialysis patients are subject to fluctuating circulatory volumes and fluid overload. Periodic bacteraemia and systemic inflammation may result in sepsis which confers an increased risk of ischaemic stroke and myocardial infarction (Corrales-Medina VF et al., 2010, Fugate JE et al., 2010) substantially increasing the 5-year risk of cardiovascular events (Dalager-Pedersen M et al., 2014).

Uraemic toxins have a causal role in the progression of renal dysfunction, they also affect various cell types:- leukocytes, endothelial cells, vascular smooth muscle cells (VSMC) and platelets with resultant cardiovascular disease. Malnutrition, chronic micro-inflammation and atherosclerosis have all been linked to impaired activation/ leukocyte response. Enhanced leukocyte oxidative activity and TNFα production increase vascular damage whilst homocysteine activates macrophage NF-κβ increasing oxidative stress and superoxide anion levels (Liabeuf S et al., 2010, Vanholder R et al., 2008). Elevated concentrations of the acute phase protein CRP and pro-inflammatory cytokine IL-6 are seen with the chronic inflammation of ESRD. CRP and IL-6 show strong correlation with cardiovascular disease and all-cause mortality (Barreto DV et al., 2010).

Endothelial dysfunction arises due to an increased number of ROS, oxidative stress, chronic inflammation and reduced NO production in CKD. Maintaining endothelial cell integrity and function are important in the prevention of atherosclerosis and cardiovascular disease progression.

In a uraemic milieu vascular smooth muscle cells (VSMC) undergo proliferation and differentiation into osteoblast-like cells (Shroff R et al., 2013, Cianciolo G et al., 2016) which produce a matrix that mineralises causing vessel thickening, arterial stiffening and calcification (Schiffrin EL et al., 2007, Moe SM et al., 2004). In addition, normal age-related vascular changes are accelerated in CKD (Maizel J et al., 2009). Platelet activation after contact with the haemodialysis membrane may also contribute to the cardiovascular disease burden in ESRD. Uraemia apportions a pro-thrombotic tendency to platelets (Bonomini M et al., 2004).

1.4.1 Accelerated vascular calcification and atherosclerosis

In the general population coronary artery calcification (CAC) scores are an independent predictor of future coronary events (Plethcher MJ et al., 2004). Every 100 unit increase in CAC score is suggested to be associated with a 20% increase in relative risk of a coronary event (Huybrechts KF et al., 2005). An increased coronary calcification burden and cardiovascular mortality are seen with abnormal calcium-phosphate homeostasis in ESRD (Chertow GM et al., 2004). Moreover, the dose of calcium-based phosphate binder is associated with the degree of vascular calcification (Goodman WG et al., 2000).

Normalisation of serum phosphate is seen with nocturnal haemodialysis (NHD) (Pierratos A et al., 2004) and patients often require supplementation of sodium phosphate to the dialysate (using a phosphate-based enema) to maintain plasma levels (Su WS et al., 2011). Low coronary calcification progression rates of 9% have been demonstrated seen with NHD (Yuen D et al., 2006). However, it was not possible to directly compare the results with progression rates in haemodialysis patients on a conventional prescription (Moe SM et al., 2004, Chertow GM et al., 2002, Tamashiro M et al., 2001) due to differences in scoring systems and study designs. Absolute change in 1-year CAC scores ranged from -46 to 489 for prevalent haemodialysis patients (dialysis vintage 17 – 77 months), with relative rates of progression reported -3 to 104%. One systematic review found insufficient evidence to compare the influence of renal replacement therapies on coronary artery calcification progression (Jansz TT et al., 2018).

Patients affected by CKD mineral bone disease (CKD-MBD) have high cardiovascular mortality, not accounted for by traditional Framingham cardiovascular risk factors. The interplay and disruption in the balance of multiple calcification stimulants; inorganic phosphate, calcium, TNFα, bone morphogenic protein-2 (BMP-2) and inhibitors can lead to vascular calcification (El-Abbadi M et al., 2007). BMP-2 exerts an osteogenic effect on blood vessels and has been shown to positively correlate with vascular calcification (Towler DA et al., 2006).

In the general population vascular calcification is confined to the intima. In ESRD calcification can affect the tunica media (Moe SM et al., 2002) as well as the valves and the arterioles; manifesting as calciphylaxis. Hyperphosphataemia in dialysis

patients is associated with vascular calcification, the use of oral phosphate binders seeks to attenuate the progression and complications of vascular calcification in ESRD (Raggi P et al., 2002).

Fibroblast growth factor-23 (FGF-23) and its co-receptor Klotho play a role in the systemic regulation of calcium and phosphate homeostasis. FGF-23 secreted by bone osteocytes regulates renal phosphate excretion (Liu S et al., 2006). In the presence of Klotho (expressed in the renal distal tubular epithelial cells, pituitary gland and parathyroid glands) FGF-23 binds with its receptor and exerts bioactivity downregulating phosphate reabsorption in the proximal convoluted tubule, inhibiting vitamin D activation and downregulating parathyroid hormone (PTH) secretion (Goetz R et al., 2007, Torres PU et al., 2007, Inaba M et al., 2006).

With the reduction of eGFR in CKD, phosphate excretion is impaired, and the phosphate pool expands. Phosphate is a direct inducer of vascular calcification; promoting the osteoblastic phenotype of VSMC's (Shanahan CM et al., 2011). Hyperphosphataemia is counteracted by compensatory stimulation of the regulatory hormone FGF-23 and the promotion of tubular phosphaturia. ESRD patients exhibit high levels of FGF-23 (reaching levels 1000-fold above the normal range), low active vitamin D levels, secondary hyperparathyroidism and hypocalcaemia (Isakova T et al., 2011, Wolf M et al., 2012). Impaired Klotho expression observed with worsening CKD may also enhance extensive vascular calcification. The typical derangements in mineral metabolism characterise CKD-MBD. Vascular calcification worsens through progressive CKD stages, with fatal cardiovascular events being the leading cause of mortality in dialysis patients.

1.4.2 Left ventricular dysfunction

Left ventricular mass (LVM) is a well-established measure and independent predictor in the general population, of adverse cardiovascular events and mortality (Levy D et al., 1990). Regression of LVM, independent of blood pressure control, is favourably associated with a reduction in risk of a major cardiovascular event (Devereux RB et al., 2004, London GM et al., 2001). However, in ESRD, LVH is common affecting up to 75% of incident haemodialysis patients (Foley RN et al., 1995). Progression is typical and a prognostic predictor of both cardiovascular events and survival in the haemodialysis population (Silberberg JS et al., 1989).

As previously described, nocturnal haemodialysis induced regression of LV mass. The mechanisms for this are likely multifactorial; improved fluid volume control, decreased nocturnal hypoxaemia (Hanly PJ et al., 2001), reduced catecholamine levels and improved endothelial function (Chan CT et al., 2003).

The MIDNIGHT feasibility study looked at thrice weekly in-centre nocturnal haemodialysis (INHD) in comparison to conventional HD over a 6-month period, prevalent patient's switched modality and dialysed in-centre for 300 – 480 mins vs. 240 mins. Reductions in serum phosphate, ultrafiltration rates, LV mass and LV end diastolic volume were seen with the INHD group. A 12% reduction in LV mass alongside a concordant reduction in myocardial fibrosis suggests INHD promotes favourable cardiac modelling (Graham Brown MPM et al., 2017). Reduction in percentage increase of LVMI to 0.46% after 4 years of NHD compared to the significantly greater increase of 22% reported with conventional in-centre

haemodialysis (See E et al., 2016). Mortality rates and cardiovascular events rise as renal function declines (Go AS et al., 2004).

1.5 History of Haemodialysis

Dialysis was first described in 1854 by a Scottish chemist who recognised that accumulating toxins needed to be removed in renal failure. He went on to develop a process of separating substances across a semi-permeable membrane using a bulb dialyser (Graham T et al., 1854). Abel, Rowntree and Turner coined the term 'artificial kidney' for their dialysis apparatus in 1914 (Alwall N, 1947).

The first haemodialysis was provided for a uraemic patient in 1924 (Benedum J et al., 1979) however it wasn't until 1943 when recovery of renal function was reported with Kolff's rotating drum dialyser in a patient with acute renal failure (Kolff W et al., 1943). Significant improvements to the dialyser were made over the next two decades; a vertical stationary drum kidney, the application of hydrostatic pressure to achieve ultrafiltration and disposable dialysers. In the 1960's Scribner's silastic shunt (an artificial fistula) provided vascular access for the CKD population and heralded the modern era of chronic haemodialysis (Clark PB, 1966). Brescia and Cimino soon after, created the native arteriovenous fistula (AVF) in 1966, a reliable and durable form of access that remains at the heart of the 2003 'Fistula First' initiative (Lok CE et al., 2007).

In-centre capacity issues led to the consideration of home haemodialysis (HHD). In 1961 Yukihiko Nosé introduced HHD in Japan, the first treatment was carried out using an electric domestic washing machine with a frame coil dialyser in an effort to

reduce costs. The abstract was rejected from the 9th American Society for Artificial Internal Organs (ASAIO) conference in 1963 as leading nephrologists at that time including Willem Johan Kolff and Belding Hibbard Scribner did not support the idea of patients dialysing at home (Nose Y, 2000).

Later in 1965, Scribner carried out the first nocturnal haemodialysis in Seattle. A similar programme was established by Stanley Shaldon in the UK; a visionary in the sphere of home haemodialysis (Bernheim J et al., 2014). The effect of increasing the frequency of haemodialysis in reducing morbidity and mortality without the need to increase total dialysis time was seen and advocated. In 1964 Shaldon pioneered self-home and overnight haemodialysis and was instrumental in transforming the lives of RRT patients.

Daily haemodialysis is an old concept, described by De Palma in 1969. At its peak in the 1970's 40 – 59% of UK dialysis patients were treated at home (De Palma JR, 1999, Blag CR et al., 1996, Agar JW et al., 1996). Numbers dwindled for several reasons in the late 1970's, although internationally HHD prevalence's varied. The introduction of continuous ambulatory peritoneal dialysis (CAPD) provided a viable alternative home therapy. The immunosuppressant Ciclosporin made routine renal transplantation a reality in the 1980's and establishing a live kidney donor program in the 1990's further improved graft survival setting the current gold standard for RRT (MacGregor MS et al., 2006).

Due to an increase in ESRD and demand for in-centre dialysis, satellite dialysis units and the number of haemodialysis stations within them multiplied rapidly in the

1990's, with >300% increase in capacity (Roderick P et al., 1998). Accessible treatment was available nearer to home. This reduced travel time and cost for patients and stress on caregivers and families. In-centre haemodialysis utilises high-efficiency dialysis over short time periods to ensure adequacy. The standard thrice weekly sessions therefore result in undulating levels of uraemic solutes and fluid volumes. Extended hour's haemodialysis avoids the peaks and troughs associated with conventional dialysis regimens, facilitating a flexible treatment option that provides both intradialytic and interdialytic stability (Perl J et al., 2009).

Standard dialysis regimens in the 1960's consisted of 6 – 8-hour sessions three times a week (Curtis JR et al., 1969). The National Cooperative Dialysis Study looked at the impact of dialysis prescription on patient mortality. There was no correlation with longer hour's dialysis and hospitalisation rates (Lowrie EG et al., 1981). Patients dialysing <3.5 hours three times a week however, had twice the mortality risk of those dialysing for four or more hours (Held PJ et al., 1991). An insufficient dialysis dose (as calculated by the time-averaged urea concentration) correlated with higher hospitalisation rates. Consequently, chronic dialysis sessions were shortened and delivered thrice weekly with high efficiency, high flux dialysers to achieve an adequate urea clearance with an equivalent Kt/V of 1.2. Current Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines continue to recommend a minimum acceptable standard Kt/V of >1.2 for haemodialysis (National Kidney Foundation KDOQI guidelines, 2000).

The assessment of the 'adequacy' of a dialysis prescription encompasses more than the Kt/V and a clinician will take into account; fluid balance, phosphate clearance

and middle molecule removal. Conventional haemodialysis (prescribed as 3 – 4.5 hours of dialysis three times a week) provides limited scope with which to significantly impact these markers.

The term RRT is really a misnomer. Conventional haemodialysis is a poor substitute for normal kidney function in terms of volume of blood filtered, aside from the other physiological actions such as tubular function, homeostasis, vitamin D hydroxylation, erythropoeitin and bicarbonate production. Renal blood flow is between 1 – 1.5L/minute, as the kidneys receive 20 – 25% of the cardiac output (Stein JH et al., 1978). This equates to a GFR of 120ml/min (or 180L/ day). In Australia and New Zealand conventional HD patients receive 15 hours dialysis at pump speeds of 300 – 350ml/min, (292.5L/ day); - 2.93% of that achieved by native kidney function. In the United States, patients are prescribed 10.5 hours at faster pump speeds of greater than 400ml/min. This equates to 252 litres, or 2.52% of normal kidney function (Agar J, 2016). In the UK, patients receive 12 hours/week dialysis with maximum blood flow rates of 350-400ml/min, an average of 272 litres equating to 2.72% of normal kidney function.

In 1994, simplified nocturnal home haemodialysis was conceived in Toronto, Ontario, Canada. Based on observations from intensive care, Uldall argued that frequent, longer sessions resulted in fewer symptoms. Its conception was based on the premise that home dialysis was more cost-effective than unit dialysis and nocturnal treatment was less disruptive than daytime treatment (Uldall R et al., 1994).

The resurgence of interest in longer hour's haemodialysis is reflective of accumulating data showing improved outcomes and patient survival. The 85%, 5-year survival for nocturnal haemodialysis is higher than that for peritoneal or in-centre haemodialysis and comparable to that of deceased donor kidney transplant recipients (Pauly RP et al., 2009).

1.6 Dialysis induced myocardial injury

Studies have demonstrated that conventional HD (4-hour treatment, three times weekly) induces global and segmental cardiac ischaemia. Two-thirds of patients suffer from recurrent HD-induced ischemic injury. This is associated with an impaired haemodynamic response to dialysis, significant elevations in cTnT and reductions in both segmental and global contractile function with elevated mortality risk (McIntyre CW et al., 2008, Dasselaar JJ et al., 2009). Previous short-term studies of alterations to HD therapy to improve haemodynamic tolerability have been shown to ameliorate this injury (Selby NM et al., 2006, Ayus JC et al., 2005) highlighting the importance of the cardiovascular-inflammatory axis of study in frequent HD patients. Key modifiable factors of HD-induced myocardial injury are ultrafiltration volume (and hence rate) and intradialytic drop in blood pressure.

Frequent dialysis therapies are characterised by reduced ultrafiltration (UF) requirements within each dialysis session, with improved treatment tolerability. In addition, the majority of patients receiving nocturnal dialysis do not require antihypertensive agents because they can achieve their target (dry) weight through slow ultrafiltration over a prolonged dialysis treatment time. This may result in advantageous effects on cardiovascular structure and function, with improved

survival (Johansen KL et., 2009). Unfortunately to date, we do not have accurate tools to help in tailoring fluid removal to avoid myocardial injury. Accurate cardiac imaging tools, such as echocardiogram, although very sensitive, are difficult to implement regularly on dialysis patients. As a result, the amount of fluid removed each session from a dialysis patient is dictated by clinical assessment (blood pressure, peripheral oedema and patient's symptoms), with the unavoidable effect of possible myocardial injury.

The emergence of non-invasive devices has opened the door for measuring haemodynamics in many research and clinical settings. Non-invasive techniques are at least as accurate as traditional invasive thermo-dilution methods, as well as being more practical and safer. Since its introduction in 2001, the ultrasound cardiac output monitor (USCOM) has been used in a wide range of clinical settings, including critical care, anaesthesia, emergency medicine, obstetrics, and neonatology. Its accuracy and reliability have been validated in animal and human studies against alternative methods including pulmonary artery thermodilution (Jain S et al., 2008, Dhanani S et al., 2011, McNamara H et al., 2014). There is widespread support for the use of Doppler-based ultrasound methods to assess haemodynamics for fluid management in resuscitation and peri-operatively (Kuper MS et al., 2011). A retrospective, observational study utilising inferior vena cava (IVC) collapse index using ultrasound suggested that appropriate volume removal was associated with an increase in cardiac output in a subset of volume overloaded critically ill patients (Kaptein MJ et al., 2019). To date there is no published data (to the author’s knowledge) regarding the value of USCOM in renal or dialysis patients. Further studies are required to establish reference standards for suprasternal doppler

assessment and address concerns that cardiac output is underestimated (Chong SW et al., 2012).

1.7 Benefits of nocturnal haemodialysis

Longer hours haemodialysis is associated with a reduction in LVM and reduced myocardial fibrosis (Culleton BF et al., 2007, Chan CT et al., 2002, Graham Brown MPM et al., 2017). This is through diminution of the 'hypervolaemic state' associated with conventional HD that is known to cause LVH and cardiac remodelling. Extended-hours treatment removes the need for rapid ultrafiltration; often associated with intradialytic hypotension and impaired tissue perfusion (Burton JO et al., 2009, Flythe JE et al. 2011, Sands JJ et al., 2014). Slower fluid removal allows for attainment of set target weights over treatments that are twice as long as can be offered with conventional 4-hour HD sessions. This reduction in hypertension results in an associated reduction in polypharmacy (Chan CT et al., 2005).

Hyperphosphataemia, along with hypercalcaemia and hyperparathyroidism contribute to vascular calcification (Palmer SC et al., 2011, Shanahan CM et al., 2011) which is highly prevalent in ESRD. The abnormal deposition of calcium salts in the medial layers of the vessels, valves and the heart occur earlier in ESRD than the general population (Goodman WG et al., 2000) and is an independent risk factor for cardiovascular mortality (Jablonski KL et al., 2013). CKD patients are routinely prescribed cheaper, calcium-based phosphate binders unless serum calcium levels are at the upper limit of normal in which case a non-calcium based binder will be prescribed. A 2018 Cochrane review included 104 studies related to phosphate binder use in CKD. No clinically important benefit was found with respect to

cardiovascular death, stroke, myocardial infarction, coronary artery calcification or fracture (Ruospo M et al., 2018). Sevelamer was found to lower all-cause mortality in dialysis patients compared to calcium-based phosphate binders, which are associated with treatment-related hypercalcaemia. Improved phosphorus clearance with longer hours haemodialysis negates the need for phosphate binders altogether, further reducing the pill burden and improving HRQoL (Mucsi I et al., 1998, Lockridge RS et al., 2004).

Nocturnal haemodialysis extends the effective duration of haemodialysis without impacting on an individual's daytime activities – improving convenience and avoiding 'institutionalisation'. Avoiding the interruption to activities of daily living, including mealtimes translates into improved nutritional status with a sustained increase seen in serum albumin (Sikkes ME et al., 2009).

Nocturnal haemodialysis is physiologically better tolerated by patients than thrice weekly in-centre haemodialysis. A survival benefit was seen for patients undergoing nocturnal haemodialysis 5 or 6 nights/ week (hazard ratio 0.36 [95% CI: 0.22 – 0.61, p=0.0001] Johanssen KL et al., 2009). A reduction in 'all-cause' mortality risk was seen with longer hours dialysis (6.4 deaths/ 100 patient-years for NHD vs. 14.7 deaths/ 100 patient-years with conventional HD). NHD patients were found to have a 33% lower adjusted risk of death (95% CI: 7 – 51%) than patients receiving conventional in-centre dialysis (Rivara MB et al., 2016). Nocturnal haemodialysis has the potential to increase longevity and reduce hospitalisation as compared to conventional unit haemodialysis. Several studies report cost savings with NHD compared to conventional non-quotidian haemodialysis (McFarlane PA et al., 2012,

Agar JW et al., 2005). The HEMO study compared standard vs. high dose dialysis (Kt/V) and low flux vs. high flux membranes. The different dialysis prescriptions had no significant impact on mortality (cardiovascular or otherwise), hospitalisation rates, infection episodes or vascular access complications. However, when ultrafiltration rates exceeded >13ml/hr/kg, cardiovascular mortality rose to over 40% (Eknoyan G et al., 2002). Chronic underdialysis due to shortened dialysis hours causes significant morbidity and mortality. Regular aversion and early cessation of a prescribed HD treatment has a negative impact on fluid status, the uraemic milieu, somatic wasting and neurobehavioural symptoms. Underdialysis however can be clinically unperceived in patients receiving their prescribed treatment. Conventional dialysis treatment of 12 hours/ week fails to equate to a GFR permissive of favourable nutritional status. Changes in the electroencephalogram (EEG) and psychometric measures of cognitive function are reported to precede deteriorations in patient scored self-evaluations in the context of underdialysis (Teschan PE et al., 1983, Teschan PE et al., 2003).

Kt/V as a measure of dialysis adequacy is not absolute and must be considered as a contributory part of holistic assessment including QOL measures, fluid status assessment, polypharmacy pill burden etc. RRT modalities are not directly comparable and options are chosen on an individual patient-centric basis. Figure 1.4 demonstrates the increase in weekly Kt/V of 7.2 achievable with 6 x daily HD (F) as compared to conventional, thrice weekly HD (B) of 3.6. The most recent KDOQI guidelines (2015 update) recommend a minimum delivered target single pool Kt/V of 1.2 for thrice weekly and 2.1 for augmented schedules (KDOQI, 2015).

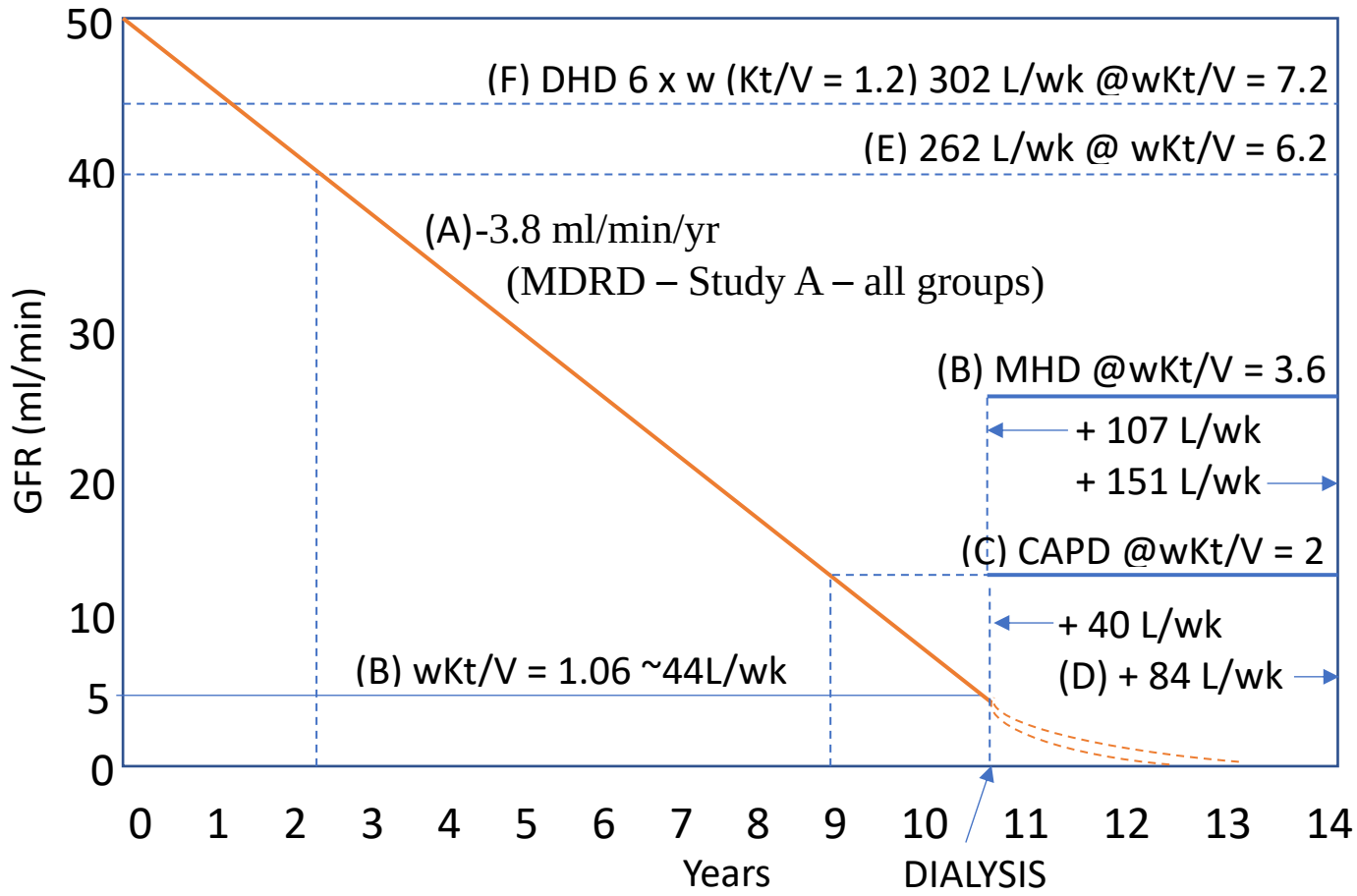


Figure 1.4 Numerical estimates comparing GFR and various dialysis prescriptions [adapted from 'Underperceived dialysis' Teschan PE et al., 2003] MDRD: modification of diet in renal disease, GFR: glomerular filtration rate, DHD: daily haemodialysis, MHD: maintenance haemodialysis (thrice weekly), CAPD: continuous ambulatory peritoneal dialysis

Many centres are providing longer hours through the provision of home haemodialysis. Short daily dialysis and nocturnal haemodialysis improve clearance and optimise toxin removal. The Tassin experience showed the importance of dialysis time; improved survival was associated with dialysis adequacy (mean Kt/V 1.67). The attainment of dry weight targets by ultrafiltration across thrice weekly 8-hour dialysis sessions resulted in 98% of patients being normotensive and cessation of blood pressure medications (Charra B et al., 1992). Resource limitations within the NHS mean times have been reduced in the UK to thrice weekly 4-hour dialysis sessions a week as standard.

Statistically significant and clinically favourable results were seen in the Frequent Haemodialysis Network (FHN) daily trial for coprimary outcomes (death and increase in LV mass) in the frequent haemodialysis group who dialysed six times/ week (standard Kt/V 3.54±0.56) as compared to the standard care group on thrice weekly haemodialysis (standard Kt/V 2.49±0.27). Other benefits included more physiologic solute removal and reduced interdialytic weight gain, however more vascular access interventions were observed (Chertow et al., 2010).

A higher standard Kt/V of ≥4.0 was achieved in 86% of nocturnal patients in the Frequent Haemodialysis Nocturnal Network (FHNN) trial who dialysed for 30.8±9.1 hours/ week (379±62mins/ session). There was a lower adherence to the dialysis prescription and more buttonhole use in the extended hours group as opposed to the conventional patients who dialysed for 12.6±3.9 hours/ week (256±65 mins/ session) where 100% obtained a standard Kt/V ≥2.0. No significant difference in death or LV mass (as determined by cardiac MRI) was demonstrated due to the limited sample

size and patient characteristics. Nocturnal patients were seen to require lower monthly IV iron doses, exhibited better control of hyperphosphatemia and hypertension with an associated reduction in hypotensive episodes. As with the FHN daily study, the extended hours arm also experienced increased vascular access events (Rocco MV et al., 2011). The higher mortality seen with the longer hour's group was explained by the large proportion of incident patients within the group (Rocco MV et al., 2015).

A dose-response relationship has repeatedly been demonstrated with longer hours dialysis and survival (Tentori F et al., 2012). The survival rate of patients receiving extended hours haemodialysis, in the day or nocturnally, was significantly higher than standard HD; confounders included age, sex, diabetes diagnosis and vascular catheter use (Jin HM et al., 2013). Intensified haemodialysis also significantly improved blood pressure control with reduced anti-hypertensive prescribing and lowered phosphate binder requirements alongside improved uraemia-related indicators and psychosocial variables (Thumfart J et al., 2014).

A recent Cochrane meta-analysis found no significant difference in mortality between NHD and standard haemodialysis [odds ratio-OR 0.75 (0.52 – 1.10) p=0.145], with fewer hospitalisations in the standard group [OR 1.54 (1.32 – 1.79) p<0.001]. Nocturnal haemodialysis was superior with regards to cardiovascular and uraemia-related outcomes; LVH [standardised mean difference-SMD -0.39 (-0.68 to -0.10) p=0.009], LVH index [SMD: -0.64 (-0.83 to -0.46) p<0.001]. Improved urea reduction rates (URR), haemoglobin, however no difference in Erythropoietin (Epo) dosage and serum albumin levels [SMD: 0.89 (0.41 to 1.36) p<0.001] were seen in the NHD

group. Significant improvements were seen in patients' quality of life as assessed by the short form-36 (SF-36), blood pressure control [SMD: -0.33 (-0.49 to -0.18) p<0.001] as well as a reduction in anti-hypertensive pill burden (Liu F et al., 2017).

A modality switch from conventional HD to NHD was associated with a sustained significant increase in serum albumin (0.70 g/L/year) [95% CI 0.10 – 1.30, p=0.02] and decrease in erythropoietin stimulating agent (ESA) resistance which translated into a 33% Epo dose reduction over the 4 year study period, as well as a non-significant reduction in pill burden for anti-hypertensives and phosphate binders (Jansz TT et al., 2018).

1.7.1 Reduction in hypertension

Enhanced blood pressure control is one of the most consistently reported benefits of extended hours haemodialysis, in both observational studies and randomised controlled trials (Nesrellah G et al., 2003, Kraus M et al., 2007, McGregor DO et al., 2001). Chazot et al., first reported the positive association between extended duration of home haemodialysis and blood pressure control (Chazot C et al., 1995). These findings were subsequently echoed by the FHN study which demonstrated a significant reduction in systolic blood pressure and requirement for antihypertensive therapy (Rocco MV et al., 2011). The means by which normotension is attained with NHD is multifactorial and includes; stabilisation of fluid balance, lowering total peripheral resistance and reducing circulating plasma catecholamines such as noradrenaline with restoration of flow-mediated vasodilation (Chan CT et al., 2003).

Hypertension is evident in 80% of CKD patients at end-stage (Graham Brown MPM et al., 2017). Reflex neurogenic vasoconstriction activates the RAAS system; increased renin release and sodium retention result in an expanded circulating volume (Converse RL et al., 1992). This increase is compounded by a paralleled impairment of sodium excretion. In ESRD the primary haemodynamic abnormality responsible for renal hypertension is an inappropriate increase in peripheral resistance (Onesti G et al., 1975). This is due to an upsurge in central sympathetic outflow stimulated by the activation of afferent renal nerves by mechano/ chemoreceptors (Joles JA et al., 2004). Sympathetic over activation also contributes to progressive loss of renal function (Schlaich MP et al., 2009). Originally thought to be due to the uraemic state, sympathetic hyperactivity has been found to persist post-transplantation even when renal function is restored. It is corrected by native nephrectomy, thereby indicating the diseased kidneys as causative (Hausberg M et al., 2002, Humphreys MH et al., 2012).

Longer hour's dialysis improves uraemic control and facilitates increased clearance of vasoconstrictors (Katzarski KS et al., 1999). Chan et al., reported lower blood pressures and regression of LVH with long-term NHD. The improvement in blood pressure was attributed to a reduction in the inappropriately elevated afterload, with no absolute change seen in extracellular fluid volume (as measured by bioimpedance) or cardiac filling pressures (Chan CT et al., 2002). It is thus postulated that a reduction in central regulation of sympathetic outflow is responsible for the regression in LVH, increase in ejection fraction and peripheral vasodilatation seen in patients receiving NHD.

NO has an unpaired electron, as such is a free radical. Produced by the vascular endothelium it has many regulatory roles. An imbalance between ROS and antioxidants lead to oxidative stress which impacts vascular endothelial function; compromising NO bioavailability (Pierini D et al., 2015, Ghosh M et al., 2004). NO production increases in pro-inflammatory states such as CKD, contributing to oxidative stress, vascular dysfunction, atherosclerosis and hypertension (Lubos E et al., 2008).

In addition to its role as a mediator of the endothelial control of VSMC, NO is also involved in intracellular signalling as a neurotransmitter, with sympathoinhibitory regulation of autonomic outflow (Patel KP et al., 2001). In rat studies, the microinjection of sodium nitroprusside, a NO donor, found a reduction in blood pressure due to sympathetic outflow, with concurrent reduction in efferent renal sympathetic outflow (Horn T et al., 1994). It is thought in addition to its neuromodulatory actions, NO may also play a role in fluid balance homeostasis (Calapai G et al., 1992).

An expansion in the circulating blood volume stimulates NO production within the paraventricular nucleus (PVN) of the hypothalamus, NO is inhibitory to the release of oxytocin and vasopressin; suppressing renal sympathetic nerve discharge with resultant diuresis and natriuresis (Gutkowska J et al., 2008, Li YF et al., 2003). An osmotic challenge such as chronic salt loading or water deprivation augments the release of oxytocin and vasopressin. Released in hypertonic states, vasopressin (also known as anti-diuretic hormone, ADH) is produced in the PVN. Mediated by vasopressin-2 receptors (V2R), the insertion of aquaporins into the apical membrane

increases the water permeability of the collecting ducts, concentrating the urine. Increased sodium reabsorption in the ascending limb augments the countercurrent multiplication system of the loop of Henle; maximising water reabsorption (Knepper MA et al., 1999).

Renin secretion, tubular sodium reabsorption and renal haemodynamics are in part regulated by efferent sympathetic renal nerves. Their surgical denervation thereby results in a reduction in renin secretion, natriuresis and improved volume homeostasis. The development of catheter-based radiofrequency and ultrasound ablation has facilitated a resurgence of interest in renal denervation as a treatment for hypertension. A procedure that was historically performed in the era preceding anti-hypertensive agents (Smithwick RH et al., 1962). Preliminary data suggests the procedure may be effective in patients without resistant hypertension, although its effectiveness has not yet been established in those patients with resistant hypertension (Kandzari DE et al., 2018, Bhatt DL et al., 2014).

1.7.2 Reduction in LVM and myocardial fibrosis

Measures to reduce LVH in ESRD have traditionally focussed on control of hypertension, managing chronic anaemia and avoiding volume overload. The first randomised controlled trial comparing nocturnal HD with conventional dialysis (often referred to as the Alberta trial; Culleton BF et al., 2007), FHN (Chertow et al., 2010) and FHNN trials (Rocco MV et al., 2011) were all designed to investigate the beneficial effect of extended hours haemodialysis on LVM. The FHNN trial did not echo the findings of the FHN trial which reported improved co-primary outcomes (in hazard ratio for death and 19g reduction in LVM) with daily dialysis. Both the Alberta

and FHNN trials found a reduction in LVM ~10.9g (CI -23.7 + 1.8) although the results were not statistically significant. Baseline characteristics between the two studies were very different. Patients were younger, with a smaller LVM (137.1 +/- 45.7g vs 181.5 +/- 92.3g) seen in the FHNN trial compared to the Alberta study. The FHNN trial was underpowered and the dialysis time was not vastly different between the two comparative dialysis arms.

Intensified dialysis may reduce the levels of circulating factors that stimulate cardiac remodelling and hypertrophy. Several studies have found elevated circulating factors to be associated with LVH and cardiovascular events; insulin growth factor-1 (IGF-1) in essential hypertension, asymmetric dimethylarginine (ADMA) and Fibroblast growth factor-23 (FGF-23) in CKD (Ito H et al., 1993, Shi B et al., 2010, Gutierrez OM et al., 2010).

FGF-23 is a 32-kilodalton protein expressed and secreted by bone matrix osteocytes and osteoblasts. Circulating levels of the phosphaturic hormone gradually rise with progressive decline in GFR and are associated with CKD-MBD; hyperphosphataemia, hypercalcaemia, secondary hyperparathyroidism, vitamin D and klotho deficiency. In the presence of its co-receptor α-klotho, FGF23 activates the endothelial NO synthase pathway inducing the release of nitric oxide and increasing the production of ROS (Haffner D et al., 2018). In CKD, α-klotho deficiency impairs endothelial mediated vasodilation, blunting NO synthesis and reducing bioavailability. ROS production overwhelms degradation, enhancing endothelial dysfunction and cardiovascular disease (Silswall N et al., 2014). Binding to the FGF receptor 4 (FGFR4) isoform in cardiac myocytes, FGF-23 acutely

increases intracellular calcium levels and cardiac contractility. However, sustained FGFR4 activation induces pro-fibrotic and pro-hypertrophic growth factors resulting in pathologic cardiac remodelling and myocardial fibrosis. FGF-23 therefore mediates progression of LVH in CKD (Gutierrez OM et al., 2008, Faul C et al., 2011, Grabner A et al., 2015). Soluble klotho and cardiac expression of FGF-23/ FGFR4 are dysregulated in dialysis patients and normalised in kidney transplant recipients (Leifheit-Nestler M et al., 2017). FGF-23 levels are higher in haemodialysis than peritoneal dialysis patients, independent of calcium or phosphate levels (Bi S et al., 2017). Dialysis clearance of FGF-23 was estimated to be 7.7ml/min in chronic dialysis patients receiving 8 hours, thrice weekly high-flux dialysis. Plasma concentrations were directly correlated to the ultrafiltration rate (Carlson N et al., 2017).

Inflammation is associated with elevated circulating FGF-23 levels as demonstrated by accumulative dialysis vintage (Isakova T et al., 2011) and an associated increase in hs-CRP (Rossaint J et al., 2017). Hepatocyte FGFR4 activation in CKD animal models, independent of α-klotho promotes the production of pro-inflammatory cytokines (Singh S et al., 2016). TNF-α and IL-6 promote cardiac hypertrophy, whilst transforming growth factor beta (TGF-β) and angiotensin II (AT-2) are pro-fibrotic molecules (Frieler RA et al., 2015). FGF-23 is expressed by macrophages and upregulated by Lipopolysaccharide-induced NF-κβ activation and IFN-γ stimulation of the Janus kinase/signal transducer and activator of transcription-1 (JAK/STAT-1) pathway (Han X et al., 2015). Infiltration of macrophages may therefore augment inflammation and fibrosis with subsequent cardiovascular and renal disease progression.

FGFR4$^{-/-}$ knockout mice were protected from phosphate diet-induced LVH whilst selective FGFR4 blockade was found to attenuate established LVH in CKD mouse models (Grabner A et al., 2017). The FGF-23/ FGFR4 pathway may provide a pharmacological target to reduce LVH in CKD. Pan FGFR blockade has been shown to cause hyperphosphataemia with subsequent tissue calcification and increased mortality (Yanochko GM et al., 2013, Shalhoub V et al., 2012). Whereas selective targeting of the FGFR4 isoform in the FGF-23 pathway affords cardioprotection, whilst concurrently maintaining the physiological actions of FGF-23.

FGF-23 causes RAAS activation through the inhibition of ACE-2 which degrades AT-1 and AT-2 into vasodilatory reagents (Dai B et al., 2012). RAAS activation also consecutively induce the synthesis of FGF-23 in cardiac myocytes (Fajol A et al., 2016). AT-2 and aldosterone promote vascular and myocardial fibrosis along with LVH, independent of hypertension (Frieler RA et al., 2015). RAAS is therefore an important regulator of cardiovascular remodelling, its feed-forward effect promotes pro-inflammatory, pro-fibrotic and pro-hypertrophic changes.

FGF-23 therefore mediates paracrine crosstalk and induces various pathologies in different cardiac cell types. It has a pro-hypertrophic effect on cardiac myocytes contributing to LVH, induces pro-fibrotic changes in fibroblasts and augments the production of pro-inflammatory cytokines by macrophages, in states of α-klotho deficiency it promotes endothelial dysfunction with resultant NO/ ROS dysregulation. FGF-23 also stimulates gene expressions within the TGF-β signalling pathway (Smith ER et al., 2017). Growth differentiation factor 11 (GDF11), a member of the TGF-β family was found to decrease with age in mice, administration of a daily

injection was found to reverse age-related, but not pressure-related cardiac hypertrophy (Loffredo FS et al., 2013). Circulating GDF11 is a negative regulator of cardiac hypertrophy and diastolic dysfunction.

High sensitivity cTnT and NT-proBNP as plasma biomarkers relate to LV dysfunction and ongoing myocardial damage (Gheorghiade M et al., 2005). Serum cTnT is elevated in 20 – 90% of CKD patients in the absence of an acute coronary syndrome and confers an increased risk of cardiovascular events and mortality (Lamb EJ et al., 2004, Goicoechea M et al., 2004). This may be due to myocardial remodeling in LVH, subclinical myocardial damage caused by silent ischaemia and myocardial stunning (Iliou MC et al., 2001, Mallamaci F et al., 2002). A statistically significant positive correlation has been demonstrated between Troponin T and LVH. An elevated serum troponin was associated with a lower 1-year survival rate in haemodialysis patients (Petrovic D et al., 2008). NT-proBNP is elevated in cardiac failure. Despite a significant hazard ratio, a lack of correlation with ultrafiltration volume precluded its use in a regulatory role for acute fluid removal (Codognotto M et al., 2010). NT-proBNP and hs-CRP have prognostic value in ESRD for all-cause mortality (Apple FS et al., 2004).

Given their stable nature within the circulation, microRNA's have been proposed as serum biomarkers (Mitchell MS et al., 2008). MicroRNA miR-133a plasma concentrations were found to correlate with high sensitivity cardiac Troponin in patients presenting with myocardial infarction and were negatively correlated with LVMI, an established indicator of LVH (Gidlof O et al., 2011, Wen P et al., 2014). The MINOS study found that miRNAs were decreased after haemodialysis, whereas

as previously reported, troponin levels remained stable (Emilian C et al., 2012). Higher levels are also reported in haemodialysis patients with vascular calcification (Lee CT et al., 2019). The study of miRNAs continues to be an area of rapidly developing biomedical research with relation to kidney disease.

1.7.3 Improved phosphorus clearance

Clinical sequelae of hyperphosphataemia in ESRD include secondary hyperparathyroidism, myocardial hypertrophy and vascular calcification, with an associated increased cardiovascular mortality risk (Neves F et al., 2004). Suboptimal phosphate removal with thrice weekly conventional haemodialysis mandates the concurrent use of phosphate binders (Block GA et al., 1998), whilst studies have consistently shown improved phosphate control with extended hours haemodialysis (Mucsi I et al., 1998, Rocco MV et al., 2011, Thumfart J et al., 2014, Jansz TT et al., 2018).

Nocturnal haemodialysis significantly improves small solute clearance, however the conventional ‘Kt/V’ urea kinetic modelling method of measuring urea clearance assumes a constant generation rate and is not validated in NHD. 75% of urea clearance occurs in the first two hours of haemodialysis, the rate then decreases over the remaining treatment (Ranganathan D et al., 2012). Urea and phosphate do not however assume the same kinetic profiles for elimination (DelSoi CA et al., 1993, Man NK et al., 2001, Gutzwiller JP et al., 2002).

Urea generation also adheres to a circadian rhythm with a fall in rate at night-time thought to be due to a cessation in food intake (Daugirdas JT et al., 2010). A

reduction in generation of up to 60% is seen in healthy individuals as a result of fasting (Garlick PJ et al., 1980). Nocturnal haemodialysis has repeatedly been shown to significantly improve small solute clearance (Suri R et al., 2003, Bugeja A et al., 2009, Lacson E et al., 2010), however an accurate calculation for measuring clearance in extended hours dialysis is yet to be determined. Clearance of middle molecules such as AGE and β2-microglobulin also increases with extended hours dialysis (Friedman AN et al., 2002).

A standard Western diet contains 1.2g/kg of protein a day. Conventional unit haemodialysis (4 hours, thrice weekly) removes 2.3 – 2.6g/week. Nocturnal haemodialysis (~8 hours, 5 – 7 nights) removes double the amount of phosphate 4.5 – 4.9g/ week allowing patients to eat a more liberal diet and removing the need for phosphate binders (Cupisti A et al., 2013). Many nocturnal patients require the addition of phosphate to the dialysate concentrate to avoid complications associated with hypophosphataemia (Su WS et al., 2011).

1.7.4 Improved nutritional status

Extended hours dialysis efficiently reduces uraemia and eliminates the need for arduous fluid and dietary restrictions. Patients report improved appetite, lean weight gain and improved physical condition (Sikkes ME et al., 2009, Ipema KJ et al., 2012). Dialysing overnight also removes the disruption to meals seen frequently with daytime dialysis, restoring normal eating patterns. In contrast, conventional thrice weekly, 4-hour haemodialysis results in malnutrition, the cause of which is multi-factorial and associated with increased morbidity and mortality (Qureshi AR et al., 2012).

A maladaptive metabolic, pro-inflammatory state exists in ESRD. Hypercatabolism due to intradialytic cytokine activation and loss of amino acids (Veeneman JM et al., 2003) leads to protein energy wasting (PEW) (Stenvinkel P et al., 1995, Raj DS et al., 2008). Prevalent patients experience deconditioning; loss of muscle mass and adipose tissue with subsequent diminished physical functioning (Johansen KL et al. 2003). Reduced food-intake due to a fluid, salt, potassium and phosphate restricted diet is further compounded by the suppressant effect that phosphate binders may or may not have on appetite (Pierratos A et al., 1998, Beberashvili I et al., 2018).

Chronic inflammation, metabolic acidosis, fatigue and nausea associated with ESRD further contribute to the malnutrition seen within the conventional dialysis cohort. Associated comorbidities and reduced physical activity further compound an overall poor nutritional state. Haemodialysis patients have a higher resting energy expenditure (REE) adjusted for muscle mass compared to healthy controls (Neyra R et al., 2003, Skouroliakou M et al., 2009,). REE prediction equations assist in the nutritional assessment of dialysis patients at risk of PEW and malnutrition.

The maladaptive inflammatory state seen in ESRD is a major contributor to the uraemic phenotype and is multi-factorial in aetiology (Cobo G et al., 2018): -

i) Therapeutic interventions including the actual dialysis treatment, exogenous factors such as the dialysis membrane and central venous catheters for vascular access.
ii) Cellular factors of oxidative stress and cellular senescence.
iii) Tissue factors including hypoxia, sodium and fluid overload.

iv) Microbial factors include immune dysfunction and alterations to the ‘gut-kidney axis’ with ensuing dysbiosis (Wang F et al., 2012, Evenepoel P et al. 2016).

v) Noxious effects from uraemic toxins; indoxyl sulphate, AGE and calcioprotein particles (CPP) which negatively interact with the inflammatory, fibrogenic and cardiovascular systems (Vanholder R et al., 2003).

Uraemic toxins are characterised as either: - small water-soluble compounds which are easily removed by dialysis, protein-bound compounds which are difficult to remove by dialysis and middle molecules which include cytokines such as IL-6, IL-18 and other pro-inflammatory mediators (Vanholder R et al., 2018). An imbalance exists in CKD with an excess of pro- to anti-inflammatory biomarkers; IL-6 in particular is associated with a poor prognostic state (Stenvinkel P et al., 2005, Sun J et al., 2016).

Unlike the small water-soluble and protein-bound solutes which are intestinal metabolites of dietary intake. Middle molecules are small proteins and peptides < 58kDa that are generated endogenously and filtered by a normally functioning kidney. β2-microglobulin is typically measured as a marker of middle molecule clearance in dialysis (Kanda E et al., 2021). Inadequate dialysis clearance results in an increasing allostatic load with its resultant comorbidities. Future therapies are targeted at reducing the production of inflammatory molecules and increasing dialytic clearance, for example with high cut off membranes where albumin losses can be substantial. Newer high-retention onset membranes have a tight pore size

distribution and target middle-to-high weight molecule clearance with minimal albumin leak. These expanded haemodialysis membranes have been developed for use in sepsis, rhabdomyolysis and haematological disorders (Ronco C et al., 2017). Expanded haemodialysis also offers a practical advantage, the high fluid volumes required to perform haemodiafiltration (HDF) are not needed. Preliminary studies indicate superior middle-molecule clearance and modulation of inflammation with IL-6 and TNF downregulation in expanded haemodialysis compared to high-flux haemodialysis and high-volume HDF (Kirsch AH et al., 2017).

1.7.5 Improved health-related QOL

Many studies have demonstrated improved QOL measures in NHD (McFarlane PA et al., 2003, Koh TJK, 2019, Dam N et al., 2019). Studies looking at the conversion of patients from conventional to nocturnal haemodialysis have found improvements in health-related quality of life indicators: physical functioning, vitality, health perceptions, pain index, emotional and social functioning (McPhatter LL et al., 1999, Pierratos A, 2001, Walsh M et al., 2005).

Benefits of NHD include improved fertility, better quality of sleep and lower hospitalisation rates (Barua M et al., 2008, Beecroft JM et al., 2008, Pauly RP et al., 2010). Most importantly NHD confers improved survival; USRDS report the mortality associated with NHD to be a third of that with conventional haemodialysis (Johansen KL et al., 2009). Survival of NHD patients is comparable to that of deceased donor transplantation (hazard ratio-HR 0.87, 95% CI 0.50 – 1.51, p=0.61) although inferior to that of the gold-standard RRT modality; live kidney donation (HR 0.51, 95% CI 0.28 – 0.91, p=0.02) (Pauly RP et al., 2009).

1.7.6 Patient and physician-related barriers to home haemodialysis

A health care model with co-production at its core, nocturnal haemodialysis is the epitome of prudent healthcare. NHD promotes independence, improves patient accessibility to treatment and offers superior clinical and patient-centred outcomes. Developing medical technology and individualised dialysis prescriptions, allow for a personalised renal replacement modality. Multidisciplinary support allows patients with ESRD to manage their own health and wellbeing; dialysing within the comfort of their own homes. In this way patients receive higher-value, high-quality care at a reduced cost (Walker R et al., 2014).

The option of home haemodialysis is a viable alternative to conventional in-centre treatment. Expanding the home haemodialysis population is a cost-effective means of reducing the burden on hospital and satellite units as dialysis providers. The enduring challenge of ‘finding slots’ for incident dialysis patients intensifies due to increasing demand and an aging population.

Patients’ perceptions regarding the difficulties of a nocturnal home-based therapy (Pipkin M et al., 2010) may seem insurmountable. Lack of motivation or confidence may impede success of the training programme, the notion of self-cannulation and undertaking of a home therapy may be overwhelming. For some, the removal of social interaction of thrice weekly in-centre dialysis can result in circumstantial isolation due to lack of family support. Outside the support network of in-centre HD the fear of adverse consequences may inhibit transition to a home therapy if there is not round-the-clock access to dialysis nursing support. A requirement therefore exists for a comprehensive in-house pre-dialysis education program to signpost

patients to the benefits and flexibility of home therapies. The home dialysis programme should include a comprehensive education and training platform to prepare patients to perform haemodialysis at home. The use of vascular access catheters is not encouraged for NHD (Rocco MV et al., 2011). Patients undertaking enhanced dialysis schedules should be made aware of the increased incidence of vascular access complications related to frequent needling.

Dialysis providers' may be hesitant initially in funding an extended hours quotidian treatment with escalated start-up costs. Ongoing logistic difficulties are encountered with regularly scheduled deliveries. Patients homes must be assessed and have adequate room for storage, a water treatment system is installed for HHD. Increasing costs of electricity and water bills can result in financial reimbursement issues (Bonenkamp AA et al., 2018).

1.8 Residual renal function

The preservation of residual renal function (RRF) is associated with improved outcomes (Steinwandel U et al., 2022). It is not known whether frequent daily or extended hours dialysis confers a protective or injurious effect on the trajectory of RRF compared to conventional in-centre haemodialysis. Reduction in residual kidney function is seen during the first 18 months of haemodialysis. The decline is multifactorial and relates to patient and treatment-related factors in addition to the primary aetiology of the ESRD (Janssen MA et al., 2012).

Chronically diseased kidneys have a reduced capacity to auto-regulate, as such are more sensitive to transient hypotension commonly seen with thrice weekly in-centre

haemodialysis. Lower ultrafiltration rates and less aggressive fluid shifts with longer hours dialysis reduce the insult of intradialytic hypotension (Chertow et al., 2010, Janssen MA et al., 2012) and facilitate the maintenance of normotension.

An expanded extracellular volume (ECV) as commonly seen with tendency towards fluid overload with peritoneal dialysis is protective of RRF (Davenport A et al., 2011). This is lost in NHD as a result of target weight attainment through ultrafiltration. Antihypertensive medications which often include ACE-I are therefore stopped. The removal of their reno-protective anti-proteinuric effect is also thought to contribute to the loss of RRF protection (Suzuki H et al., 2004).

Frequent NHD alters the concentration of osmotically active solutes, volume status and therefore blood pressure, all drivers of residual kidney function. As compared to the trajectory of decline with conventional haemodialysis, NHD was found to accelerate loss of RRF and was apparent after 4 months (Daugirdas JT et al., 2013).

Longer hours dialysis involves extended ‘blood-to-dialysis circuit’ contact with resultant platelet activation (Daugirdas JT et al., 2012), an increased inflammatory response and oxidative stress worsening CKD. Platelet counts are reduced in CKD and haemodialysis patients (Gafter U et al., 1987), however near normal counts are seen in peritoneal dialysis (Linthorst GE et al., 2002). In addition, haemodialysis patients are prescribed antiplatelet agents such as aspirin and dipyridamole for fistula patency. Exposure to the extracorporeal circuit and heparin promote platelet agglutination, activation and degranulation. In nocturnal dialysis blood-to-circuit contact activation is occurring for up to 48 hours a week.

A small prospective observational study found no significant difference in rate of GFR change, urea and creatinine clearance or β2microglobulin clearance with NHD. However, there was a non-significant trend towards a reduction in urine volume seen in conventional haemodialysis patients (p=0.06) (Skeat L et al., 2018).

1.9 Overall objective of research

The purpose of this prospective, non-randomised, longitudinal pilot study was to compare the cardiovascular response of two different forms of dialysis; conventional in- centre (4-hour treatment, 3 times weekly) or conventional haemodialysis versus extended hours ‘nocturnal haemodialysis’. Frequent, or short daily dialysis was not assessed.

The study incorporated three arms; with participants matched for age, gender and socioeconomic status (by postcode):

1) Participants receiving conventional haemodialysis (n=10).
2) Participants receiving ‘nocturnal’ haemodialysis (n=10).
3) Healthy non-CKD controls (n=10).

Frequent, extended hours haemodialysis is believed to ameliorate much of the haemodynamic instability of conventional thrice weekly HD. The objective of this study was to examine and compare the effect of two forms of haemodialysis on the cardiovascular system through longitudinal evaluation of: -

I) Cardiovascular biomarkers and cardiac imaging.
II) Oxidative stress and inflammation.

It is hypothesised that nocturnal haemodialysis exerts a favourable effect on cardiac function by i) reducing the generation of inflammatory and oxidative stress markers and ii) avoiding myocardial injury induced by intradialytic hypotension. Cardiac function was assessed dynamically using a practical intradialytic tool previously unreported in the dialysis population with ultrasound cardiac output monitoring

(USCOM) in addition to comparative speckle-tracking echocardiography (STE) and computerised tomography coronary artery calcification (CT-CAC) assessment scores to evaluate the cardiovascular effect of both therapies for incident haemodialysis participants, using their own imaging as a control, over a period of time.

1.9.1 Primary objective and endpoints

The primary objective was to compare the effect of NHD versus conventional HD on myocardial strain. Endpoints included mean change in left ventricular global longitudinal strain (LV GLS), using STE and mean changes in cardiac biomarkers NT-proBNP and cTnT.

1.9.2 Power calculations

Based on available literature (Yingchoncharoen T et al., 2013) the normal range for the primary outcome; - LV GLS is -15.9% to -22.1% (mean = -19.7, standard deviation-SD = 0.614). Due to the lack of published data concerning GLS and RRT we have had to rely on clinical observations. Those patients requiring dialysis are observed to have a worsening GLS between 10% to 20%, therefore we are assuming that on average 15% increase from the mean, giving a GLS score of -16.79%. The variance documented in meta-analysis of the healthy population ranged between 0.24% and 0.94% (average 0.61%) however based on a smaller study of those requiring haemodialysis, we assumed this variance would be larger, around 1.5%.

Table 1.1 Simulated LV GLS population characteristics

		Baseline			Follow up		
Group	N	Mean GLS	SD	Min, Max	Mean GLS	SD	Min, Max
Healthy volunteers	10	-19.76	1.89	-21.55, -17.49	-19.29	1.42	-20.72, -17.34
Nocturnal dialysis	10	-16.70	1.46	-19.74, -14.48	-19.63	1.33	-21,57, -17.04
Conventional dialysis	10	-16.84	1.42	-18.34, -14.43	-15.23	1.47	-16.51, -13.27

LV: left ventricle GLS: Global Longitudinal Strain, SD: standard deviation

In terms of the experimental conditions we have made the assumptions, based on clinical observations, that those on conventional haemodialysis will either remain at a similar level of GLS or worsen giving a predicted mean at follow up of -14.9% and a standard deviation (SD) of 1.5 (equating to 50% having a score worse than -16.69%), assuming that those receiving nocturnal dialysis tend to either remain at a similar level of GLS or improve, therefore providing a mean score of -18.9% and a SD of 1.5 (equating to 50% of participants having a score at or above -16.69%). Based on these values simulated data were created, see Table 1.1. The simulation was repeated and tested with a repeated measure ANOVA 100 times and we were able reject the null hypothesis 99 times suggesting adequate power.

This was a pilot study to look for differences that would be used to inform and generate a larger study. Temporal changes in biomarkers and cardiac imaging parameters over the study period (baseline, 3 months and 9 – 12 months) were compared across the groups using a t-test or non-parametric tests if the data was not normally distributed. Paired analysis was performed to look for temporal changes at baseline, 3 months and 9 – 12 months for all participant groups.

1.9.3 Secondary objectives and endpoints

The principal secondary aims were:

I) To compare the effect of nocturnal HD versus conventional HD on intradialytic changes in cardiac function, measuring cardiac output and cardiac index parameters with USCOM.

II) The effect of nocturnal HD on the rate of increase of coronary calcification as a marker of coronary disease burden was assessed by measuring the mean change in CT-CAC scores.

III) To further assess the impact of the two forms of haemodialysis, the mean change in markers of oxidative stress and inflammation was measured; AGE, IL-6, IL-18, MCP-1, VEGF, hs-CRP, Hepcidin and TAOS.

IV) To explore the impact of these two treatment modalities on patient's quality of life, a short form health survey (SF-36) was completed to assess the mean change in vitality domain across the study period.

Absolute values and changes from baseline in laboratory parameters; blood pressure (BP), heart rate (HR) and body mass index (BMI) were also measured.

CHAPTER 2

METHODOLOGY

2.1 Background of study

Approximately half of patients diagnosed with ESRD are suitable for the gold standard and undergo kidney transplantation (55.2%). A 'Home first' approach is promoted with suitable patients undertaking peritoneal dialysis (5.4%), however a large proportion of CKD stage 5 patients receive in-centre conventional haemodialysis (37.3%) and only a small proportion (2%) dialyse at home (21st UKRR Annual Report, 2020).

The United Kingdom Renal Registry (UKRR) collects data returned from nephrology centres across the UK, including information concerning RRT modalities including haemodialysis. Day 90 RRT modalities for incident patients have largely remained static over recent years, see table 2.1.

Table 2.1 RRT modality at day 90 for incident ESRD patients (21st UKRR Annual Report, 2020)

Modality	Percentage
Kidney transplant	10.2%
Peritoneal dialysis	20.3%
In-centre Haemodialysis	68.6%
Home Haemodialysis	0.8%

The high burden of cardiovascular disease is well recognised amongst haemodialysis patients and is responsible for around half of deaths. Foley et al., reported a 10 – 20 increase in mortality from cardiovascular disease amongst dialysis patients compared with the general population (Foley et al., 1995). Similarly,

De Jager et al. reported an age-adjusted 8.8 increase in cardiovascular mortality in dialysis patients (De Jager DJ et al., 2009). 24.4% of UKRR reported deaths in the first 90 days (with cause of death data), were due to cardiac disease. The burden of cardiovascular disease in haemodialysis is associated with cardiac remodeling, LVH, myocardial stunning, hypertension, decreased heart rate variability, coronary calcification and endothelial dysfunction.

Dialysis patients are exposed to traditional and dialysis-related cardiovascular risk factors. Cardiovascular disease is linked to inflammation, a chronic state that characterises ESRD (Kaysen et al., 2001). Due to the nature of dialysis, the immune system is under constant stimulation. It is known that infection and cardiovascular disease are interrelated; bacteraemia (access or other-related) is associated with an acute, transient risk in vascular events (Smeeth et al., 2004), with infection being the second biggest cause of mortality amongst dialysis patients. Conversely, chronic volume overload and heart failure (associated with elevated TNF-α) may elicit conditions favourable for the development of infections and be mutually aggregative (Stenvinkel P et al., 2005, Jager KJ et al., 2011).

Standard in-centre dialysis consisting of thrice weekly 4-hour sessions is far-fetched in replacing the physiological functions of the native kidneys. Longer, more frequent dialysis, administered as nocturnal haemodialysis provides more efficient clearance. Conversion from standard to extended hours dialysis has been associated with improved blood pressure control, reduction in polypharmacy, regression of LVH, improved LV function and stabilisation of coronary calcifications. These beneficial effects have been associated with better extracellular fluid volume control, improved

endothelial vasodilatory functioning, decreased total peripheral resistance and restoration of heart rate variability (Roumeliotis et al., 2021).

The cause for the increased cardiovascular morbidity and mortality seen in ESRD is not yet fully understood. In part it is due to the incomplete mitigation of the uraemic milieu and inflammatory response due to inadequate dialysis. In addition, the risk is augmented by oxidative stress and inflammation stimulated by haemodialysis.

2.2 Study sample and recruitment of participants

A full protocol was submitted to the Swansea University and Swansea Bay University Health Board Joint Study Review Committee (JSRC) outlining the pilot study. Following approval by chairman's action an Integrated Research Application System (IRAS) application was completed [IRAS ID 250304]. and the protocol was submitted for NHS Ethics and research and development (R&D) approval. As Principal Investigator (PI) I prepared and submitted all necessary paperwork and attended the Research Ethics Committee (REC) review which received a favourable opinion and Health Research Authority (HRA) approval [REC reference 18/WA/0317].

Participants were approached for recruitment into the study if they were >18 years of age at the time of consent with advanced CKD. Individuals with low-clearance (defined as an eGFR <15mil/min, approaching the need for RRT) or whom had recently started RRT (within the last 6 months) were approached. Individuals who met inclusion and exclusion criteria were identified from home haemodialysis training waiting lists and new starter unit haemodialysis lists. Patients commenced their

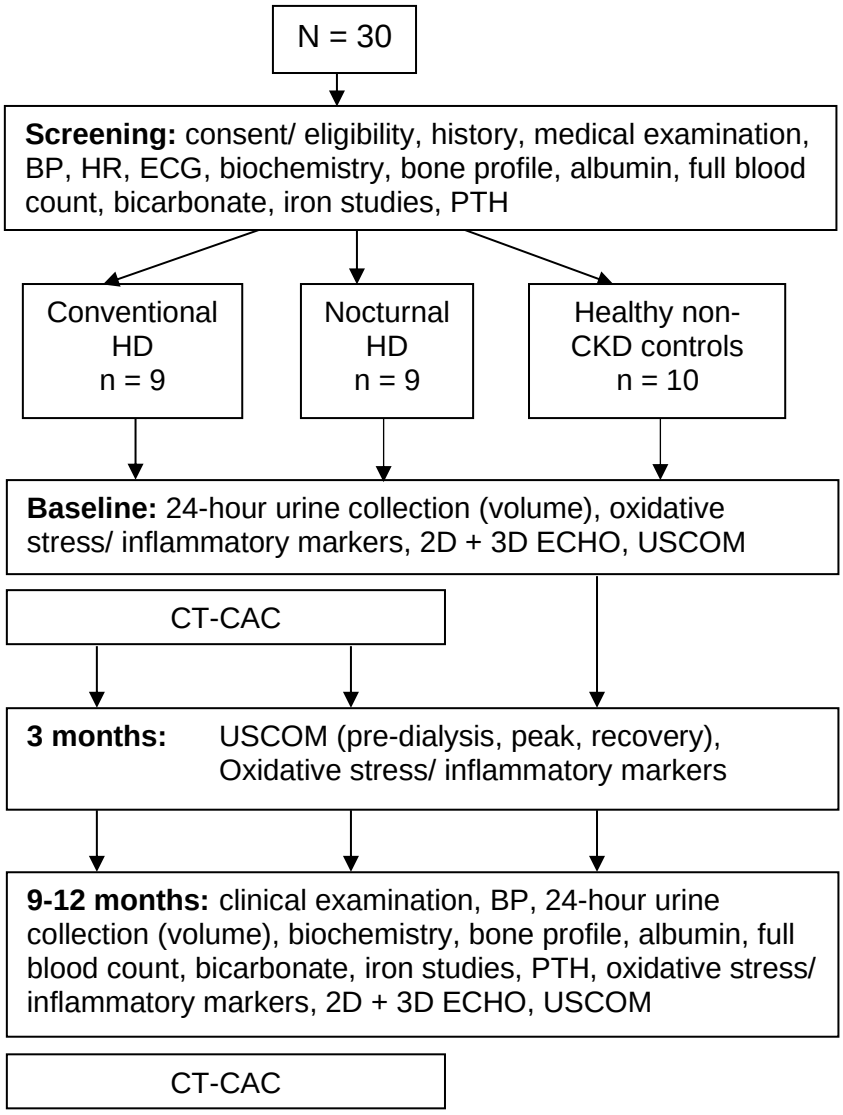
chosen modality: - conventional haemodialysis (HD) or nocturnal haemodialysis (NHD) as opted for following routine 'pre-dialysis counselling' by the CKD nurses.

Individuals were not eligible to participate if they were planned recipients of a live kidney donor (LKD), related or unrelated, within a 12-month period. Exclusion criteria also included those with advanced malignancy, heart or liver failure or any life-limiting condition that may limit life expectancy to <12 months. Any individual with chronic atrial fibrillation, a paced rhythm or more than mild valvular stenosis was also excluded. Criteria for withdrawal and discontinuation of the study included premature withdrawal of consent by the participant, recovery of renal function, receipt of renal transplant or change in dialysis modality i.e. to peritoneal dialysis.

Healthy volunteers (HV) were recruited from local advertisements for Swansea Bay University Health Board (SBUHB) staff on the hospital intranet and Facebook pages (see Appendix). The invitation to participate was extended to the South West Wales Renal Unit staff and relatives. Exclusion criteria for healthy volunteers included: - subjects with type 2 diabetes requiring insulin therapy, subjects requiring more than 2 antihypertensive agents, an eGFR <60ml/min, a history of heart failure, or requiring anti-failure medications. Healthy volunteers attended study visits at the Clinical Research Unit (CRU) at Morriston Hospital, Swansea.

All participants attended study visits at baseline and visit 1 with follow up study visits conducted at 3 and 9-12 months as outlined in Figure 2.1 and Table 2.2

Figure 2.1 Study scheme diagram



2.2.1 Participants and recruitment

The rate-limiting step for study recruitment was due to capacity to train individuals within the nocturnal training programme. All individuals commencing home dialysis training were approached for consideration for inclusion in the study and initial screening. Twelve individuals met exclusion criteria, 1 withdrew consent following screening for the study, 1 received a cadaveric transplant and was therefore

withdrawn from the study due to a change in modality. Screening and recruitment for the study took place between November 2018 and was completed in January 2020.

Participants were recruited to the study in matched triplets. Following recruitment of a nocturnal haemodialysis patient, efforts were made to identify a unit haemodialysis match by age, gender and post-code within the incident in-centre cohort (commenced dialysis < 6 months). New-starter lists were accessed for dialysis units in Swansea Bay University Health Board and satellite units in Hywel Dda University Health Board. Potential matches were approached for consideration of recruitment to the study. Nine individuals declined involvement or met study exclusion criteria.

Fifty-six healthy volunteers responded to recruitment advertisements: - participants were selected for screening based upon the closest match to the nocturnal and unit haemodialysis pair demographics. Two participants were not eligible to participate as they met exclusion criteria, one individual withdrew consent to ongoing participation of the study (HV group n=10).

Ten nocturnal haemodialysis patients were recruited that met screening, inclusion and exclusion criteria and were entered into the study: - 1 patient [ND009] had vascular access issues which affected her ability to go home, the baseline cardiac imaging was then delayed as a complication of COVID-19 and she was unable to participate in the study (NHD group n=9). Ten conventional haemodialysis patients were recruited that met screening, inclusion and exclusion criteria and were entered into the study. One patient [32 years] passed away following screening [HD008], a suitable replacement match was not found within the time limitations of the study

(two potential individuals that were appropriately matched for age declined to take part). It is unusual for young patients to receive conventional haemodialysis, as a pre-emptive LKD transplant or peritoneal dialysis are preferable modality options. One individual from the conventional dialysis group [HD010] crossed over to nocturnal haemodialysis mid-way through the study period (HD group n=9).

Table 2.2 Schedule for each study visit

Protocol activity (visits ±1 week) (All visit timings are relative to Day 1)	**Screening Week (-2 to -1)**	**Treatment Period: Day 1 through Week 52**					
		Day 1	Week 4	Week 8	Week 12	Weeks 16, 20, 24, 28, 32, 36	Weeks 40 - 52
Informed Consent	X						
Assess eligibility	X						
History: medical examination [(1)]	X	X					
Biochemistry, bone profile, albumin, full blood count, bicarbonate, iron studies, PTH	X						X
SBP/DBP and HR [(2)]	X	X	X	X	X	X	X
ECG[(3)]	X	X					X
ST-Echocardiogram		X					X
Non-contrast CT CAC score		X					X
USCOM[(4)]		X			X		X
NT-proBNP, Hs-Troponin T		X			X		X
AGEs, TAOS, TBARS, IL-6, MCP-1, IL-18, VEGF, BMP-6, hs-CRP and Hepcidin[(5)]		X			X		X
AE Assessment		X	X	X	X	X	X
24-hour urine collection (volume)		X					X
SF-36 questionnaire		X			X		X

[(1)] Medical history/ hospitalisation events will be re-checked on screening week or day 1. [(2)] SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: heart rate (single readings unless otherwise indicated). [(3)] ECG: electrocardiogram (conducted at Week -2 visit or at Day 1). [(4)] USCOM: ultrasound cardiac output monitor (performed on dialysis; with pre-dialysis imaging, peak (15 minutes pre-wash back) and recovery phase scanning). [(5)] AGE: Advanced Glycation End-products, TAOS: Total Antioxidant capacity of Serum, TBARS: Thiobarbituric Acid Reactive Substances, MCP-1: Monocyte Chemoattractant protein, VEGF: Vascular Endothelial Growth Factor. BMP-6: Bone Morphogenetic Protein, hs-CRP: high sensitivity C Reactive Protein, NT-proBNP: N-terminal pro B-type Natriuretic Peptide, cTnT: cardiac Troponin T. AE: adverse event, SF-36: 36-item Short Form health survey

2.2.2 Study visit settings

During the screening period, baseline biochemical measurements, electrocardiogram (ECG), 24-hour urine output (volume) and concomitant medication use was recorded. Compliance with dialysis therapy (defined as missing 0-1 dialysis sessions over the screening period) was an essential requirement for enrolment of participants in the dialysis arms. Informed written consent was obtained for all participants by the PI before enrolment.

2.2.3 Sample collection

10mls of blood was obtained by venepuncture (non-fasting samples) as a part of routine monitoring with monthly blood tests for individuals in the haemodialysis groups or by the CRU nurses at routine clinical visits where possible. The study was conducted within the Renal Department at Morriston Hospital, Swansea at either the Self-care unit for nocturnal haemodialysis patients or on the dialysis units.

Single sample volumes of 10ml were taken at baseline, 3 months and between 9 - 12 months. The timing of plasma sampling is of utmost importance as it is known that levels are altered by haemodialysis. All serum samples were therefore taken immediately after connection, before commencing haemodialysis treatment in order to avoid interdialytic variation in parameters. Samples were immediately centrifuged and stored at -80°C on site at the CRU by the research nurses. Investigations at baseline and follow up study visits at 9 - 12 months were timed to coincide with scheduled clinical visits to Morriston Hospital where possible.

2.2.4 Non-standard of care laboratory assessments

Tests required for the study protocol in addition to those provided as standard care for dialysis patients are defined as 'non-standard of care' laboratory assessments. These were processed by the hospital laboratory under a non-commercial service level agreement (SLA). Samples were collected using the trial specific laboratory medicine request form T257 (see appendix).

Table 2.3 Sample analysis procedures

Analyte	Assay	Equipment/Analyser
Sodium, potassium	Roche Cobas (Ion-Specific Electrode)	Roche COBAS 8000
CRP	Roche Cobas (CRPL3)	Roche COBAS 8000
Albumin	Roche Cobas (ALB2)	Roche COBAS 8000
Creatinine	Roche Cobas (CREJ2)	Roche COBAS 8000
Urea	Roche Cobas (UREAL)	Roche COBAS 8000
Bicarbonate	Roche Cobas (CO2L)	Roche COBAS 8000
Calcium	Roche Cobas (Ca2)	Roche COBAS 8000
Albumin	Roche Cobas (Alb BCG2)	Roche COBAS 8000
Phosphate	Roche Cobas (PHOS2)	Roche COBAS 8000
ALP	Roche Cobas (ALP2)	Roche COBAS 8000
Transferrin saturation	Roche Cobas (TRSF2)	Roche COBAS 8000
Ferritin	Roche Cobas Elecsys (FERR)	Roche COBAS 8000
High-sensitivity Troponin T	Roche Cobas Elecsys (TnT hs V2)	Roche COBAS 8000
Parathyroid hormone	Roche Cobas Elecsys (PTH)	Roche COBAS 8000
Full Blood Count	Sysmex XN reagents	Sysmex XN 9000
Reticulocyte count	Sysmex XN reagents	Sysmex XN 9000

CRP: C reactive protein, ALP: alkaline phosphatase

Tests were performed using the Roche and Sysmex assays and analysers. Haematological and biochemical parameters were analysed for the healthy volunteers as outlined in Table 2.3. These included a full blood count, iron studies [ferritin, transferrin saturation (TSAT), reticulocyte count, reticulocyte-haemoglobin equivalent (Ret-He)], urea and electrolytes, serum bicarbonate, albumin, alkaline phosphatase, bone profile and parathyroid hormone (PTH).

2.3 Plasma markers of cardiac injury, oxidative stress and inflammation

Markers of cardiac injury, oxidative stress and inflammation were measured from Ethylenediaminetetraacetic acid (EDTA) plasma samples taken at baseline, 3- and 9-12-month study visits. The panels were processed at the Diabetes Research Unit Cymru (DRUC) by Dr Sarah Prior, Senior Lecturer Diabetes Research Group.

2.3.1 Measures of inflammation and markers of endothelial function

Advanced glycation end products (AGE), monocyte chemotactic protein-1 (MCP-1), vascular endothelial growth factor (VEGF), interleukins-6 and -18, bone morphogenic protein-6 (BMP-6) and Hepcidin were measured using commercially available enzyme-linked immunosorbent assays (ELISA) from EDTA plasma samples.

ELISA is a quantitative analytical method that shows antigen-antibody reactions through a colour change. This colour change is achieved via an enzyme-linked conjugate and substrate that when compared to a known concentration, i.e. a standard curve, can determine the concentration of specific molecules.

AGE was analysed using a Relative kit, therefore data concerning the inter- and intra-assay detection levels and coefficients of variation (CV) was not available. MCP-1, VEGF, BMP-6 and Hepcidin were all analysed using DuoSet kits; - data was also not available for the inter- and intra-assay detection levels or CV.

IL-18 was analysed using a DuoSet kit, data was therefore not available for the inter- and intra-assay detection levels or CV. IL-6 was measured using a Quantikine kit; - inter- and intra-assay detection levels with CV are presented in Table 2.4.

Table 2.4 Serum/ plasma assay for IL-6 (Quantikine ELISA)

	Intra-assay precision			Inter-assay precision		
Sample	1	2	3	1	2	3
n	20	20	20	20	20	20
Mean (pg/mL)	16.8	97.7	186	17.2	101	191
SD	0.7	1.6	3.8	1.1	3.3	7.2
CV (%)	4.2	1.6	2.0	6.4	3.3	3.8

SD: standard deviation, CV: coefficient variation

2.3.1.1 Advanced glycation end products

AGES are formed via the classical Maillard reaction (Singh R et al., 2001) and their presence is closely related to hyperglycaemia; implicated in oxidative stress, atherosclerosis and the accelerated vascular damage of diabetic microvascular disease (Sugiyama S et al., 1996). AGE interact with the NF-κB pathway and lead to oxidative stress in inflammatory states. Hyperglycaemia is not a pre-requisite for accumulation and uraemia is associated with very high AGE concentrations (Raj DS et al., 2000). The formation of AGE induces free-radical production and depletes NO

concentrations, leading to oxidative stress. NO is vasodilatory and has an antiproliferative effect on smooth muscle cells. AGE accumulation could therefore result in vascular thickening with loss of elasticity, hypertension and endothelial dysfunction. Carbonyl intermediates accumulate due to a reduction in detoxification or renal clearance. They can cause damage themselves as ‘carbonyl stress’ or go on to form AGE. Carbonyl stress has been proposed as a mechanism for accelerated vascular damage causing glomerular insult and ESRD in diabetes (Suzuki D et al., 1999). Molecular weight affects clearance; free, not protein-bound AGE are removed by peritoneal dialysis and haemodialysis (Miyata T et al., 1997). AGE concentrations fall following renal transplantation; survival improvement may therefore be related to a reduction in AGE-induced toxicity (Friedman EA et al., 1999).

2.3.1.2 Monocyte chemotactic protein-1

MCP-1 also known as chemokine (C-C motif) ligand 2 (CCL2) is one of the key chemokines that recruits and activates leucocytes to sites of tissue damage and infection. It is implicated in the pathogenesis of atherosclerosis; MCP-1 exhibits a direct pro-atherogenic effect on vascular smooth muscle cells with IL-6 release. MCP-1 can activate tubular epithelial cells, contributing to tubulointerstitial inflammation and ultimately fibrosis associated with loss of renal function (Lloyd Cm et al., 1997). MCP-1 also causes glomerular damage and is involved in the primary inflammatory phase of crescentic glomerulonephritis (Viedt C et al., 2002).

2.3.1.3 Vascular endothelial growth factor

VEGF along with HIF, are the main mechanisms of oxidative stress-induced angiogenesis. Endogenous ROS stimulate the induction of VEGF expression in

macrophages, smooth muscle and endothelial cells with resultant endothelial dysfunction. VEGF production by foam cells and macrophages may aggravate atherosclerosis (Yang PY et al., 2003).

2.3.1.4 Interleukins (IL-6 and IL-18)

Hyperglycaemia-induced oxidative stress and advanced glycation end products have been suggested to induce inflammatory cytokines. IL-6 is secreted by T cells and macrophages, its role as an anti-inflammatory cytokine is mediated through its inhibitory effects on pro-inflammatory mediators: - TNF-α and IL-1 with activation of IL-10. IL-6 mediates the acute phase response and stimulates acute-phase protein synthesis. IL-6 expression in the kidney is related to mesangial proliferation and the degree of tubular atrophy; highlighting its role in the progression of renal disease (Rivero A et al., 2009) It also induces the expression of hepcidin causing functional iron deficiency and renal anaemia. IL-18, a potent inflammatory cytokine is secreted by renal tubular epithelia, activated monocytes and macrophages that activates IFN-ɣ. It stimulates the production of other cytokines including IL-1, IL-6 and TNFα and may precede their release in the cascade. There is a positive correlation in diabetic patients between IL-18 and level of microalbuminuria (Thomas JM et al., 2021).

2.3.1.5 BMP-6

BMPs are key mediators of inflammation. BMP signalling promotes the inflammatory phenotype of endothelial cells in atherosclerosis, with resultant vascular calcification and aberrant tissue fibrosis. BMP-6 regulates hepcidin transcription (Babitt JL et al., 2006). BMP-6 expression is regulated by iron levels and deficiency leads to hepcidin deficiency (Wu, DH et al., 2019). BMP-6 has a pivotal role as the predominant ligand

in iron homeostasis and chronic inflammation via the BMP-SMAD pathway (Steinbicker AU et al., 2011) thereby affecting haematopoiesis with consequent anaemia and erythropoietin stimulating agent (ESA) resistance; - the target of which hypoxia inducible factor (HIF) stabiliser therapy aims to ameliorate (Crugliano G et al., 2021).

2.3.1.6 Hepcidin

Hepcidin, a key mediator of iron homeostasis is a type II acute-phase reactant induced by IL-6. Elevated iron concentrations and inflammation increase hepatocyte hepcidin production, which in turn is suppressed by erythropoietic activity. Extrahepatic sources of hepcidin mRNA include macrophages and to a lesser extent adipocytes. Hepcidin inhibits ferroportin transporter mediated iron efflux preventing intestinal absorption by enterocytes, macrophage recycling and release from iron stores. Hepcidin accumulation occurs in the chronic inflammatory state of CKD due to impaired clearance. It contributes to iron sequestration in macrophages with functional iron deficiency of renal anaemia, oxidative stress and atherosclerosis.

2.3.1.7 High sensitivity-C reactive protein

Hs-CRP was measured using direct photometry. The Randox Daytona Plus is a system for immunoturbidimetry and clinical chemistry analysis, providing rapid measurement of CRP in serum and plasma. Samples were run alongside quality control samples (Multisera Levels 2 and 3) and calibrated using Saline and Calibration Serum Level 3 (Randox). The instrument uses direct photometry to measure a coloured endpoint to determine hs-CRP levels from EDTA plasma samples.

C-reactive protein inhibits production of nitric oxide by eNOS causing endothelial dysfunction. The endothelium produces pro-inflammatory cytokines e.g. IL-6 (increased CRP production/ down regulates eNOS, reduces NO availability), TNF-α which stimulate adhesion molecules and increase chronic vascular inflammation and cardiovascular risk. Inflammation causes production of ROS, subsequent endothelial dysfunction and impaired vasodilation.

2.3.2. Plasma markers of oxidative stress

Oxidative stress is defined as the imbalance between pro-oxidant and antioxidant systems (Reuter S et al., 2010). TBARS measures lipid peroxidation end product malondialdehyde which is seen to be elevated in association with smoking (Miller ER et al., 1997), cardiovascular disease (Walter MF et al., 2004) and atherosclerotic plaque progression (Salonen JT et al., 1997).

2.3.2.1 Total antioxidant capacity of the serum

TAOS can be calibrated to indicate the degree of oxidative stress or increased susceptibility to oxidative damage. Plasma TAOS is based on Laights photometric microassay allowing the determination of TAOS values via its capability to inhibit the peroxidase-mediated formation of the 2,2-azino-bis-3-ethylbensthiazoline-6-sulfonic acid (ABTS+) radical. Due to it being inversely related to oxidative stress, the inhibition of ABTS+ formation is proportional to the samples antioxidant capacity and therefore a low level of oxidative stress will result in a high TAOS value. Hydrogen peroxide acts as a free radical donor that causes the formation of ABTS+ radicals, thus producing a colourmetric change.

Phosphate buffer saline (PBS) is used as a control as it contains no antioxidant molecules allowing the reaction to go to completion. Upon the addition of a plasma sample the reaction is prevented from going to completion and the degree of inhibition is dependent upon the level of antioxidants within the sample. The percentage inhibition of the reaction is represented by the difference in absorbance divided by the control absorbance determined from EDTA plasma samples.

2.3.2.2 Thiobarbituric acid reactive substances

In diabetes patients, TBARS, a marker of oxidative stress, and IL-6 levels are independently correlated with CRP (Arnalich F et al., 2000). TBARS were quantified using colorimetric assays and TAOS was determined using a photometric assay. The TBARS assay is based on the chemistry that thiobarbituric acid (TBA) forms a 2:1 adduct with MDA, which can be quantified colourimetrically from EDTA plasma samples.

Table 2.5 Cell culture supernates, cell lysates, serum, plasma, and urine assay for TBARS (Parameter chemical analysis)

	Intra-assay precision			Inter-assay precision		
Sample	1	2	3	1	2	3
N	20	20	20	20	20	20
Mean (µM)	2.57	6.07	9.26	2.39	5.71	8.76
SD	0.025	0.078	0.109	0.125	0.242	0.322
CV (%)	1.0	1.3	1.2	5.2	4.2	3.7

SD: standard deviation, CV: coefficient variation

Lipid peroxidation is a well-defined mechanism for measuring cellular damage as a result of oxidative stress. Cells that have decomposed due to oxidative stress result in the release of complex natural lipid peroxidase byproducts such as malondialdehyde (MDA). TBARS was analysed using a Parameter kit; - inter- and intra-assay detection levels with CV are presented in Table 2.5.

2.3.3 Plasma markers of cardiac strain

Hs-cTnT and NT-proBNP as plasma biomarkers are related to LV dysfunction and ongoing myocardial damage (Gheorghiade M et al., 2005). Cardiac enzymes NT-proBNP and cTnT were also assessed at baseline, 3- and 9-12 month follow up. NT-proBNP was analysed using a DuoSet kit, data was therefore not available for the inter- and intra-assay detection levels or CV.

2.3.3.1 Cardiac Troponin T

Serum cTnT is elevated in 20 – 90% of CKD patients (Lamb EJ et al., 2004)**Error! Bookmark not defined.** in the absence of an acute coronary syndrome and confers an increased risk of cardiovascular events and mortality (Goicoechea M et al., 2004). This may be due to myocardial remodeling in LVH, subclinical myocardial damage caused by silent ischaemia and myocardial stunning (Iliou MC et al., 2001, Mallamaci F et al., 2002).

The Roche Elecsys Troponin T assay is based on a sandwich test principle, using two monoclonal antibodies specifically directed against epitopes in the central part of the human cardiac troponin T protein (amino acid positions 125-131 and 136-147).

During the incubation period, two monoclonal antibodies; a biotinylated monoclonal anti-cardiac troponin T-specific antibody and an antibody labelled with a ruthenium complex and streptavidin-coated microparticles react and form a sandwich-shaped immune complex comprising the capture and detect antibodies. Microparticles are magnetically captured onto the surface of the electrode from the measuring cell aspirate. A chemiluminescent emission is produced by the application of a voltage to the electrode, which is measured by photomultiplier. Results are determined via a calibration curve.

2.3.3.2 N-terminal pro B type natriuretic peptide

NT-proBNP is elevated in cardiac failure (Codognotto M et al 2010). Despite a significant hazard ratio, a lack of correlation with ultrafiltration volume precluded its use in a regulatory role for acute fluid removal. NT-proBNP and hs-CRP have prognostic value in ESRD for all-cause death (Apple FS et al., 2004). The DuoSet ELISA measures natural and recombinant human NT-proBNP. The mouse anti-human capture antibody is diluted in PBS, for the assay procedure the biotinylated rat anti-human detection antibody is added to the sample in reagent diluent. Working dilution of streptavidin conjugated to horseradish peroxidase prior to incubation and addition of substrate solution. The optical density of each well is determined using a microplate reader with wavelength correction set to 540nm.

2.4 Cardiovascular assessment

Baseline cardiac function was assessed by ECG. Cardiac imaging consisted of 2-dimensional (2D) and 3-dimensional (3D) transthoracic echocardiography (TTE), including STE and CT-CAC as a non-invasive marker of ischaemia. Each test was

repeated upon completion of the study. Temporal comparisons were made, firstly using each patient as their own control and secondly among the two groups of patients exposed to 2 different modes of dialysis, each at baseline and after a treatment interval of 9-12 months. ILS radiographers and the cardiac sonographer were blinded to the type of dialysis treatment patients were undertaking.

2.4.1 Speckle tracking ECHO

Various renal replacement modalities can have differential effects on LV function. Diastolic function is impacted before systolic function in a large variety of cardiac conditions. The left atrium acts as a 'barometer' of diastolic function, and modern imaging techniques allow measurement of subtle changes in its diastolic performance.

Patients underwent 2 and 3D TTE performed by the same British Society of Echocardiography accredited sonographer to remove inter-user variability as a factor (overseen by Dr Daniel Obaid, Consultant Cardiologist). ECHO scans were performed at the same point in time (<60 minutes pre-dialysis) within the dialysis cycle, in order to avoid spurious results from major differences and variation in volume status in the Cardiac Physiology Department, Morriston Hospital, Swansea. The transthoracic examinations were performed with the patient in the left lateral decubitus position and the transducer in the left parasternal position. Measurements were acquired using the Vivid 7 machine and GE Echopac software; including 3 loops in end expiratory apnoea; -

1. Parasternal long axis (PS Lax), gray scale imaging and colour flow mapping (CFM) over aortic valve (AV), mitral valve (MV) – individuals were excluded if more than mild mitral regurgitation (MR) or atrial regurgitation (AR).
2. Subcostal short axis (S-Ax) at papillary muscle level. Apical views (2, 3, and 4 chamber) in gray-scale imaging (with and without the atria included), CFM AV; colour wave (CW) Doppler if PS LAx suggested aortic stenosis (AS) – individuals excluded if peak velocity >2m/s, pulsed wave doppler (PWD) of MV inflow, ratio of trans-mitral doppler early filling velocity to tissue doppler early diastolic mitral annular velocity (E/e' ratio) at lateral annulus and at ventricular septum, tricuspid valve (TV) CFM, TV CW Doppler, inferior vena cava (IVC) size and collapsibility from subcostal view.

All linear dimensions and also 2D and 3D volumes of all chambers were measured; GLS in LV, LA, E/e', E, A, deceleration time of the early mitral inflow velocity (Dec T MV), Peak tricuspid regurgitation (TR) velocity, IVC size and collapse% with inspiration.

2.4.2 CT Coronary artery calcification scoring

Calcification is a recognised feature of advanced atherosclerosis (Yingchoncharoen T et al., 2013). The CAC score (CACS) is a representation of total coronary plaque burden and is well established as a powerful predictor of future cardiac events (Stary HC et al., 1995). The radiation dose required to obtain a CAC score is low (0.5msv – 1.5mSv) substantially lower than the rate of background radiation in 1-year making repeat measurements feasible (Polonsky TS et al., 2010). Progression of CAC score has been observed in patients undergoing renal replacement therapy but the effect

of using different modalities, in particular nocturnal haemodialysis, is still unknown (Voros S et al., 2011).

CACS were performed on a Siemens Somatom Definition 128 slice CT scanner (Siemens, Germany) at the Institute of Life Science-2 (ILS-2), Swansea University. Non-contrast enhanced prospective ECG-gated images were acquired at a tube voltage of 120kV during a single breath hold with a slice reconstruction of 3mm. Images were transferred to a dedicated cardiac CT workstation (Vitrea, Vital images, USA) and coronary plaque with attenuation >130 Hounsfield units, designated as calcified was summed to give a coronary artery calcium score (Agatston score) in keeping with the current established consensus (Jansz TT et al., 2017). Healthy controls did not have CT-CAC assessments to avoid radiation exposure.

2.4.3 USCOM measurements

Dynamic cardiac assessment was evaluated on haemodialysis using USCOM as a non-invasive assessment of haemodynamic status; cardiac output and systemic vascular resistance. USCOM readings were measured at baseline, 3- and 9 – 12 months. Conventional and nocturnal haemodialysis patients underwent dynamic USCOM scanning on routine dialysis sessions; with pre-dialysis imaging, peak (15 minutes pre-washback) and recovery phase scanning. Nocturnal haemodialysis patients attended the self-care unit for routine assessment of technique and underwent dynamic USCOM scanning whilst on their usual dialysis settings within working hours. Patients did not dialyse the day before assessments.

USCOM is a direct derivative of echocardiography, which uses CW Doppler ultrasound to provide measurements of hemodynamic indices. Using either the suprasternal insonation window for the AV, or the left parasternal window for the PV, the device measures the velocity time integral (VTI) of the ejection flow and heart rate (HR). A proprietary algorithm based on height (in subjects greater than 50 cm) or weight (less than 50 cm) is used to derive the cross-sectional area (CSA) of the two valves, and stroke volume (SV) is calculated as SV = CSA x VTI.

Heart rate is calculated from the interval between systolic ejections, while concurrent systolic and diastolic blood pressure values (SBP, DBP) are entered manually, from which mean arterial pressure (MAP) is calculated as MAP = DBP + ([SBP - DBP]/3). From these data, USCOM derives values for cardiac output (CO = SV x HR), systemic vascular resistance (SVR = MAP/CO), and other haemodynamic parameters. Flow time (FT) is the systolic ejection time in milliseconds. Stroke volume variation is defined as (SVmax -SVmin x 100)/([SVmax + SVmin]/2). Currently, the USCOM measures or derives 22 hemodynamic variables simultaneously. Body surface area (BSA) is calculated by the USCOM using the formula of Du Bois and Du Bois (1916), from which BSA-indexed values for CO, SV, and SVR were derived (CI, SVI, and SVRI) (Cattermole GN et al., 2010, Chan SSW et al., 2013).

2.5 Quality of life assessment using Short Form-36

All participants were asked to complete the Short Form-36 (SF-36) a multidimensional, self-reported mental and physical well-being scale questionnaire, with 36 items from 10 sets of questions. At baseline, 3-month and upon completion

at the 9 -12-month study visits. Eight dimensions are covered by self-reported questions concerning physical functioning and role limitations, bodily pain, general health perceptions, energy/ vitality, social functioning, emotional role limitations and mental health.

2.6 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics software (version 26, SPSS Inc, Chicago, USA) with statistical significance set at $p < 0.05$. Normality of data was assessed by one-sample Kolmogorov-Smirnov (1-KS) tests. One-way analysis of variance (ANOVA) was used to compare differences between groups (healthy volunteers, conventional haemodialysis and nocturnal haemodialysis). Data are represented as mean ±SD or discrete variables documented as numbers with percentage of participants in brackets.

Non-parametric data that did not follow a normal distribution (as assessed by 1-KS) are represented as median and interquartile ranges. Mann-Whitney U test and Kruskal-Wallis tests were used for analysing differences between groups. The normality and expression of each dataset are included in the footnotes of each respective table. The Pearson's (normal distribution) correlation and the Spearman's (non-parametric) correlation were used. Chi-square analysis was used to compare differences between nominal data. Statistical methods employed are described in more detail in the individual methods chapters. The SF-36 was analysed using the SF-36 module in STATA.

2.7 My role in study and help from others

I drafted the Joint Scientific Research Committee (JSRC) and Integrated Research Application System (IRAS) applications and attended the Research Ethics Committee (REC) panel review. I prepared the study file materials including the clinical research file (CRF) documents, patient information sheet (PIS) and consent forms for all groups. I undertook participant selection and recruitment. I organised and co-ordinated patient study visits. I undertook USCOM readings, managed the database, assembled the data and results. I performed the statistical analysis with support from Professor Jeffrey Stephens and Dr Giles Greene, who kindly analysed the SF-36 data using STATA (Ryan P et al., 1999). I drafted and published the posters and oral presentations that were presented in various conferences including The American Society of Nephrology (ASN) and UK Kidney Week (UKKW).

I performed all USCOM readings pre-dialysis at the individual's dialysis unit or in the CRU, Morriston Hospital. Adam Fowell performed all echocardiography cardiac imaging in the cardiac physiology department at Morriston Hospital. Shelley Treadwell performed the CT-CAC scans at ILS-2, Swansea University and the images were reviewed and scored by Dr Daniel Obaid. Claire Stafford and her team of clinical research nurses performed venepuncture and assisted in biochemical sample preparation, they also performed all clinical observations and undertook electrocardiogram recording at the clinical research unit. Dr Rachel Still and her team from the biochemistry department at Morriston Hospital performed the laboratory analysis for the relevant samples. Dr Sarah Prior and her team from the Diabetes Research Group performed the laboratory analysis for the markers of inflammation and oxidative stress in the Diabetes Research Unit Cymru, Swansea University Medical School.

CHAPTER 3

DEMOGRAPHIC ROUTINE CLINICAL AND INVESTIGATIONAL BIOCHEMICAL PARAMETERS BASELINE CHARACTERISTICS AND BIOCHEMICAL PARAMETERS OF STUDY GROUP PARTICIPANTS

3.1 Baseline clinical parameters

Study visits for haemodialysis patients were undertaken in their usual dialysis centre as close to their usual session times as possible to reduce the impact of study participation. CT imaging was carried out pre-dialysis for all haemodialysis patients. Nocturnal participants were seen in the self-care unit at 7am immediately after their ECHO in order to complete their usual 8-hour dialysis treatment. USCOM readings were measured pre-dialysis, 15 minutes before the end of the dialysis treatment and after wash-back. Healthy volunteers (HV) attended the clinical research unit (CRU) at 9am. Informed consent was taken, baseline observations were recorded, venepuncture was performed as well as 3 USCOM readings in order to derive the mean average reading from data collected. Participants then attended the cardiac physiology department for their ECHO, HV were not required to attend for CT-CAC measurements on account of the ionising radiation involved. Baseline clinical and demographic variables were characterised for all participants. Conventional (HD) and nocturnal haemodialysis (NHD) groups were matched with HV as for controls by:
- age, gender and socioeconomic status (post-code) to reduce variation between cohorts. The baseline clinical and demographic variables of the individual participants who were recruited to the study are outlined in Table 3.1.

Ten participants were recruited to each study arm, all patients dialysed via arteriovenous fistulas. 1 participant in the NHD group experienced vascular access complications and was unable to commence home dialysis at the time anticipated. This delay was further exacerbated by the impact of COVID-19 on obtaining the baseline cardiac imaging so the patient was excluded from analysis. One participant in the conventional HD group died following screening and was therefore also excluded from analysis. One participant changed modality from conventional HD to NHD after 193 days and was therefore analysed as a crossover in the NHD arm. Final numbers for analysis were control group n = 10, HD n = 9 and NHD n = 9. There was no difference in the median study duration (months) between haemodialysis groups. Conventional HD 12.5 [11.4 – 15.1] vs. NHD 11.6 [9.7 – 19.2], p=0.897.

3.2 Baseline biochemical parameters of study group participants

Baseline biochemical parameters of the study group participants with respect to measures of renal anaemia (haemoglobin and indicators of iron status: - TSAT, ferritin and Ret-He), markers of inflammation (CRP and albumin), mineral bone disease (MBD:-Ca^{2+}, PO_4^{3-} and PTH) and renal function are outlined in Table 3.2.

Serum phosphate (PO_4^{3-}), PTH, haemoglobin and albumin were statistically different at baseline for dialysis groups as compared to healthy controls. Dialysis duration, baseline urine output, and prescription of antihypertensives, antiplatelet or anticoagulants, modifiers of mineral bone disease, immunosuppressants (including glucocorticoids) and treatment of renal anaemia also reached statistical significance

($p < 0.05$). These are either recognised complications of, or treatments for ESRD prescribed for patients receiving haemodialysis, not seen in the healthy population.

Table 3.1 Baseline characteristics of study group participants

Dialysis Group	Healthy volunteers (n=10)	Haemodialysis (n=9)	Nocturnal Haemodialysis (n=9)	p value[a]	p value[b]
Demographics					
Age (years)	54 ± 14.17	53 ± 10.98	53 ± 13.06	0.934	0.701
Female (n,%)	3 (30)	3 (33)	3 (33)	0.866	0.599
Weight (kg)	85.9 ± 21.5	79.7 ± 16.6	82.9 ± 15.2	0.763	0.679
Body surface area	2.05 ± 0.3	1.95 ± 0.24	2.02 ± 0.23	0.681	0.554
Systolic blood pressure (mmHg)	134 ± 19	154 ± 19	147 ± 29	0.163	0.521
Diastolic blood pressure (mmHg)	83 ± 12	83 ± 13	78 ± 13	0.611	0.384
Ex/smoker (n,%)[$]	2 (20)	5 (56)	5 (56)	0.299	0.819
Urine output (ml)[#]	2000 [1550 – 2425]	1500 [900 – 1850]	15 [0 – 750]	**0.002***	**0.011*†**
CKD vintage (years)		2.8 [1.4 – 7.3]	6 [3.6 – 12.8]		0.173
Number of previous RRT modality		0	1 [1 – 2.5]		
'episodes' (PD/ HD/ transplant)			(0/ 11/ 4)	(0.762/ **<0.001*†/** 0.315)	
Dialysis vintage (days)		148 [79 – 176]	595 [398 – 1446]		**0.004*†**
Dialysis duration (days)[#]		148 [79 – 176]	123 [97 – 396]		0.757[†]
Co-morbidities					
Hypertension (n,%)[$]	1 (10)	6 (67)	7 (78)	**0.007***	0.814
Diabetes (n,%)[$]	0	2 (22)	4 (44)	0.089	0.502
Ischaemic heart disease (n,%)[$]	0	1 (11)	2 (22)	0.345	0.671

Normally distributed data expressed as mean ± standard deviation. *statistically significant P value <0.05. [#]non-parametric data [median, interquartile range] reported. [$]Nominal data, P value calculated by Pearson Chi-Square test. P value[a] comparison of 3 groups calculated by one way ANOVA, p value[b] comparison of unit and nocturnal haemodialysis at baseline. P value calculated by independent 2 tailed t-test. [†]Non-parametric data P value calculated by Mann-Whitney test. CKD: chronic kidney disease, RRT: renal replacement therapy, PD: peritoneal dialysis, HD: haemodialysis (conventional).

Table 3.1 Baseline characteristics of study group participants (cont)

Dialysis Group	Healthy volunteers (n=10)	Haemodialysis (n=9)	Nocturnal Haemodialysis (n=9)	p value[a]
Aetiology ESRD				
Diabetes		2 (22)	4 (44)	0.261
Glomerulonephritis		3 (33)	3 (33)	0.261
Hypertensive/ ischaemic nephropathy		3 (33)	0	0.261
Mechanical/ obstructive uropathy		1 (11)	2 (22)	0.261
Medication				
ACE/ ARB (n,%)[$]	0	3 (33)	2 (22)	0.599
Antihypertensive (n,%)[$]	1 (10)	8 (89)	8 (89)	0.765[¶]
Antiplatelet/coagulation (n,%)[$]	2 (20)	9 (100)	8 (89)	0.5[¶]
MBD (n,%)[$]	0	8 (89)	8 (89)	0.765
Phosphate binder doses		4.5 [0.75 – 6]	1.5 [0 – 6]	0.460
Immunosuppression (n,%)[$]	0	0	3 (33)	0.103[¶]
Statin (n,%)[$]	2 (20)	3 (33)	4 (44)	0.5[¶]
Erythropoietin (n,%)[$]	0	9 (100)	8 (89)	0.5
Iron (n,%)[$]	0	8 (89)	6 (67)	0.288

Normally distributed data expressed as mean ± standard deviation. *statistically significant P value <0.05. [#]non-parametric data [median, interquartile range] reported. [$]Nominal data, P value calculated by Pearson Chi-Square test. P value$_a$ comparison of unit and nocturnal haemodialysis at baseline. P value calculated by independent 2 tailed t-test. [†]Non-parametric data P value calculated by Mann-Whitney test. [¶]P value calculated by Fishers exact test. ESRD: end stage renal disease, ACE/ARB: angiotensin-converting enzyme/ angiotensin-2 receptor blocker, MBD: mineral bone disease

Table 3.2 Baseline biochemical parameters of study group participants

Dialysis Group	Healthy volunteers (n=10)	Haemodialysis (n=9)	Nocturnal Haemodialysis (n=9)	p value[a]	p value[b]
Renal anaemia					
Haemoglobin (g/L)	139 ± 15	110 ± 19	110 ± 14	**<0.001***	0.969[†]
Ferritin (ug/L)	162 [28 – 286]	209 [179 – 516]	302 [132 – 621]	0.175	1.00[¶]
TSAT (%)	22 [18 – 30]	24 [18 – 33]	22 [15 – 54]	0.561	0.888[¶]
Ret-He[#] (pg)	34 ± 1	34 ± 3	34 ± 4	0.925	0.762[†]
Inflammatory markers					
CRP[#] (mg/L)	-	19 ± 18	8 ± 6	0.274	0.150[†]
Albumin[#] (g/L)	47 ± 3	39 ± 3	42 ± 4	**<0.001***	0.173[†]
Mineral bone disease					
PO_4^{3-}[#] (mmol/L)	1.08 ± 0.16	1.71 ± 0.51	1.21 ± 0.53	**0.013***	0.068[†]
Ca^{2+}[#] (mmol/L)	2.41 ± 0.09	2.38 ± 0.17	2.28 ± 0.1	0.066	0.155[†]
PTH (pmol/L)	3.8 [3.3 – 5.9]	35.8 [20.2 – 50.6]	36.7 [21.4 – 50.7]	**0.002***	0.959[¶]
Na^{+}[#] (mmol/L)	141 [140 – 141]	139 [138 – 141]	138 [136 – 140]	**0.037***	0.436[¶]
K^{+}[#] (mmol/L)	4.3 [4.2 – 4.3]	4.5 [4.2 – 5.7]	4.7 [3.9 – 5.2]	0.261	0.666[¶]
Urea (pre-dialysis, mmol/L)[#]	5.6 [4.5 – 6.3]	17.8 [15.2 – 22.9]	10.25 [8 – 13]	**<0.001***	**0.008***[¶]
Creatinine (pre-dialysis, umol/L)[#]	82 [75 – 89]	593 [307 – 675]	501 [391 – 713]	**<0.001***	0.387[¶]

Normally distributed data expressed as mean ± standard deviation. P value[a] comparison of 3 groups calculated by one way ANOVA, *Statistically significant p value <0.05, P value[b] comparison of unit and nocturnal haemodialysis at baseline, [†]p value: independent samples t-test. [#]Non-parametric data [median, interquartile range] reported. [¶]P value: Mann-Whitney test. TSAT: transferrin saturation, Ret-He: reticulocyte haemoglobin equivalent, CRP: C reactive protein, PO_4^{3-}: serum phosphate, Ca^{2+}: serum calcium, PTH: parathyroid hormone, Na^{+}: serum sodium, K^{+}: serum potassium

Healthy volunteers were selected for the control group on the basis of the absence of CKD and its related complications. It was expected therefore that there would be a statistically significant difference in the control and dialysis groups as related to medication requirement, physiological and biochemical parameters.

Dialysis participants were anaemic when compared to the healthy volunteer population, which was reflected in the high level of Epo and intravenous iron prescriptions across the two groups. The mean haemoglobins and SD (g/L) for each dialysis group (HD 110 ± 19, NHD 110 ± 14) were within the recommended range for patients receiving dialysis [100 – 120g/L] as highlighted by the Time to Reconsider Evidence for Anaemia Treatment (TREAT) study (Goldsmith D et al., 2010) and recommended as a clinical standard for practice in subsequent Renal Association (RA) guidelines.

Dialysis participants were also prescribed medications for the renal complications associated with mineral bone disease including calcium (and non-calcium based) phosphate binders, activated vitamin D in the form of alfacalcidol and the calcimimetic, cinacalcet for tertiary hyperparathyroidism. A high proportion of conventional and nocturnal dialysis participants were prescribed cardiovascular risk modification treatments at baseline. A proportion of the nocturnal group were prescribed immunosuppression (prednisolone, tacrolimus or ciclosporin) to avoid necrosis of failed in-situ kidney transplants.

Baseline urea levels were lower in the NHD group 10.25 [8 – 13] than the conventional HD group 17.8 [15.2 – 22.9], p=0.008, likely due to the increased

frequency and total hours of clearance received by the extended hours group: - with an average of 40 hours/ week as compared to the standard 12 hours/ week schedule.

3.2.1 Dialysis vintage and residual renal function

Residual renal function (RRF) is the function remaining after the onset of chronic progressive renal disease and is inversely related to cardiovascular mortality; - with left ventricular hypertrophy, uncontrolled hypertension and increased erythropoietin requirements (Perl J et al., 2009, Shafi T et al., 2010). Preservation of patient's residual RRF is important as it allows continuous clearance of middle-sized molecules (i.e. Cystatin C and β2-microglobulin) and protein bound solutes. However, it is recognised to decline and often be lost in the first year of conventional incident haemodialysis. Patients with preserved RRF (defined as a urine output at baseline of >250ml/day) reported improved HRQoL in terms of better social functioning, vitality, cognitive functioning and quality of life over a year (Mitema D et al., 2016).

Dialysis vintage before recruitment to the study was statistically significant between conventional and nocturnal dialysis ($p=0.004$). Participants in the conventional HD group were incident patients commencing haemodialysis from advanced CKD followed up in a low-clearance clinic, or dialysis-dependent acute kidney injury (AKI) requiring chronic haemodialysis. Participants in the nocturnal study arm were more complex from a renal perspective, it is not yet standard practice in the UK to be able to train and directly go home. As a consequence of previous RRT modality failures ($p<0.001$) the nocturnal group had lost residual renal function ($p=0.01$) which

commonly occurs after 18 months of haemodialysis treatment. A greater number of participants commencing nocturnal haemodialysis following a switch from conventional haemodialysis were anuric or recorded lower 24-hour urine output volumes. The median and interquartile range for individuals commencing nocturnal haemodialysis was [15, 0 – 750ml] vs. incident patients with advanced CKD commencing conventional haemodialysis [1500, 900 – 1850ml], p=0.012. Healthy volunteers, as expected demonstrated higher, typical 24-hour urine volumes, in the region of ~2000ml.

Attainment of euvolaemia with haemodialysis is associated with loss of the benefits that preservation of RRF affords, as can be seen with peritoneal dialysis (PD). The FHN trial found frequent nocturnal haemodialysis to accelerate the decline of residual kidney function when studied in prevalent patients, the affect was sustained at 1 year (Daugirdas JT et al., 2013). These findings contrast the clinically recognised effects of extended hours haemodialysis related to a reduction in aggressive fluid and solute shifts. Skeat et al., looked at RRF in incident haemodialysis patients and found a significant decline in 48-hour urinary volume [2794 ± 1662 mL to 601.7 ± 315.3 mL (p=0.01)] in the nocturnal haemodialysis arm vs. conventional haemodialysis [2399 ± 950 mL to 1943 ± 1087.0 mL] (Skeat L et al., 2020).

These findings were reflected in our study where participants in the NHD group were anuric [0ml] as compared to individuals undertaking conventional HD (1000 [400 – 1550ml] after 12 months treatment (p=0.001), however participants in the conventional HD group had statistically significant higher 24 hour urine volumes at

baseline as compared to the NHD group (p=0.011). There was a non-significant change in urine output in the NHD group (p=0.109), a significant loss in urine output was observed in the conventional HD group from 1500 [900 – 1850ml] vs. 1000 [400 – 1550ml] over 12 months (p=0.012).

Patients in the nocturnal haemodialysis arm were more likely to have undertaken previous renal replacement therapy modalities, with a longer dialysis vintage. This was therefore a key difference between the groups and which accounts for the difference in urine outputs between the conventional and nocturnal haemodialysis groups. The presence of anuria would likely have further disadvantages to the nocturnal population and may in part contribute as a confounding factor for CKD related complications.

3.3 Physiological parameters of study group participants at 12 months

There was no difference in paired systolic or diastolic blood pressures (p=0.851 and 0.519 respectively), weight (p=0.211) or body surface area (BSA) (p=0.144) at baseline and 12 months between conventional HD and NHD groups. Table 3.3 shows the physiological parameters at the conclusion of the study.

There was a significant difference in anti-hypertensive requirement between conventional HD and NHD groups (p=0.043) after 12 months extended hours dialysis, with a reduction in the number of anti-hypertensives prescribed for nocturnal participants from a median average of two, to a single agent as shown in Table 3.4.

Table 3.3 Physiological parameters at 12 months

Dialysis Group	Healthy volunteers (n=10)	Haemodialysis (n=8)	Nocturnal Haemodialysis (n=10)	p value[a]	p value[b]
Study duration (months)	12 [9.75 – 16.75]	12.5 [11.4 – 15.1]	11.6 [9.7 – 19.2]		0.897
Weight (kg)	83.94 ± 22.32	80.87 ± 16.2	85.57 ± 12.65	0.847	0.503
Body surface area	2.03 ± 0.31	1.97 ± 0.22	2.06 ± 0.18	0.752	0.378
Systolic blood pressure (mmHg)	139 ± 19	151 ± 25	148 ± 24	0.535	0.814
Diastolic blood pressure (mmHg)	80 ± 12	85 ± 18	82 ± 15	0.794	0.729
Antihypertensive medications	0	3 [1.25 – 4]	1 [0 – 1.25]		**0.043*†**
Urine output (ml)[#]	2000 [1850 – 2513]	1000 [400 – 1550]	0	**<0.001***	**0.001*†**

Normally distributed data expressed as mean ± standard deviation. *statistically significant P value <0.05. [#]non-parametric data [median, interquartile range] reported. P value[a] comparison of 3 groups calculated by one way ANOVA, p value[b] comparison of unit and nocturnal haemodialysis at 12-months. P value calculated by independent 2 tailed t-test. [†]Non-parametric data p value calculated by Mann-Whitney test.

Table 3.4 Anti-hypertensive prescription at baseline and 12 months

Anti-hypertensive prescription (average number) [#]	Haemodialysis (n = 8)	Nocturnal haemodialysis (n = 10)	p value
Baseline	3 [1.5 – 3.75]	2 [1 – 2.25]	
12 months	3 [1.25 – 4]	1 [0 – 1.25]	**0.043*[¶]**

[#]Non-parametric data [median, interquartile range] reported. [¶]P value: Mann-Whitney test.

Table 3.5 Biochemical parameters of study group participants at 12 months

Dialysis Group	Healthy volunteers (n=10)	Haemodialysis (n=8)	Nocturnal Haemodialysis (n=10)	p value[a]	p value[b]
Renal anaemia					
Haemoglobin (g/L)	139 ± 15	115 ± 14	98 ± 18	**<0.001***	**0.038*†**
Ferritin (ug/L)	194 ± 150	582 ± 179	162 ± 151	**<0.001***	**<0.001***
TSAT (%)	23 ± 9	26 ± 7	19 ± 20	0.565	0.331†
Ret-He# (pg)	34.6 [34 – 35.4]	36.8 [34.2 – 39.1]	30.1 [29 – 34.9]	**0.007***	**0.012*¶**
Inflammatory markers					
CRP# (mg/L)	-	5 [5 – 16]	7 [5 – 38]	0.571	0.535¶
Albumin# (g/L)	45 [44 – 50]	41 [37 – 43]	39 [36 – 44]	0.426	0.299¶
Mineral bone disease					
PO_4^{3-}# (mmol/L)	1.2 [1.05 – 1.35]	1.7 [1.21 – 1.78]	1.1 [0.9 – 1.48]	0.395	**0.016*¶**
Ca^{2+}# (mmol/L)	2.4 [2.35 – 2.46]	2.45 [2.31 – 2.59]	2.42 [2.26 – 2.45]	0.618	0.299¶
PTH (pmol/L)	6.7 ± 3.6	39 ± 30	37 ± 15	**0.001***	0.867†
Na^+# (mmol/L)	139 [139 – 141]	132 [130 – 138]	136 [133 – 139]	0.395	0.436¶
K^+# (mmol/L)	4.2 [4 – 4.5]	4.6 [3.7 – 6.1]	4.4 [4.2 – 5.3]	0.929	0.666¶
Urea (pre-dialysis, mmol/L)#	5.9 [3.9 – 7.1]	14.8 [6.2 – 18.1]	7.8 [4.2 – 14.8]	0.848	0.258¶
Creatinine (pre-dialysis, umol/L)#	80 [68 – 88]	593 [307 – 675]	493 [316 – 740]	**<0.001***	0.931¶

Normally distributed data expressed as mean ± standard deviation. P $value_a$ comparison of 3 groups calculated by one way ANOVA, *Statistically significant p value <0.05, p $value_b$ comparison of unit and nocturnal haemodialysis at baseline, †P value: independent samples t-test. #Non-parametric data [median, interquartile range] reported. ¶P value: Mann-Whitney test. TSAT: transferrin saturation, Ret-He: reticulocyte haemoglobin equivalent, CRP: C reactive protein, PO_4^{3-}: serum phosphate, Ca^{2+}: serum calcium, PTH: parathyroid hormone, Na^+: serum sodium, K^+: serum potassium

3.4 Biochemical parameters of study group participants at 12 months

3.4.1 Parameters of renal anaemia

Haemoglobin (Hb) levels (g/L) were slightly lower in the NHD group than the conventional HD group (98 ± 18 vs. 115 ± 14, p=0.038). Serum ferritin levels (ug/L) were much lower in NHD than conventional HD participants (162 ± 151 vs. 582 ± 179, p<0.001, there was no statistical difference in serum ferritin levels between NHD and the control group (p=0.638). The haemoglobin content of reticulocytes (Ret-He) used as a marker of iron depletion, was lower in the NHD group as compared to conventional HD but still within the normal range 28 – 36pg (30.1 [29 – 34.9] vs. 36.8 [34.2 – 39.1], p=0.012 as outlined in Table 3.5.

Intravenous (IV) iron at our centre is usually administered as low volume, high frequency i.e. Diafer 100mg/ once a week for patients receiving conventional haemodialysis. The mean average dose administered for the study duration for conventional HD participants was 84 ± 41mg/ week (144 ± 71mg/ month). This was lower in the NHD group 53 ± 35mg/ week (91 ± 59mg/ month) but not statistically different (p=0.1) who received a higher volume, reduced frequency of doses in order to minimise hospital attendance. This was a variation from standard practice (monthly in-centre administration) for home therapy patients to mitigate and reduce the risk of contracting Coronavirus during the global COVID-19 pandemic (from March 2020 onwards).

The dose of erythropoietin stimulating agent (ESA) was calculated from the prescription. Erythropoeitin doses were adjusted by a dose factor to standardise to 1

unit of Epoetin Alfa (Eprex). Methoxy Polyethylene Glycol-Epoetin Beta (Mircera) by 240, Darbepoetin Alfa (Aranesp) by 300 and Epoetin Beta (NeoRecormon) by 0.66. The average ESA dose in units/week was lower in the NHD group, although this did not reach statistical significance (p=0.315). The ESA resistance index (ERI) (Deborah R et al., 2006) was calculated by the average weekly ESA dose (units/ week) divided by the average blood haemoglobin level at baseline, 3- and 12-months. The prescribed and administered ESA dose/ week and ERI are outlined in Table 3.6. There was no statistical significance between the groups (p=0.360), where for conventional HD the median ERI was 42 [31 – 105] vs. NHD 25 [1-72].

Table 3.6 ESA prescription and resistance index

	Haemodialysis	**Nocturnal haemodialysis**	**p value**
	n = 8	**n = 10**	
ESA dose calculated from	282000	110400	0.274
prescription (units)[#]	[194900 – 646150]	[6000 – 465120]	
Average ESA dose/ week	4743	2469	
(units) [#]	[3349 – 12159]	[90 – 7432]	0.315
Average Haemoglobin (g/L)	112±10	107±14	
ERI [#]	42	25	
	[31 – 105]	[1 – 72]	0.360

[#]Non-parametric data expressed as median [IQR], p value calculated by Mann-Whitney test, ESA: erythropoietin stimulating agent, ERI: ESA resistance index

To ascertain correlation between variables, Pearson's method was used for data following a normal distribution. Spearman's method was used to establish correlation for non-parametric data. The administered iron dose correlated with the prescribed ESA dose for conventional HD (p=0.001, r =0.9) and ESA dose/ week (p=0.004, r=0.89) but not for NHD (p=0.159, r=0.5).

The weekly iron dose correlated with the interval change in haemoglobin between the start and end of the study period; ΔHb (p=0.004, r =-0.8) for NHD. The prescribed ESA dose and administered weekly dose correlated with Hb at 12 months (p=0.021, r=-0.7) for NHD. Administered weekly ESA dose correlated with Hb at 12 months for conventional HD (p=0.023, r=0.8). There was no correlation in dose for TSAT, ferritin or Ret-He for conventional HD with Epo or iron administered. In the nocturnal group, the administered iron dose correlated with Ret-He at 12 months p=0.049867, r =-0.7. There was no correlation with TSAT or ferritin with iron or Epo prescriptions.

3.4.2 Parameters of mineral bone disease

Serum phosphate levels were significantly lower after 12 months treatment in the NHD group as compared to conventional HD 1.1 [0.9 – 1.48] vs 1.7 [1.21 – 1.78], p=0.016. There was no statistical difference demonstrated between serum calcium and PTH levels.

Eighty-six percent (n=7) of conventional HD participants had an increased binder or medication burden (including antihypertensives), there was no change to the prescription for the remaining in-centre dialysis participants. Fifty percent (n=5) of participants in the nocturnal group had a reduction in binder prescription, eighty percent (n=8) had a total reduction in medication burden including antihypertensives. For 50% there was no change from baseline with no requirement for a phosphate binder. At the end of the study, only one nocturnal participant required a phosphate binder as compared to all the in-centre conventional haemodialysis participants, which were prescribed one or more phosphate binders. The change in binder

prescription was significant between conventional HD and NHD groups ($p<0.001$), with an associated significant reduction in pill burden seen in the NHD group (accounting for MBD and anti-hypertensive prescriptions) $p=0.004$.

3.5 Discussion and study limitations

Conventional haemodialysis is commonly used as the incident modality for ESRD particularly in “crash-landers” on account of AKI or not being known to nephrology. Nocturnal haemodialysis is often currently considered when all else fails as a last resort for prevalent ESRD patients despite the recognised benefits including: - a reduction in Epo dose requirement and medication burden, no ongoing requirement for anti-hypertensives and optimised blood pressure control attained through the provision of gentler, longer haemodialysis. Prevalent patients are usually anuric and have lost residual renal function, this is reflected in the urine output data contrasting between truly incident patients and those new to nocturnal haemodialysis as a modality who due to current clinical practice are expected to have a more significant dialysis vintage. The characteristics of the participant groups were reflective of what would be seen in normal clinical practice aside from the management of renal anaemia which was impacted by COVID-19.

The main impact on the completion of study visits was due to COVID-19; a novel coronavirus which caused a global pandemic in 2020. The study was consequently suspended for 7-months due to the risk of potential infection for participants. Following re-initiation, several participants declined to attend study visits due to the fear of contracting COVID-19. Three nocturnal participants declined to attend the ECHO and CT-CAC for the final study visit. Study visits planned for weeks 40-52

were delayed in some cases up to 8-months due to hospital, CRU and ILS-2 COVID restrictions.

As a pilot study it is acknowledged that the sample size is small. The restriction on recruitment of nocturnal participants was due to a capacity limitation in service delivery. This was due to a cap on the number of patients that were able to enter or be trained at a point in time and the training duration requirement for each individual of twelve weeks. Difficulties with staff retention and recruitment in the self-care area further exacerbated patient flow and recruitment to the study.

As a single centre study, matching of nocturnal dialysis participants to incident conventional haemodialysis participants was also a rate-limiting step in recruitment. Echocardiography and CT CAC were conducted prior to a study participant's dialysis shift on a Friday. This required moving dialysis slots from morning or twilight sessions to the afternoon and days from Tuesday/ Thursday/ Saturdays to a Friday. This required direct liaisal and frequent communication with the dialysis shift co-ordinator (often with a need to accommodate the patient in a different dialysis unit), patient transport services, the cardiac physiologist and the radiologist to organise and co-ordinate the necessary scan timings.

CHAPTER 4

QUANTITATIVE MEASURES OF LEFT VENTRICULAR STRUCTURE AND FUNCTION

4.1 Introduction

4.1.1 Left ventricular dysfunction

Patients with ESRD have multifactorial cardiovascular disease and are often diagnosed with causative hypertension, uraemic cardiomyopathy, valvular and ischaemic heart disease. LV dysfunction is the final common pathway, presenting clinically as heart failure.

Negative cardiac remodelling is associated with worse outcomes. An increase in mortality is associated with an increase in end-systolic and end-diastolic volumes (Hammermeister KE et al., 1979). The increased afterload of hypertension causes LVH, impaired cardiac filling and relaxation results in diastolic dysfunction leading to heart failure with preserved ejection fraction (HFpEF). Coronary artery disease causes myocardial ischaemia, remodelling and fibrosis with reduced contractility and impaired cardiac output leading to systolic dysfunction or heart failure with reduced ejection fraction (HFrEF).

4.1.2 Myocardial stunning

The term “myocardial stunning” was coined in by Braunwald and Kloner in 1982 to describe a state of prolonged myocardial contractile dysfunction following a transient ischaemia-reperfusion insult. Metabolic and cellular influences include production of free-radical ROS (Bolli R et al., 1996) and an increase in cytosolic calcium (Ehring T et al., 1992) with subsequent desensitisation of myofilaments (Kloner R et al., 2020) due to reduced calcium responsiveness. Microvascular and endothelial dysfunction contributes to the demand vs. supply interplay and resultant myocardial stunning.

4.1.3 Dialysis-related myocardial stunning

The excess cardiovascular mortality seen in haemodialysis patients cannot be explained by traditional risk factors alone. Elevated cTnT levels are common in CKD; postulated due to chronic cardiac damage secondary to LVH and increased vascular calcification associated with hyperphosphataemia (Chuang AM et al., 2020). In dialysis patients, elevated cTnT levels are predictive of increased mortality (Khan NA et al., 2005).

Haemodialysis itself is increasingly recognised as an independent risk factor in developing cardiac dysfunction. Inherent with the electrolyte, acid-base and large-scale haemodynamic shifts are frequent complications such as intradialytic hypotension. Cardiovascular deaths in haemodialysis patients are more frequently related to sudden cardiac death than myocardial infarction (Herzog CA et al., 2005). Myocardial hibernation leads to cardiac remodelling, with scarring and loss of contractile function, aberrant conduction and life-threatening arrhythmias.

McIntyre et al., demonstrated haemodialysis-induced segmental LV dysfunction using positron-emission tomography. Patients without significant coronary artery disease exhibited demonstrably reduced myocardial blood flow with matching regional wall motion abnormalities (RWMA) (McIntyre et al., 2008). Repetitive myocardial stunning results in reduced contractile function and LV dysfunction. Burton et al., demonstrated haemodialysis induced LV dysfunction to affect more than half of their patients (Burton JO et al., 2009). Increased all-cause mortality is associated with the development of an increasing number of LV segments

developing regional wall motion abnormalities with prevalent haemodialysis treatment (Assa S et al., 2012).

In dialysis patients an interplay between metabolic demands and vascular supply results in regional coronary ischaemia and myocardial stunning. Low serum albumin associated with malnutrition, a reduction in adenosine triphosphate (ATP) levels and impaired oxidative phosphorylation contribute to the metabolic dysregulation of coronary blood flow. Calcium channelopathies and increased ROS associated with inflammation exert deleterious vascular and cardiac muscle effects. Vascular regulation of blood flow is further impaired with endothelial dysfunction, decreased coronary flow reserve and altered ventricular wall energetics (Zuidema MY et al., 2012).

The effects of inflammation in dialysis patients are far-reaching: - Atherosclerosis, endothelial dysfunction (adenosine di-phosphate-induced platelet dysfunction), systemic and myocardial pro-inflammatory cytokine effects, NO-dependent negative inotropy and myocardial inflammatory cell infiltrates contribute to impaired cardiovascular haemodynamics and subsequent myocardial stunning.

The underlying aetiologies of patients with ESRD are also contributory. For example, the inflammatory state associated with hyperglycaemia of diabetes affects vascular function. Glucose degradation products (GDP) cause cardiac myotoxicity and hypokalaemia, increasing the arrhythmogenic potential. Altered gut permeability, splanchnic hypotension and endotoxinaemia drive systemic inflammation, oxidative stress and atherosclerosis. In addition to the contamination of dialysate water,

endotoxin levels are known to rise throughout CKD and increase in dialysis patients (Raij L et al., 1973), the degree of which correlates with increased severity of myocardial stunning (McIntyre CW et al., 2011).

Frequent haemodialysis avoids the associated haemodynamic compromise of large volume ultrafiltration (Jefferies HJ et al., 2011) with a lower incidence of myocardial stunning, improved LV mass and quality of life (Chertow GM et al., 2010).

4.1.4 Assessment of LV systolic function

Echocardiography parameters used to assess LV systolic function include conventional 2D measures of left ventricular ejection fraction (LVEF), stroke volume (SV), cardiac output (CO) and end systolic volume (ESV). More contemporary techniques include 3D assessment of the same measurements and speckle-tracking echocardiography (STE) analysis of strain.

Historically the assessment of LV systolic function by LVEF has played a central role in the evaluation of cardiac disease directing management and informing prognosis. The current recommended method for 2D quantification is the Modified Simpson Biplane method, this tracks the endocardial border in apical 2 and 4-chamber views accounting for the change in LV volume between systole and diastole. Normal LVEF values are >52% and >54% for male and females respectively.

SV can be calculated as the product of the parasternal long axis view LV outflow tract (LVOT) cross-sectional area (CSA) and apical 5-chamber view LVOT velocity time integral (VTI). The range in a healthy individual is 70 – 100ml. The cardiac

output (CO) is the total volume of blood moved by the heart in a minute. Calculated using the Doppler VTI method, it is a product of LV stroke volume and heart rate (Blanco P et al., 2020) as calculated below: -

CO (L/min)= [LVOT CSA (cm) x LVOT VTI (cm) = SV (ml/cycle)] x HR (bpm).

ESV is the residual volume of blood in the ventricle at the end of systole. An increase in afterload, impedes the ability of the ventricle to eject blood and causes a resultant reduction in ESV.

3D volumetric assessment allows acquisition of the entire LV in a single beat. 3D measurements for LVEF, SV, CO and ESV produced highly correlate with cardiac MRI, the gold-standard (Luis SA et al., 2019).

4.1.5 LV diastolic parameters

The ‘E/A ratio’ measured by pulse wave Doppler across the mitral valve is a marker of LV relaxation, when impaired it signifies diastolic dysfunction. The normal flow profile has 2 peaks; E wave peak velocity represents ‘early’ diastole and accounts for ~80% of ventricular filling. The A wave of late diastole is caused by atrial contraction contributing the remaining stroke volume. Ventricular stiffening e.g. LVH due to longstanding hypertension, leads to reduced filling with reversal of the E/A ratio (Caballero L., et al 2015).

‘E/e’ ratio’ is a measure of the rate of change in the long axis reflecting left ventricular relaxation and volume and can be measured as a septal or lateral ratio,

obtained by tissue Doppler imaging is central to the assessment of diastolic dysfunction. In a normal cardiac cycle with preserved LV function, myocardial relaxation, assessed by early diastolic mitral annular velocity (e') precedes LV passive filling as assessed by the mitral peak velocity (E).

Left ventricular failure results in reduced passive filling and an associated increase in LA pressure (Rovner A et al., 2005). With diastolic dysfunction, cardiac motion (e') can then be due to filling (E) (Oki T et al., 1997). The E/e' ratio therefore correlates highly to LA pressure. Normal E/e' ratio measurements are <8 and abnormal >15 (Ommen SR et al., 2000).

End diastolic volume is a measure of preload; or the filled volume of the ventricle at the point of maximum distension prior to systolic contraction, which can be indexed to body surface area (BSA). Average LV EDV is reported as 142 ± 21 ml (Maceira A et al., 2006). EDV can be measured by 2D & 3D methods. An increase in EDV results in an increase in stroke volume, where SV = EDV – ESV.

4.1.6 Global longitudinal strain

Global longitudinal strain (GLS) is a measure of LV contractility. Obtained using speckle tracking echocardiography (STE), strain analysis is more sensitive than the volume-based measurement of LVEF as a measure of systolic function. Derived from speckle tracking, it enables detection of subclinical myocardial deformation (or Lagrangian strain) enabling detection of systolic dysfunction beyond conventional LVEF assessment. Prognostication for LVEF is present for heart failure with reduced ejection fraction (HFrEF) when EF<40%.

The term ‘strain’ reflects measures of shortening and elongation along the three cardiac axes: longitudinal, circumferential and radial (and thereby 3D deformation) of a segment of the myocardium during the cardiac cycle. Elongation of segment length is termed ‘positive strain’ and shortening ‘negative strain’. Measures are referred to however, as an increase or decrease in the absolute value of strain (%). During systole the left ventricle undergoes longitudinal and circumferential shortening with radial thickening.

STE utilises interference patterns formed by natural acoustic markers as speckles within the myocardial tissue. Tracking these points between consecutive frames throughout the cardiac cycle produces a displacement curve from which strain can be calculated along the cardiac axes. Systolic strain is load dependent and should be interpreted in the context of blood pressure (Morbach C et al., 2020). Variations in GLS are also seen with age and gender (Andre F et al., 2015). Images are recorded in standard apical 2, 3 and 4 chamber views where closure of the aortic valve is used to time end-systole (Lang RM et al., 2015). In healthy individuals normal GLS determined from meta-analysis is reported to be -19.7% ± 0.61 [-18 to -20%] (Smiseth OA et al., 2016), borderline GLS -16 to -18%, reduced <-12 – -16%, severe <-12%, very severe GLS <-8%. Therefore, more negative values of LV GLS denote better systolic function.

LV systolic strain is displayed as time to strain curves and a polar map of the 17 myocardial wall regions. The strain velocity curves of the individual myocardial segments are indicated by unique colours. Normally, all segments move in parallel, with the basal segments showing lesser excursion than the apical segments. The

sequence of image analysis is done for six segments of the apical long-axis view (APLAX), apical four-chamber view (4CH), and apical two-chamber (2CH) view. A bull's eye picture represents the 17 segments of the left ventricle with measured peak systolic longitudinal strain values and the mean of the peak global longitudinal systolic strain. The colour of each segment also represents the strain: - normal strain will be depicted in dark red and reduction of strain as light pink. If the segments lengthen instead of shortening, they are coloured blue.

It is thought that GLS may be superior to LVEF in terms of its sensitivity to left ventricular systolic dysfunction (LVSD) by LVEF and its incremental ability to predict cardiovascular outcomes. In the general population the risk of composite acute myocardial infarction, heart failure and cardiovascular death appears to be 3 times greater for the highest versus lowest GLS quartiles (Kalam K et al., 2014).

The presence of LVH impairs assessment of systolic function, which may be overestimated by LVEF. The subendocardium is the layer most susceptible to ischaemia, it contains predominantly longitudinal myocardial fibres therefore reduction in subendocardial GLS may precede reductions in EF. Impaired GLS in the presence of normal LVEF is seen in asymptomatic patients in the general population with diabetes mellitus (Ernande L et al., 2014), hypertension and obesity. In cardiotoxicity surveillance studies impairment is defined as a >15% relative reduction in GLS from baseline.

Conventional haemodialysis is associated with negatively prognostic cardiac remodelling and significant cardiovascular mortality. Cardiovascular benefits of

extended hours haemodialysis are well recognised with attainment of normotension and regression of LV mass. Cardiac MR is not easily accessible within clinical practice, 2D speckle tracking echo offers non-invasive sensitive, reproducible assessment of cardiac risk. Abnormal GLS is highly prevalent among HD patients and identifies LV systolic dysfunction in patients with preserved ejection fraction. Mean LV GLS in the prevalent haemodialysis population is significantly impaired [-11.5% ± 4.42] (Huang SH et al., 2014). LV systolic dysfunction (defined as GLS ≤-15.2%) has been identified in 32% of CKD stage 3B – 5 patients with preserved LVEF ≥50% (Hensen LC et al., 2018). GLS as a novel method has superior prognostic value in predicting cardiovascular and all-cause mortality within the CKD and dialysis population.

4.2 Aims of the chapter

The aim of the study was to compare and evaluate the cardiovascular impact of two forms of haemodialysis; conventional vs. extended hours nocturnal haemodialysis with a matched control group. The aim of this chapter is to appraise the assessment of LV volume and function using standard echocardiography measures. In addition, STE was utilised to assess strain, as measured by GLS.

4.3 Results

4.3.1 Echocardiography measurements of LV volume and function

Standard 2D parameters were recorded for each participant at baseline and after 12 months, at the end of the study. Transthoracic echocardiographic examinations were performed according to the British Society of Echocardiography standards, with patients in the left lateral decubitus position for image acquisition in the left

parasternal and apical windows. In addition to standard 2D protocol image evaluation, study visits included longitudinal strain imaging and three-dimensional evaluation of ventricular size and function. The same sonographer conducted all full-sequence scans in order to reduce intra-observer variability. Visits were pre-dialysis for patients in the conventional and nocturnal haemodialysis groups in order to obtain images at the same point in the dialysis cycle.

4.3.2 Assessment of LV volume

Assessment of LV volume included end-systolic and diastolic volumes in 2D and 3D as outlined in Table 4.1. Baseline ESV was higher in the nocturnal group as compared to the control group (p=0.027). No other statistical differences were observed (Mann-Whitney U test) between variables for healthy volunteers, conventional HD and NHD comparing measurements at baseline and 12-months. No correlation (Spearman's method) was seen with SBP/ DBP at baseline and follow up for all groups. Table 4.2 outlines the interval change between scans (Δ), no statistical difference was observed between the control and dialysis groups.

4.3.3 Assessment of LV function

Measures of LV function included ejection fraction, stroke volume, cardiac output, 3D ejection fraction, 3D stroke volume, 3D cardiac output, average E/E' septal and lateral ratios and average 2, 3 and 4 chamber GLS as outlined in Table 4.3. Patients acted as their own controls, allowing analysis of any change in parameter measured over time (Δ). Interval change in parameters was also compared between dialysis groups and with the healthy control group.

In terms of GLS as a marker of LV function, the control population were not as ‘healthy’ as expected (baseline -17.4 [-18.3 to -14.4] to -16.5 [-17.9 to -16.1] p=0.889. Conventional HD patients had consistently impaired GLS (consistent with reported -13.4 ± 3.5%) (Chiu D et al., 2016), NHD patients showed an absolute improvement of 2% (15% as compared to baseline) from a more impaired baseline figure of -13.8 to -15.8, returning towards the normal range with extended hours treatment (p=0.04967 analysed as intention to treat) this became non-significant if crossover patient included in analysis for NHD group. As the GLS was >-15.2% it was no longer classified as LVSD. There was no difference in ΔGLS between groups p=0.743 (see Table 4.4). As a pilot study, it was not adequately powered to detect a significant effect. However, given that an improvement was seen in a group with loss of residual renal function and a longer dialysis vintage the trend warrants further investigation.

Table 4.1 Left ventricle volume analysis: interval change in parameters (Δ)

Dialysis group	HV_a	HV_b	$^+$p value	HD_a	HD_b	$^+$p value	NHD_a	NHD_b	$^+$p value
LV Volume:									
ESV (ml) $^\#$	45 [41 – 72.75]	43 [40.75 – 70.25]	0.683	51 [46 – 88]	54 [36.5 – 88]	0.722	56 [53.5 – 86.25]	60.5 [49 – 72.5]	0.553
EDV (ml) $^\#$	99 [89.75 – 157.25]	101.5 [94.75 – 148.75]	0.332	122 [106 – 161]	119 [93.5 – 170]	0.767	119.5 [104.25 – 157.75]	128 [106.25 – 144.5]	0.499
3D ESV (ml) $^\#$	51.5 [42.5 – 78.4]	48 [44.5 – 83.5]	0.722	69.5 [48.25 – 76.25]	59 [47 – 73.5]	0.208	53 [46.5 – 85.25]	49.5 [46.5 – 79.5]	0.270
3D EDV (ml) $^\#$	95 [88.5 – 129.5]	106 [96 – 158.5]	0.726	137 [117.5 – 176]	138 [100 – 158.5]	0.953	135 [115.75 – 160.5]	115 [102 – 166.75]	0.674

$^\#$non-parametric data expressed as median [IQR], ^{a}baseline result, ^{b}final study result. $^+$p: Paired analysis between 0 and 12 months in groups (Wilcoxan Signed Ranks Test) and between groups (Mann-Whitney U test) assessed using Spearman's correlation. HV: healthy volunteer, HD: conventional haemodialysis, NHD: nocturnal haemodialysis, ESV: end systolic volume, EDV: end diastolic volume

Table 4.2 Comparison of parameter change (Δ) between groups

Dialysis group	HV	HD	NHD	$^+$p value
ΔESV (ml) $^\#$	-1.5 [-4.75 – 14.5]	-3 [-22.5 – 15.5]	-3 [-26 – 7]	0.614
ΔEDV (ml) $^\#$	3.5 [-5.75 – 14.75]	1 [-34 – 22]	-9 [-26 – 15]	0.627
Δ3D ESV (ml) $^\#$	-1.5 [-31.25 – 7.95]	-4 [-15 – 10]	-7 [-12 – 3.75]	0.931
Δ3D EDV (ml) $^\#$	12.5 [-63.5 – 72]	10 [-55 – 22]	-10 [-31 – 20.75]	0.974

$^\#$non-parametric data expressed as median [IQR], $^+$p: independent analysis between Δ in groups (Kruskal-wallis test). No statistical difference observed in Δ (interval change between scans) between control and dialysis groups (Mann-Whitney tests) ESV: end systolic volume, EDV: end diastolic volume

Table 4.3 Left ventricle function analysis: interval change in parameters (Δ)

Dialysis group	HV_a	HV_b	$^{+}$p value	HD_a	HD_b	$^{+}$p value	NHD_a	NHD_b	$^{+}$p value	$^{\$}$p value^{a}	$^{\$}$p value ^{b}
LV function:											
EF%	55.5 ± 4.17	53.8 ± 4.98	0.277	51.56 ± 11.38	52.44 ± 9.63	0.670	48.88 ± 4.67	52.59 ± 5.95	0.407	0.188	0.901
SV	61.5 ± 18.46	60.1 ± 13.43	0.563	64.11 ± 10.41	65.78 ± 14.33	0.687	62.88 ± 12.85	67.88 ± 17.38	0.909	0.927	0.523
CO$^{\#}$	3.75 [2.85 – 4.1]	3.55 [2.775 – 4.075]	0.646	4.1 [3.65 – 4.9]	4.3 [3.55 – 4.8]	0.674	4.45 [3.6 – 5.225]	4.4 [3.8 – 5.3]	0.865		
3D EF%$^{\#}$	51.5 [46.25 – 55.75]	51 [48 – 57.5]	0.672	51.5 [50.25 – 58]	55 [50 – 57.5]	0.262	55 [50.75 – 58.5]	54.5 [51.5 – 55]	0.943		
3D SV$^{\#}$	58.5 [44.75 – 78.5]	61 [51.5 – 72.5]	0.859	72 [61 – 77.5]	80 [55 – 83.5]	0.575	72 [49.75 – 80.5]	63.5 [55 – 84.5]	0.326		
3D CO$^{\#}$	3.4 [2.9 – 4.95]	4 [3.2 – 5.2]	0.396	4.35 [3.75 – 5.075]	4.75 [3.525 – 5.45]	1.00	4.5 [3.15 – 6.075]	4.5 [3.425 – 4.975]	0.438		
GLS avg$^{\#}$†	-17.35 [-18.3 - -14.375]	-16.5 [-17.85 - -16.05]	0.889	-14 [-18.1 - -11.45]	-14.3 [-16.35 - - 14.05]	0.812	-13.8 [-15.475 - - 12.475]	-15.8 [-17.2 - -6.26]	***0.04967**		
GLS avg$^{\#}$‡	-17.35 [-18.3 - -14.375]	-16.5 [-17.85 - -16.05]	0.889	-15.35 [-17.75 - - 12.55]	-15.1 [-17.9 - -14.125]	0.483	-13.9 [-16.1 - -12.85]	-16.2 [-17.2 - -12.25]	0.260		
Average E/E' s/l ratios$^{\#}$	7.4 [6.4 – 8.7]	8 [5.9 – 11.5]	0.374	14.1 [9.6-17.3]	12.7 [7.3 – 16.9]	0.735	11.3 [10.1-16.4]	12.5 [9.3-16.4]	0.799		

$_a$ baseline visit, 0 months, $_b$ final study visit. Normal data expressed as mean ±SD. $^{\#}$non-parametric data expressed as median [IQR], $^{+}$P: paired analysis between 0 and 12 months in groups (paired t-test) for normally distributed data, (Wilcoxon signed ranks test) for non-parametric data, $^{\$}$one way ANOVA comparing HV, conventional HD and NHD groups at $_a$ and $_b$. †intention to treat analysis, ‡crossover analysis. EF: ejection fraction, SV: stroke volume, CO: cardiac output, GLS: global longitudinal strain, avg: average, E/E' s/l: E to E prime septal and lateral ratios.

Table 4.4 Rate of change ΔGLS in each group

ΔGLS	HV	HD	p value[a]	NHD	p value[b]	p value[c]
Mean	-0.0077	-0.07	0.315	-0.0839	0.101	0.963
Median	0	-0.1357		-0.0764		0.743

p value[a] HV vs l HD, p value[b] HV vs NHD, p value[c] HD vs NHD, HV: healthy volunteer, HD: conventional haemodialysis, NHD: nocturnal haemodialysis, GLS: global longitudinal strain

A trend towards improvement in GLS with in-centre nocturnal haemodialysis has previously been reported (Graham-Brown MPM et al., 2017). Other authors reported no change in GLS following conversion from conventional to nocturnal haemodialysis with a static GLS of -17 ±4% (Chan et al CT et al., 2012). Albeit a non-significant improvement in GLS, this study adds to evidence base for improved outcomes with extended hours haemodialysis. Figures 4.1 and 4.2 show examples of time to strain curves and polar map with regional peak systolic strain values. A contrasting result is seen as illustrated between a deterioration in an individual's LV GLS with conventional HD from -18.1 to -14.3% (Figure 4.1) and an improvement in another individual's LV GLS with NHD from -15.4 to -18.5% (Figure 4.2).

In terms of correlation between cardiac imaging and cardiac biomarkers: - baseline and final GLS measures both highly correlated with cTnT (p=0.038 and p=0.049 respectively, r=0.7) for conventional haemodialysis patients, but not with NT-proBNP. There was no correlation between ΔGLS and ΔcTnT (p=0.5). However, ΔGLS and ΔIL-18 (p=0.061, r=-0.65) tended towards significance. No correlation was seen within the NHD group between GLS and troponin or NT-proBNP. The final hepcidin level correlated with the change in ΔGLS for NHD patients p=0.01 (r=-0.83). Baseline TBARS also correlated with ΔGLS p=0.01 (r=0.83).

The effect of a significantly reduced EF% (p=0.007) was lost with NHD treatment over time as an improvement in cardiac function was seen [increase from 49 ± 5 to 53 ± 6 (p=0.407)] although this did not reach statistical significance (as demonstrated in Tables 4.3 and 4.5).

Table 4.5 Comparison of LV function parameters between groups

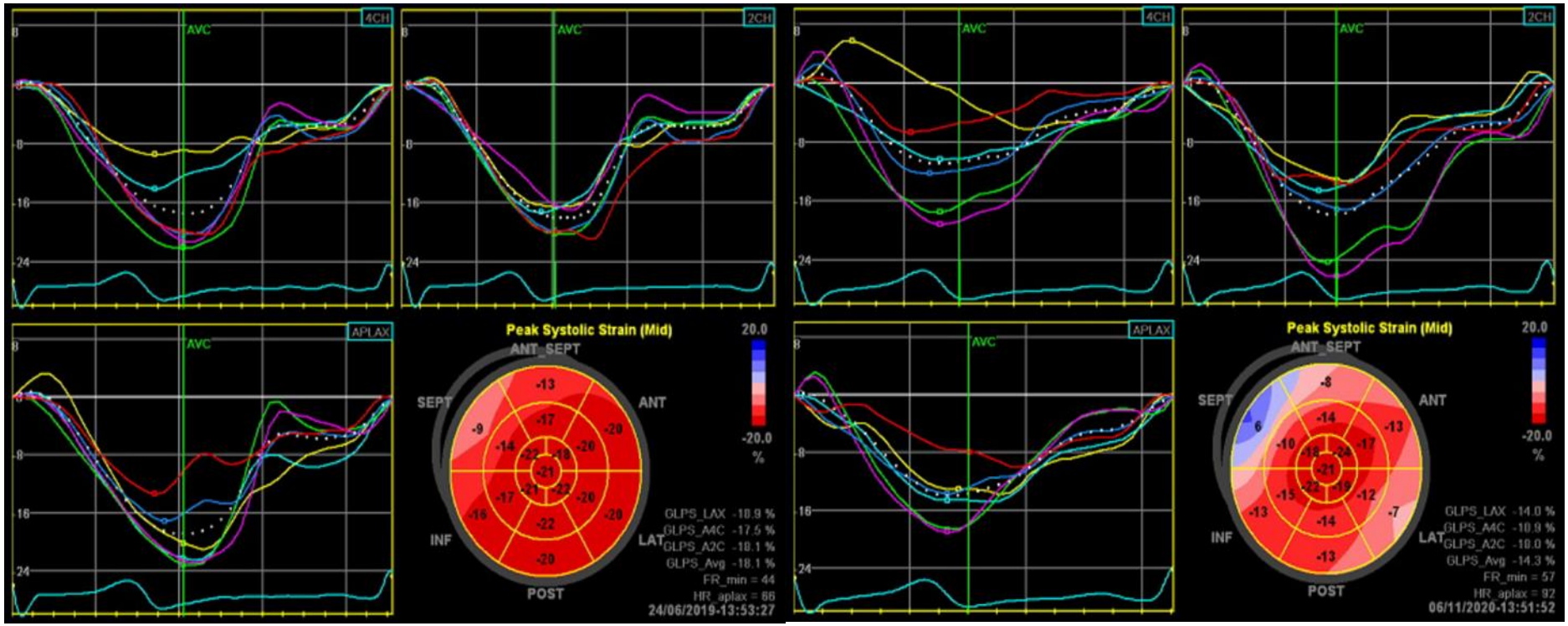
Dialysis group	HV + HD +p value	HV + NHD +p value	HD + NHD +p value
LV function:			
EF% 0	0.34	***0.007**	0.53
EF% 12	0.71	0.65	0.97
SV 0	0.71	0.86	0.83
SV 12	0.39	0.32	0.79
CO# 0	0.95	0.24	0.89
CO# 12	0.79	***0.04**	0.68
3D EF# 0	0.7	0.32	0.65
3D EF# 12	0.73	0.82	0.67
3D SV# 0	0.31	0.46	0.96
3D SV# 12	0.19	0.54	0.67
3D CO# 0	0.32	0.32	0.8
3D CO# 12	0.61	1	0.57
GLS avg# 0	0.21	***0.01**	0.67
GLS avg# 12	0.08	0.18	1
Av E/E' s:l ratios# 0	0.5	0.27	0.3
Av E/E' s:l ratios# 12	0.24	0.48	0.65

Normally distributed data +P value (independent t-test), #non-parametric data, +P value (Mann-Whitney test). HV: healthy volunteer, HD: conventional haemodialysis, NHD: nocturnal haemodialysis, LV: left ventricle, EF: ejection fraction, SV: stroke volume, CO: cardiac output, GLS: global longitudinal strain, Av E/E' s:l ratios: average E/ E prime septal and lateral ratios.

Table 4.6 Comparison of Δ parameters between groups

Dialysis group	HV	HD	p value[x]	NHD	p value[y]	p value[z]	[$]p value
ΔEF%	-1.7 ± 4.64	0.89 ± 6.03	0.315	1.71 ± 5.09	0.183	0.77	0.380
ΔSV	-1.4 ± 7.38	1.67 ± 11.96	0.518	-0.86 ± 19.08	0.945	0.77	0.864
ΔCO[#]	-0.1 [-0.975 – 0.65]	0.3 [-0.65 – 0.75]	0.447	-0.1 [-0.8 – 1.8]	0.740	0.758	0.727
Δ3D EF%[#]	0 [-2 – 4]	4 [-2.5 – 7.5]	0.489	0 [-3.5 – 3.75]	0.743	0.236	0.462
Δ3D SV[#]	-1 [-7.95 – 7]	3 [-6 – 15.5]	0.489	-2 [-12 – 5]	0.743	0.2	0.446
Δ3D CO[#]	0.45 [-0.525 – 0.75]	-0.3 [-0.4 – 0.5]	0.613	-0.1 [-0.875 – 0.175]	0.195	0.867	0.502
ΔGLS avg[#]	0 [-1.67 – 0.925]	-1.8 [-2.65 – 2.7]	0.447	-1.1 [-2.575 - -0.425]	0.101	0.743	0.321
ΔAverage E/E' s/l ratios[#]	-1.9 [-3.8167 - -0.6]	-3.225 [-4.0792 - -0.8375]	0.673	-3.525 [-5.4875 - -2.325]	0.139	0.328	0.283

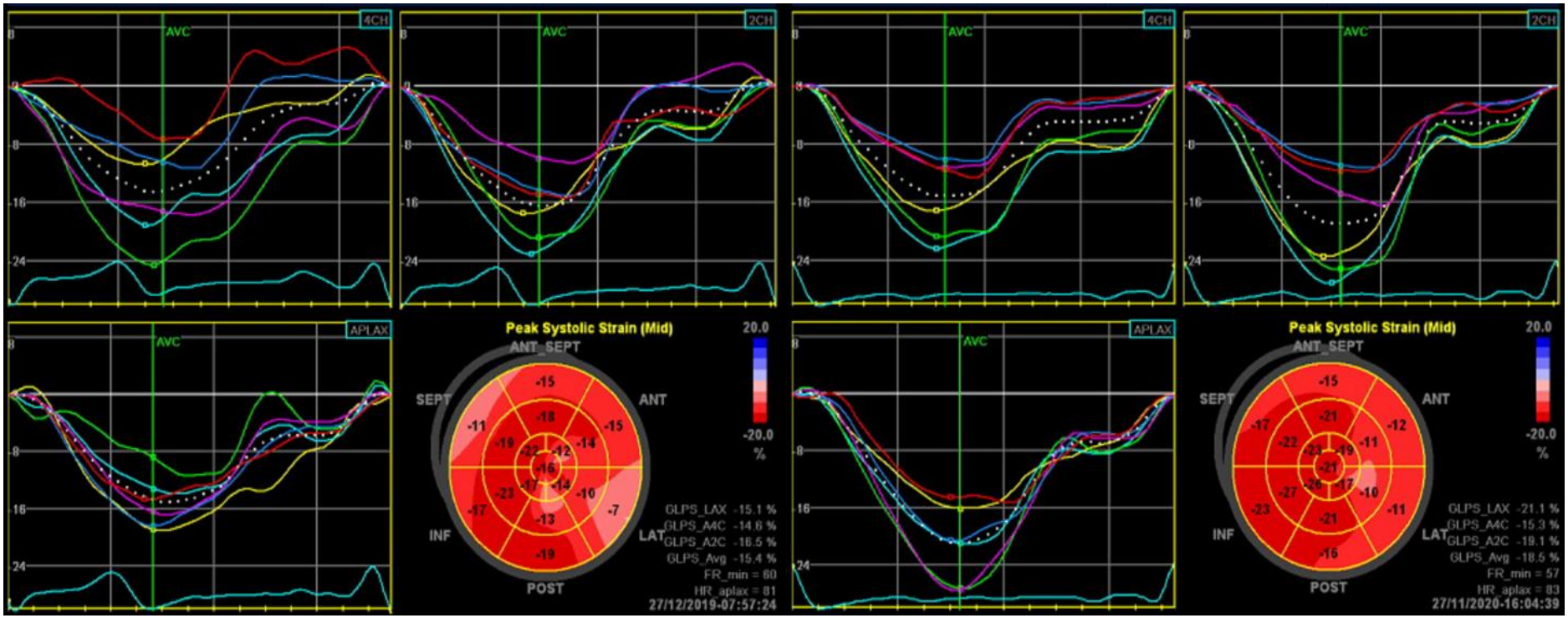
Normally distributed data expressed as mean ±SD, p value$_x$: HV vs HD, p value$_y$: HV vs NHD, p value$_z$ HD vs NHD (independent t-test). [#]non-parametric data expressed as median [IQR], p value$_x$: HV vs HD, p value$_y$: HV vs NHD, p value$_z$ HD vs NHD (Mann-Whitney test). [$]P: independent analyses between Δ in groups, one way ANOVA comparing normally distributed data in HV, HD and NHD groups, non-parametric data (Kruskal wallis test). HV: healthy volunteer, HD: conventional haemodialysis, NHD: nocturnal haemodialysis, LV: left ventricle, EF: ejection fraction, SV: stroke volume, CO: cardiac output, GLS: global longitudinal strain, Av E/E' s:l ratios: average E/ E prime septal and lateral ratios



A) **B)**

Figure 4.1 Time to strain curves and bull's eye polar map with regional peak systolic strain values: deterioration in LV GLS seen with participant on conventional haemodialysis from an average of A) -18.1 on the left, to B) -14.3% on the right image.

The strain velocity curves of the individual myocardial segments are indicated by unique colours. Normally, all segments move in parallel, with the basal segments showing lesser excursion than the apical segments. The sequence of image analysis is done for six segments of the apical long-axis view (APLAX), apical four-chamber view (4CH), and apical two-chamber (2CH) view. A bull's eye picture represents the 17 segments of the left ventricle with measured peak systolic longitudinal strain values and the mean of the peak global longitudinal systolic strain. The colour of each segment also represents the strain: - normal strain will be depicted in dark red and reduction of strain as light pink. If the segments lengthen instead of shortening, they are coloured blue.



A) **B)**

Figure 4.2 Time to strain curves and bull's eye polar map with regional peak systolic strain values: Improvement in LV GLS seen with participant on nocturnal haemodialysis from A) -15.4 on the left, to B) -18.5% on the right image.

4.3.4 Left ventricular mass

LVM is a well-established marker of risk-stratification, predictor of cardiovascular events (including sudden cardiac death) and mortality (Drazner MH et al., 2004). Cardiac magnetic resonance (cMR) imaging is considered gold standard for assessment of ventricular volumes, function and mass (Farber NJ et al., 2014). TTE offers a practical alternative due to more widespread availability and lower cost of delivery.

LVM and LVH provide incremental prognostic information in addition to traditional cardiovascular risk factors. The Framingham heart study established the relative risk for coronary disease in the general population/ 50g increase in LVM was 1.67 for men and 1.60 for women (Levy D et al., 1989). Regression of LVH is associated with improved outcomes (Verdecchia P et al., 1998).

LVM is a strong and independent predictor of survival and cardiovascular events in patients undergoing dialysis and is known to increase progressively with ESRD and haemodialysis. Hypertension and renal anaemia are known to be contributors to LVH (Levin A et al., 1999). The incidence of LVH is high with up to 75% of incident haemodialysis patients showing LVH on echocardiography. End-diastolic images are used to calculate LVM by echocardiography. Left ventricular mass varies with body size, gender, ethnicity and exercise. LVM is estimated by LV cavity dimension and wall thickness at end-diastole and indexed to body surface area (BSA) or height$^{2.7}$. LVM (g) was calculated according to the Devereux formula: -

$$0.8\{1.04[([LVEDD + IVSd + PWd]^3 - LVEDD^3)]\} + 0.6$$

Table 4.7 LV mass indexed by BSA for each dialysis group

Dialysis group	$LVMi_{Baseline}$ (g)	$LVMi_{End\ of\ study}$ (g)	$^{+}$p value
HD	114 [90 – 138]	118 [78 – 139]	0.314
NHD	105 [96 – 149]	107 [97 – 125]	0.374

$^{+}$p value: Wilcoxon signed ranks test. HD: conventional haemodialysis, NHD: nocturnal haemodialysis, LVMi: left ventricular mass index

Table 4.8 LV mass indexed by height$^{2.7}$ for each dialysis group

Dialysis group	$LVMi^{2.7}_{Baseline}$ (g)	$LVMi^{2.7}_{End\ of\ study}$ (g)	$^{+}$p value
HD	128 [114 – 144]	128 [100 – 154]	0.374
NHD	130 [107 – 171]	122 [116 – 137]	0.594

$^{+}$p value: Wilcoxon signed ranks test. HD: conventional haemodialysis, NHD: nocturnal haemodialysis, LVMi: left ventricular mass index

Table 4.9 LV mass indexed by BSA (LVMi) for each group

Dialysis group	HV_a	HV_b	$^{+}$p value	HD_a	HD_b	$^{+}$p value	NHD_a	NHD_b	$^{+}$p value
LVM index (g/m^2) – Male	91$^{\#}$ [67 – 105]	87$^{\#}$ [74 – 98]	0.398	113$^{\#}$ [91 – 148]	121$^{\$}$ [82 – 140]	0.463	100$^{\#}$ [93 – 137]	114$^{\#}$ [96 -127]	1
LVM index (g/m^2) – Female	70$^{\#}$ [45 – 91]	70$^{\#}$ [50 – 97]	0.285	**114¶ [77 – 130]**	**100$^{\$}$ [70 – 139]**	0.593	**156$^{¥}$ [100-134]**	**104$^{\$}$ [76 – 80]**	0.180

$^{+}$p value: Wilcoxon signed ranks test. Non-significant difference (p <0.05) between all group comparisons HV, HD and NHD for each gender with Mann-Whitney test. $^{\#}$within normal reference range for gender (F 43-95, M 49-115), $^{\$}$mildly abnormal (F 96-108, M 116-131), ¶moderately abnormal (F 109-121, M132-148), $^{¥}$severely abnormal for gender (F ≥122, M ≥149). HV: healthy volunteer, HD: conventional haemodialysis, NHD: nocturnal haemodialysis, LVMi: left ventricular mass index

Table 4.10 LV mass indexed by height$^{2.7}$

Dialysis group	HV_a	HV_b	$^{+}$p value	HD_a	HD_b	$^{+}$p value	NHD_a	NHD_b	$^{+}$p value
LVM/ height$^{2.7}$ – male	103.47$^{\#}$ [77.47 – 139.98]	99.38$^{\#}$ [84.39 – 123.35]	0.398	135.61¶ [119.87 – 152.42]	136.86¶ [101.6 – 163.4]	0.6	120.73$^{\$}$ [103.88 – 144]	121.71$^{\$}$ [117.4 – 136]	0.612
LVM/ height$^{2.7}$ – female	78.14 $^{\#}$ [49.63 – 95.25]	84.28$^{\#}$ [55.76 – 99.84]	0.109	124.5$^{¥}$ [101.55 – 134.44]	115.81¶ [91.45 – 139.13]	0.285	185.5$^{¥}$ [98.65 – 179.6]	124.48$^{¥}$ [83 – 103.7]	0.180

$^{+}$p value: Wilcoxon signed ranks test. Non-significant difference (p <0.05) between all group comparisons HV, HD and NHD for each gender with Mann-Whitney test. $^{\#}$within normal reference range for gender (F 43-95, M 49-115), $^{\$}$mildly abnormal (F 96-108, M 116-131), ¶moderately abnormal (F 109-121, M132-148), $^{¥}$severely abnormal for gender (F ≥122, M ≥149). HV: healthy volunteer, HD: conventional haemodialysis, NHD: nocturnal haemodialysis, LVMi: left ventricular mass index

Table 4.11 Change in LVMi and LVM/ height$^{2.7}$ with sub-group analysis by gender

	$^{+}$p value
ΔLVMi	0.825
ΔLVM/ height$^{2.7}$	0.691
ΔLVMi – male	0.391
ΔLVMi – female	0.083
ΔLVM/ height$^{2.7}$ – male	0.668
ΔLVM/ height$^{2.7}$ – female	0.083

p value: HD vs NHD (Mann-Whitney test), LVMi: left ventricular mass index

The results concerning LV mass as calculated by TTE are outlined in Tables 4.7, 4.8, 4.9, 4.10 and 4.11. There was no change in LVM indexed for BSA (LVMi) for the control group for male or female participants. A deterioration in LVMi was seen with male conventional HD participants to mildly abnormal (p=0.463) and an improvement in median LVMi for female conventional HD participants from moderately to mildly abnormal (p=0.593). There was no change in LVMi for male NHD participants who remained within the normal reference range, an improvement from severely abnormal to mildly abnormal LVMi was observed for female NHD participants (p=0.180).

Female participants in both dialysis groups saw an improvement with regression of LVMi seen for both conventional and extended hours haemodialysis which trended towards significance (p=0.083). Male gender participants saw a deterioration with progression of LVMi in the conventional HD group. This was in contrast to the NHD group where there was no change in LVMi, the same for the control group participants.

BSA in dialysis patients is influenced by both nutritional and body fluid volume status; malnutrition (overestimates LVM) and fluid retention (underestimates LVM). Therefore, LVM was recalculated and indexed by height (LVM/ height$^{2.7}$). For this correction there was no significant difference in ΔLVMi or ΔLVM/ height$^{2.7}$ by gender between dialysis groups, although changes again trended towards significance within the female sub-population (p=0.083).

LVM in men is known to be 25 – 38% greater than that in women (De Simone G et al., 1991) due to physiological myocyte hypertrophy. In the general population, Rider et al. demonstrated that in the absence of traditional cardiovascular risk factors obese men predominately developed concentric hypertrophy (without associated LV cavity dilatation) which is more strongly associated with cardiovascular mortality (Gerdts E et al., 2008, Rider OJ et al., 2013). Women developed both concentric and eccentric hypertrophy with LV cavity dilatation observed.

Concentric left ventricular hypertrophy is a consequence of pressure overload. Wall thickness increases as a result of new sarcomeres being added in-parallel (Mihl C et al., 2008). Chronically increased afterload i.e. hypertension is known to be mediated by AT2 blockade with ACE-inhibitor therapy (Du Toit EF et al., 2005). Eccentric hypertrophy is a result of increased filling pressure of the left ventricle. In diastolic overload, new sarcomeres are added in-series to accommodate volume-related loading.

When calculated by height, there was no change in LVM ($LVMi^{2.7}$) over the study period in the conventional HD group. A 6% regression in LV mass was seen in the NHD group, although this didn't reach significance, p=0.730. Average change in LVMi (g) for conventional patients was -11.3 [-16.5 to +9.5] and $LVMI^{2.7}$ (g) -9.8 [-17.9 to +11.6] for nocturnal patients -9 [-22.5 to +11.4] and $LVMI^{2.7}$ (g) -12 [-23 to +15].

Regression of LV mass has been reported in patients converting from conventional to in-centre nocturnal haemodialysis (Wald R et al., 2012). A -15.3g reduction in LV

mass was reported by Culleton et al. after 6 months extended hours haemodialysis (Culleton BF et al., 2007). As previously discussed, The FHN and FHNN trials also demonstrated a reduction in LV mass with more intensive dialysis prescriptions -13.1 and -10.9g respectively (Rocco MV et al., 2011).

Regression of LVH with intensive haemodialysis is associated with favourable outcomes. Trinh et al. reported a reduction in composite end point of all-cause mortality, modality failure or hospitalisation due to a cardiovascular cause was associated with a hazard ratio of 0.42 for intensive home dialysis as compared to conventional haemodialysis (Trinh E et al., 2016).

4.4 Discussion

LVH is an independent risk factor in patients on conventional haemodialysis for cardiovascular mortality, arrhythmias, myocardial infarction and heart failure. The aetiology pertaining to LVH progression in ESRD is multifactorial;- renal anaemia, hypertension, volume overload, uraemia and sleep apnoea. LVM in ESRD is a validated surrogate marker for mortality (Zoccali C et al., 2007).

Abnormal GLS thought to be a precursor of uraemic cardiomyopathy (interstitial fibrosis and myocyte hypertrophy) reflective of haemodialysis-related myocardial stunning. GLS may be the test of choice in the future for monitoring myocardial insult associated with haemodialysis. It is more sensitive as an early marker of subclinical LV systolic dysfunction than LVEF (longitudinal shortening or strain precedes circumferential/ radial dysfunction in pressure overload before LVH) and when impaired > -15%; a predictor of all-cause mortality, including those with LVH.

As a strong predictor of cardiovascular events and all-cause mortality compared to LVEF, GLS is validated in CKD, dialysis and transplant populations. The prognostic value of improvement in GLS in dialysis patients is unknown. In acute HF patients a 1% absolute improvement in GLS has a HR of 0.95, a 5% decrease in mortality (Ashish K et al., 2019).

Albeit a non-significant improvement in GLS, the results of this study add to the evidence base for improved outcomes with extended hours HD. GLS is a more precise predictor of cardiovascular mortality than conventional echocardiography derived EF (Terhuerne J et al., 2021). An adequately powered, multi-site prospective study required to further investigate the incremental prognostic value of GLS, with longer follow up to allow for cardiac event outcome analysis. GLS has potential for use as a cardiovascular marker of outcome in our high-risk cohort of ESRD patients. In an era of precision-medicine, GLS can inform clinical decision making with regards to modality choice and outcomes.

CHAPTER 5

QUANTITATIVE MEASURES OF LEFT ATRIAL DYSFUNCTION

5.1 Introduction

5.2 Left atrial volume and function

The LA modulates LV filling and performance, contributing up to a third of cardiac output (Matsuda Y et al., 1983). Its function is complex and facilitates 3 roles across the cardiac cycle; in LV systole it acts as a reservoir, during early LV diastole it functions as a conduit and during late LV diastole as a pump (Leung DY et al., 2008). LA preload is predominantly volume dependent; LA afterload increases with elevated LV filling pressures and more severe diastolic dysfunction (Yoshida N et al., 2009, Stefanadis C et al., 2001).

LA size has a prognostic role in informing risk for atrial fibrillation, heart failure, cardiovascular and all-cause mortality. Increase in LA size is a consequence of long-standing elevated LV pressures (Abhayaratna WP et al., 2006, Appleton CP et al., 1993). LA function is dependent upon LV diastolic properties, where reduction in LA function may be an early marker of LV diastolic dysfunction (Eshoo S et al., 2009). Reduced early diastolic filling and a compensatory increase in late diastole occur with impaired LA reservoir function, which precedes cardiac remodelling and subsequent LA enlargement. The role of LA strain as a biomarker of functional cardiac capacity is under evaluation (Vieira MJ et al., 2014).

CKD is an independent factor affecting cardiac mechanics including; - impaired LA reservoir strain and LV global longitudinal strain. Following multivariate adjustment, Unger et al., demonstrated that an impaired eGFR was independently associated with a reduction in LA reservoir strain (Unger ED et al., 2016).

In terms of LA volume, 3D echocardiography measurements correlate with standard 2D assessment, but offer no incremental prognostic advantage (Anwar AM et al., 2008).

5.3 Left atrial dysfunction in CKD

Left atrial enlargement is well reported and an independent prognostic factor in CKD (Tripepi G et al., 2006). LA volume and LVMI are known to increase in patients with ESRD along with a decline in diastolic function (Li C et al., 2019). Changes in LV systolic dysfunction, hypertrophy and fluid overload in ESRD may modify LA size and function. Alterations in LA strain affecting reservoir function precede changes in LA volume and are impaired in CKD (Kadappu KK et al., 2014, Kadappu KK et al., 2016). LA strain was found to be impaired in CKD patients with normal LA size greater than that for hypertensive and non-CKD control groups (Ohara Y et al., 2013, El-Sherbeny W et al., 2019).

Nakanishi et al looked at the relationship between CKD and left atrial volume and function. They observed that subjects with CKD (eGFR <60ml/min/1.73m^2) had a higher prevalence of hypertension and use of antihypertensive medications, increase LVMI and a higher prevalence of diastolic dysfunction than those without CKD. Left atrial minimum volume index ($LAVI_{min}$) and left atrial emptying fraction (LAEF) were significantly different showing impaired LA reservoir function. eGFR was significantly associated with left atrial ejection fraction (LAEF), independent of age, LVMI and diastolic dysfunction ($p < 0.05$) in patients without overt cardiovascular disease (Nakanishi K et al., 2017). LA reservoir dysfunction was found to precede LA enlargement (Gupta DK et al., 2014). The chronic inflammatory state of CKD leads

to a deterioration in LA function; Rao et al., described the association of elevated serum CRP levels with increased LA volume (Rao AK et al., 2008). Chronic renin-angiotensin-aldosterone activation causes myocardial fibrosis and reduced LAEF. Sympathetic stimulation and oxidative stress are also thought to be contributory mechanisms (Sun Y et al., 1997, Fukunaga N et al., 2012). Myocardial fibrosis manifests earlier and is more evident in the left atrium due to its thin walled nature (Gan GCH et al., 2021).

Li et al., observed eGFR to be independently correlated with PALS (peak atrial longitudinal strain) on apical 4 chamber views. LA longitudinal strain together with index of left atrial volume (LAVI) and LVMI were found to be independently associated with impaired diastolic function (Li C et al., 2019).

5.4 Aims of the chapter

The aim of the study was to compare and evaluate the cardiovascular impact of two forms of haemodialysis; conventional vs. extended hours nocturnal haemodialysis and a matched control group. The aim of this chapter is to appraise the assessment of LA volume and function using standard echocardiography measures. In addition, STE was utilised to assess LA strain, as measured by GLS.

5.5 Results and Discussion

5.5.1 Echocardiography measurements of left atrial volume and function

Assessment of left atrial volume included 2, 3 and 4 chamber systolic volumes, ESV and mean ESV as outlined in Table 5.1. No statistically significant change was found in terms of LA volume as assessed by paired samples t-test at baseline and after 12-

months. There was no statistical difference in the interval change (Δ) in mean ESV as assessed by Kruskal-wallis test between conventional and nocturnal dialysis groups (p=0.418). Assessment of left atrial function included 2, 3 and 4 chamber endocardial global longitudinal strain by 2D STE as outlined in Table 5.2. Longitudinal strain (endoGLS) and strain rate curves were generated for each of the six atrial segments from apical views. No statistically significant change was found in terms of LA function as assessed by paired samples t-test at baseline and after 12-months. A one-way ANOVA was non-significant for mean endoGLS at 0 and 12 months (p=0.419, 0.799 respectively). No significant difference for Δmean EndoGLS between conventional HD and NHD, p=0.336. In conclusion, no significant difference in atrial volume or function was detected between control and dialysis groups.

5.5.2 Left atrial global longitudinal strain

Peak systolic left atrial strain is a supplementary index of LV filling pressure, measured using STE. Developed for LV function assessment its use for assessing LA function has not yet been fully validated. At present its utility is still limited to research settings and it is currently measured using software developed for the assessment of LV strain. There is a lack of standardisation for strain analysis depending on the number of segments and whether QRS complex systolic gating or P-wave diastolic gating is used.

Newer STE parameters are less load dependent and have a higher sensitivity in assessing LA function than traditional parameters. Strain can be measured throughout the cardiac cycle enabling the assessment of the 3 components of LA systolic and diastolic function (Hoit BD et al., 2014). Morris et al., reported normal

values for PALS in healthy subjects to be 45.5 ± 11.4% with the lowest expected value of 23.1% (Morris DA et al., 2015).

The assessment of LA strain is relatively unaffected by the motion of adjacent myocardial wall segments. LA strain is reduced in diastolic dysfunction due to LA stiffness (Wang Z et al., 2008, Kurt M et al., 2009). The assessment of myocardial deformation parameters in conjunction with time points of the cardiac cycle allows in-detail analysis of relaxation and contractile functions of the left atrium (Vianna-Pinton R et al., 2009). Global diastolic strain as assessed by 2D STE is a preload independent parameter. Reduced LA longitudinal strain (<30%) during systole is associated with increased LV filling pressures (Wakami K et al., 2009). The use of STE adds to the knowledge base of LA dynamics and functional remodelling. LA strain has been shown to be an independent predictor of all-cause mortality in the evaluation of populations with diastolic dysfunction (Santos ABS et al., 2016).

5.6 LA reverse remodelling

LA enlargement follows maladaptive structural and functional LA remodelling and is of prognostic importance in atrial fibrillation and LV diastolic dysfunction. The left atrium is considered a biomarker for adverse cardiovascular outcomes where early functional changes have prognostic implications (Thomas L et al., 2017). Changes in atrial structure and function result from pressure and/ or volume overload consequent to LV diastolic dysfunction and co-stimulant pro-fibrotic pathways (Kallergis EM et al., 2008).

Table 5.1 LA volume analysis

Dialysis group	HV_a	HV_b	$^+$p value	HD_a	HD_b	$^+$p value	NHD_a	NHD_b	$^+$p value
LA Volumes:									
2 chamber ESV (ml)	89 ± 30	84 ± 20	0.640	107 ± 30	89 ± 27	0.169	84 ± 13	81 ± 24	0.787
3 chamber ESV (ml)	72 ± 31	62 ± 10	0.431	75 ± 10	67 ± 23	0.353	76 ± 22	74 ± 23	0.880
4 chamber ESV (ml)	79 ± 25	67 ± 17	0.174	91 ± 23	85 ± 26	0.410	73 ± 19	77 ± 24	0.702
Mean ESV (ml) (2/3/4 ch)	83 ± 26	67 ± 17	0.191	91 ± 17	80 ± 22	0.193	77 ± 16	76 ± 23	0.905

Normally distributed data expressed as mean ± SD, $^+$p: paired analysis between 0 and 12 months in groups (paired samples t-test) for normally distributed data. HV: healthy volunteer, HD: conventional haemodialysis, NHD: nocturnal haemodialysis, LA: left atrial, ESV: end systolic volume

Table 5.2 LA function analysis

Dialysis group	HV_a	HV_b	$^+$p value	HD_a	HD_b	$^+$p value	NHD_a	NHD_b	$^+$p value
LA function:									
2 chamber endoGLS	29 ± 14	30 ± 13	0.785	26 ± 8	30 ± 8	0.437	31 ± 15	34 ± 14	0.380
3 chamber endoGLS	22 ± 13	29 ± 10	0.169	30 ± 6	30 ± 9	0.904	28 ± 8	28 ±9	0.925
4 chamber endoGLS	23 ± 6	29 ± 10	0.168	32 ± 13	28 ± 13	0.637	25 ± 10	30 ± 12	***0.058**
Mean endoGLS (2/3/4 ch)	24 ± 9	30 ± 10	0.122	29 ± 7	29 ± 8	0.954	28 ± 10	31 ± 11	0.186

Normally distributed data expressed as mean ± SD, $^+$p: paired analysis between 0 and 12 months in groups (paired samples t-test) for normally distributed data. HV: healthy volunteer, HD: conventional haemodialysis, NHD: nocturnal haemodialysis, LA: left atrial, endoGLS: endocardial global longitudinal strain

5.7 Discussion

LA strain has been found to correlate with NT-proBNP in larger studies (Kurt M et al., 2012). Left atrial strain plays a pivotal role in modulating LV performance and has proven diagnostic and prognostic value in a variety of clinical scenarios. In the CKD population impaired eGFR is independently associated with a reduction in LA reservoir strain (Unger ED et al., 2016). LA volume and LVMI are known to increase in patients with ESRD along with a decline in diastolic function (Li C et al., 2019). Alterations in left atrial reservoir strain (LASr) occur before changes in LA volume (Vianna-Pinton R et al., 2009). In a prospective study of 243 stage 3/4 CKD patients LASr was found to be an independent predictor of cardiovascular death and MACE; superior to traditional echocardiography measures of LV function or LA volume. This pilot study was however not adequately powered to identify a difference in LA strain measures. With regards to segmental strain analysis there may be benefit in looking at the difference between two dialysis groups and whether the strain varies as assessed by 2 or 4 chamber GLS. Utility of LA strain is largely confined to research at present, future evaluation of LA phasic function by strain analysis may provide an accessible, reproducible method of assessing diastolic dysfunction (Santos ABS et al., 2016) and functional capacity in a multi-morbid, frail ESRD population (Gan GCH et al., 2021).

CHAPTER 6

VASCULAR CALCIFICATION AND ATHEROSCLEROSIS

6.1 Introduction

6.1.1 Cardiovascular risk assessment

Historically cardiac risk assessment has taken into account traditional risk factors; non-modifiable contributors include male gender, older age and a significant family history of cardiovascular disease. Modifiable risk factors include smoking status, diabetes mellitus, hypercholesterolaemia, hypertension and more recently obesity and physical inactivity. The predictive value of traditional risk factors in older people and younger <55 years has been inconsistent with the incremental predictive value of some risk factors found to be uncertain or to add no additional value (Van Bussel EF et al., 2020).

QRISK® is a predictive algorithm that utilises traditional cardiac risk factors to estimate an individuals' 10 year and lifetime risk of a cardiovascular event (Hippisley-Cox J et al., 2017). QRISK® is now recommended by the National Institute for Health and Care Excellence (NICE) and has superseded the Framingham risk score (Wilson PW et al., 1998) which was developed over 20 years ago to facilitate predictive individualised cardiac risk stratification.

CKD is a major risk factor for cardiovascular disease and is associated with a markedly elevated risk as illustrated in Figure 6.1. Risk prediction scores underestimate an individual's cardiovascular risk within the CKD population as they are not validated and do not use the consensus definition of CKD stages 3 – 5 (Stevens SL et al., 2016).

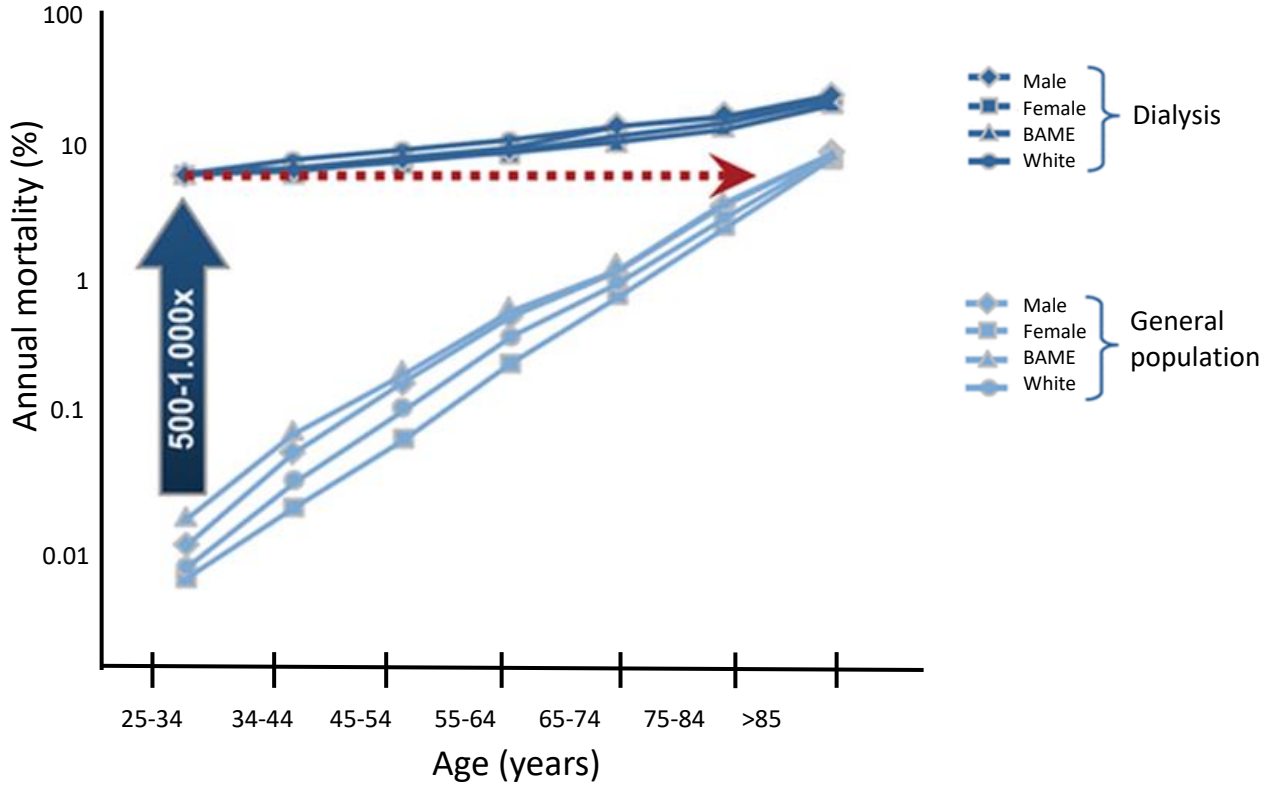


Figure 6.1 Cardiovascular mortality in the general population and in patients with ESRD. (adapted from Foley et al, 1998, Jankowski J et al., 2021)

The addition of eGFR and albuminuria status enhance the accuracy of predictive risk scores using a “CKD patch” that was developed from a dataset of 9 million patients to incorporate CKD into cardiovascular risk prediction calculators. The Pooled Cohort Equation (PCE) for Atherosclerotic Cardiovascular Disease (ASCVD) and Systematic Coronary Risk Evaluation (SCORE) for cardiovascular disease mortality assessment were quantitatively enhanced by the “CKD patch” for patients with reduced eGFR and higher albuminuria; https://ckdpcrisk.org/ckdpatchscore/ which was superior in informing the risk for cardiovascular disease (accounting for LVH and diastolic dysfunction) heart failure above that of atherosclerotic cardiovascular disease (Matsushita K et al., 2020).

CKD causes a chronic, systemic inflammatory response part of the complex interplay that contributes to the pathogenesis of vascular and myocardial remodelling. The CKD accelerates the cardiovascular aging process enhancing atherosclerosis, vascular and valvular calcification and myocardial fibrosis.

In addition to the increase prevalence of traditional cardiovascular risk factors in patients with CKD, non-traditional risk factors include complications of mineral bone disease (MBD) such as vascular calcification, the imbalance of electrolytes i.e. magnesium and the loss of its inhibitory effect on vascular calcification, inflammation and proteinuria (Ter Braake AD et al., 2017). A reduction in eGFR <60ml/min is independently associated with an increased risk of major cardiovascular events, cardiovascular death and all-cause mortality (p <0.001) as illustrated in Figure 6.2.

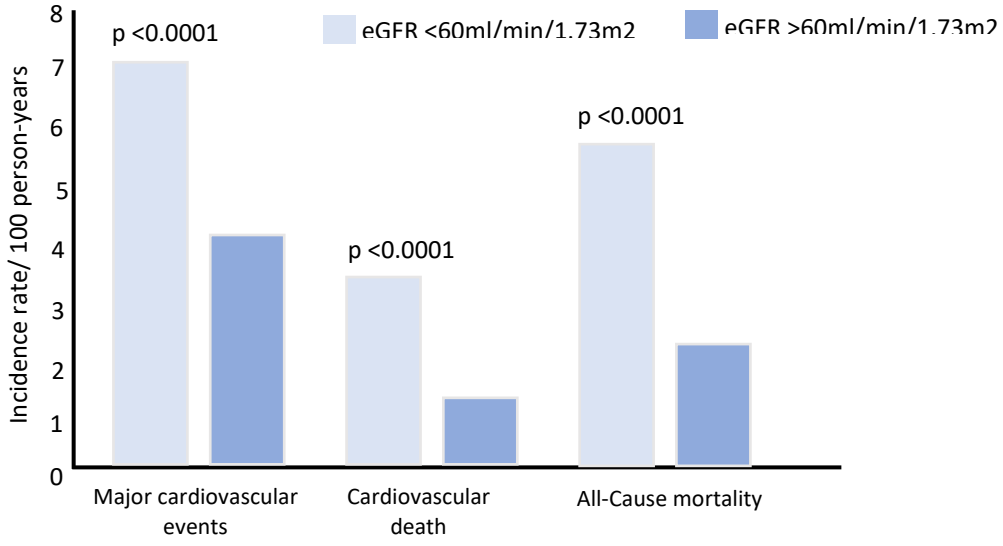


Figure 6.2 Independent association of kidney function with cardiovascular mortality (adapted from Gansevoort RT et al., 2013, Jankowski J et al., 2021).

6.2 CT calcium scoring

Computerised tomography coronary artery calcification (CT-CAC) scoring is a non-invasive method of assessing coronary artery disease (CAD). The more recent use of imaging for cardiac risk assessment allows accurate detection of the presence and extent of atherosclerotic disease. However, CAC assessment only detects the calcified part of coronary plaque, which accounts for 10 - 20% of the total atherosclerotic burden alongside lipids and fibrotic tissue (Rumberger JA et al., 1995).

The Agatson method for standardised CAC quantification was established in 1990 (Agatson AS et al., 1990). A density weighting is applied to the distribution of coronary calcium deposits to produce a CAC score for each vessel and a total CAC score. An Agatson score of >100 Hounsfield Units (HU) indicates at least moderate coronary artery atherosclerotic plaque burden and a score of >400 extensive atherosclerotic plaque. Patients are deemed to be high risk with a high likelihood of at least one significant coronary artery stenosis (Rumberger JA et al 1999). Patients with the absence of calcification (CAC zero) have a highly favourable prognosis.

Detrano et al., demonstrated a doubling of CAC score to be associated with a 25% increase in probability of a cardiac event over a 3.8 year follow up period (Detrano R et al., 2008). Patients with CAC progression (defined as >15% annualised change in CACS) in the Multi-Ethnic Study on Atherosclerosis (MESA) study were found to have a >3-fold increase in all-cause mortality (Budoff MJ et al., 2010). CAC progression (5-year scan interval) added predictive value to the significance of a baseline CACS (Lehmann N et al., 2018).

CAC scores are superior to traditional risk factor assessment (Carr JJ et al., 2017) and a validated tool for atherosclerotic cardiovascular risk prediction in the general population. CAC progression has been shown to increase the probability of a cardiac event. An annualised progression rate of 20-25% is expected in non-dialysis patients of average Framingham risk (Maher JE et al., 1999).

In the Heinz Nixdorf Recall (HNR) study, Erbel et al., found coronary artery calcification progression to follow a given exponential curve when CAC >10, based on an individual's age and baseline calcification score. With an inter-scan interval of 5 years, gender-specific exponential progression curves can be used to predict when patients are likely to be at high risk (CAC >400HU) and require rescanning (Erbel R et al., 2014).

CACS provide incremental prognostic value superior to traditional risk stratification and are established as an independent predictor of adverse coronary events (Sarwar A et al., 2009). A diagnosis of diabetes and elevated LDL lipids have been shown to be independently associated with accelerated plaque progression (Kim U et al., 2018, Tamarappoo B et al., 2018).

6.3 Vascular calcification in haemodialysis

Rapid progression of vessel calcification is seen with chronic haemodialysis. In addition to classical atherosclerotic intimal and subintimal calcification, dialysis patients exhibit characteristic medial calcification (Gross ML et al., 2007). Raggi et al., found CAC to be present in >83% of 200 chronic haemodialysis patients (Raggi P et al., 2002). CAC was found to be an independent predictor of death in dialysis

patients (Matsuoka M et al., 2004). However, the poor correlation of CAC with the gold-standard angiography, means the role of CAC as a prognostic indicator within the ESRD population is inconclusive (Tabriziani T et al., 2019). This may be explained by the intimal distribution of calcification seen in the non-CKD and severe medial calcification observed in ESRD populations (Shroff RC et al., 2008).

6.4 CAC progression in ESRD

CAC as a representation of total coronary plaque burden is a well-established powerful predictor of cardiac events. Every 100 Agatson unit increase is associated with a 20% increase in relative risk of a major coronary event (Cano-Megías M et al., 2019). Jansz et al., found no difference in CAC progression in ESRD patients over a 3 year follow up period on conventional haemodialysis and followed up those that changed modality to nocturnal haemodialysis or underwent kidney transplantation (Jansz TT et al., 2020). Niu et al., observed no difference in baseline, follow up or delta CAC scores in patients receiving peritoneal dialysis and haemodialysis. After accounting for variables there was no significant difference in CAC progression (Niu Q et al., 2020).

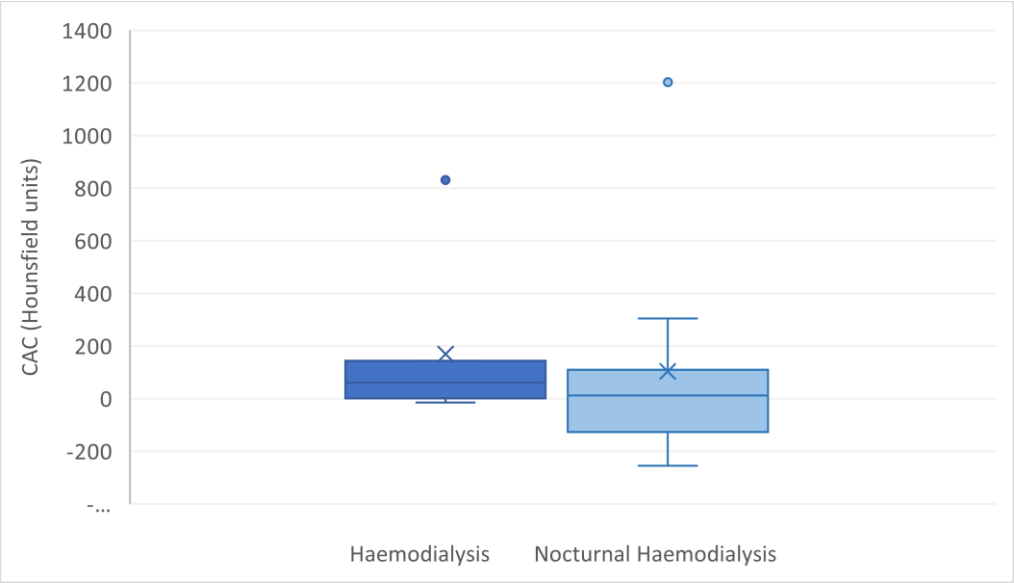
6.5 Aims of the chapter

The aim of the study was to compare and evaluate the cardiovascular impact of two forms of haemodialysis; conventional vs. nocturnal haemodialysis. The aim of this chapter is to appraise the assessment of CACS using CT quantification of calcification and to assess the progression of CAC in groups as defined by progressor status.

6.6 Results

6.6.1 CAC scores

CAC scores (CACS) were measured in both conventional and nocturnal haemodialysis groups at baseline with an interval scan after 12 months to assess for CAC progression. A significant difference in CACS was seen in the conventional haemodialysis group in calcification of the right coronary artery (p=0.028) and total CAC (p=0.043). A significant increase was not seen in the nocturnal haemodialysis group. A statistically significant difference was seen in CAC progression across the study period between the conventional dialysis group and the extended hours nocturnal haemodialysis group; with a 71.2% and 6.7% respective increase in calcification (p=0.043). A median increase in CACS of 62HU [1 – 152] was observed in the conventional dialysis group as compared to 9HU [-138 – 91] in the nocturnal haemodialysis group. Figure 6.3 shows the change in ΔTotal CAC (HU)/ study period ($CAC_{12\ months}$ - $CAC_{baseline}$).



CAC: coronary artery calcification, HU: Hounsfield units

Figure 6.3 ΔTotal CAC (HU)/ study period ($CAC_{12\ months}$ - $CAC_{baseline}$)

Table 6.1 CAC scores (Agatson method, HU) for individual coronary arteries and total CACS

	Haemodialysis			Nocturnal Haemodialysis		
	Baseline	**12 months**	**⁺p value**	**Baseline**	**12 months**	**⁺p value**
LMS	0 [0 – 81]	1 [0 – 88]	0.109	0 [0 – 1]	0 [0 – 3]	0.715
LAD	109 [4 – 254]	118 [7 – 295]	0.249	148 [16 – 584]	167 [23 – 611]	0.114
LCx	0 [0 – 55]	1 [0 – 95]	0.197	15 [0 – 222]	24 [0 – 122]	0.237
RCA	37 [10 – 144]	61 [27 – 166]	***0.028**	95 [21 – 1161]	199 [14 – 993]	0.889
Total	244 [18 – 398]	304 [34 – 504]	***0.043**	298 [79 – 1984]	338 [95.25 – 1837]	0.799

Non-parametric data, [median, interquartile range] reported ⁺p value comparing baseline and 12 months: Wilcoxon signed ranks test. LMS: left main stem, LAD: left anterior descending, LCx: left circumflex, RCA: right coronary artery

Table 6.2 Change in CAC (Δ) across interval scan period (HU)

	Haemodialysis	**Nocturnal Haemodialysis**	**⁺p value**
Δ LMS	0 [0 – 7]	0 [-0.5 – 0.3]	0.193
Δ LAD	7 [0 – 33]	12 [-2 – 17]	0.740
Δ LCx	0 [0 – 21]	3 [0 – 26]	0.740
Δ RCA	22 [4 – 51]	-2 [-59 – 86]	0.088
Δ Total CAC	60 [1 – 144]	12 [-127 – 110]	0.270
Δ Total change in CAC/ year	62 [1 – 152]	9 [-138 – 91]	0.230
Δ % change CAC/ study period	0.71 [0.25 – 1]	0.067 [-0.1 – 0.4]	***0.043**
(Δ total / $total_{baseline}$) %	**71.2% increase**	**6.7% increase**	

Non-parametric data, [median, interquartile range] reported ⁺p value comparison between dialysis groups: Mann-Whitney test, LMS: left main stem, LAD: left anterior descending, LCx: left circumflex, RCA: right coronary artery, CAC: coronary artery calcification

A statistically significant increase in coronary artery calcification was demonstrated in the conventional haemodialysis group, with a median average increase of 244 [IQR 18 – 398] to 304 [34 – 504] p=0.043 as shown in Table 6.1 and Figure 6.4. When comparing the Δ change in CAC across the study period there was a 71.2% increase in coronary calcification in the conventional dialysis group as compared to their baseline vs a 6.7% increase in the nocturnal dialysis group, p=0.043 as shown in Table 6.2.

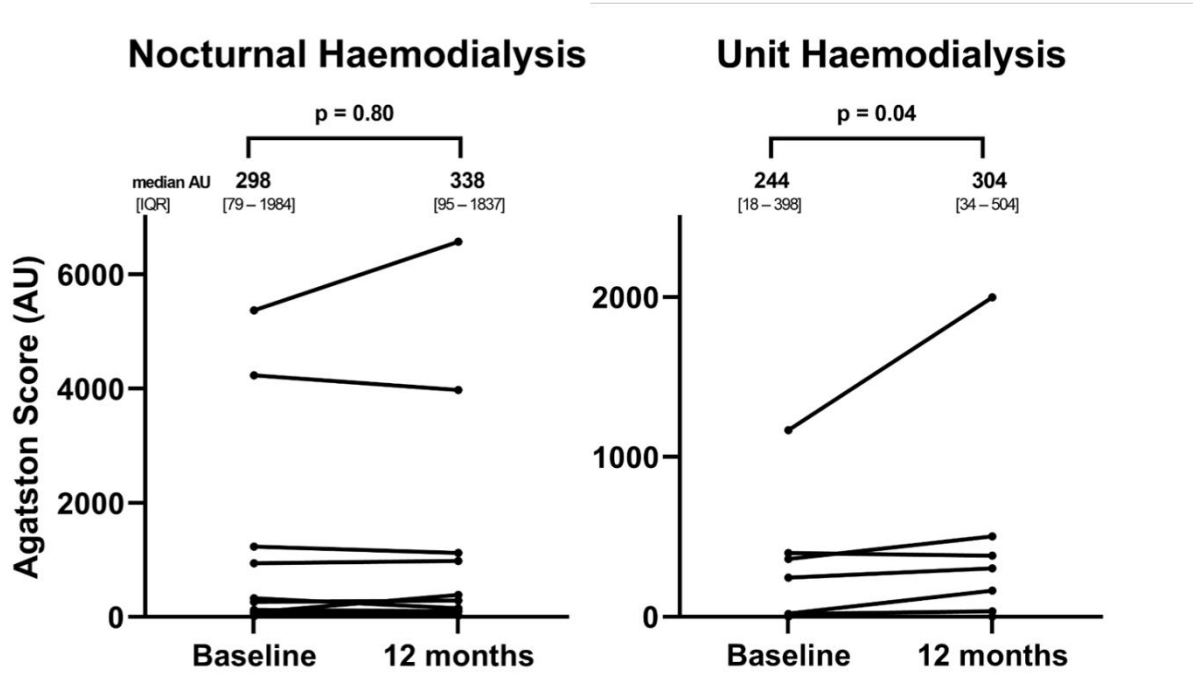


Figure 6.4 Comparison of CAC progression between conventional unit haemodialysis and nocturnal haemodialysis groups

6.6.2 Linear regression analysis

The association between CAC progression and dialysis type was assessed using linear regression analysis. Table 6.3 shows the change in CAC by dialysis type.

Table 6.3 Change in CAC score by dialysis type

Dialysis group	Δtotal CAC (HU)	p value	95% CI range
Haemodialysis	234	0.455	-416 – 884
Nocturnal Haemodialysis	-65	0.726	-456 – 325

CAC: coronary artery calcification, HU: Hounsfield units, CI: confidence interval

The unweighted raw data showed some effect, however due to the small sample size and variability it is hard to interpret. A weighting was therefore applied to groups for different ΔCAC score parameters to look at the significance of a clinical as opposed to a statistical effect.

Table 6.4 Weighting applied to calcification score determined by clinical significance of change in CACS

Δinterval CACS	>100HU	>0 – 100	<0	<-100
Weighting	-1	0	1	2

CACS: coronary artery calcification score, HU: Hounsfield units

The weighting was allocated according to the clinical significance of the change in calcification i.e. progression, non-progression and regression in calcification as illustrated in Table 6.4. Following application of the weighting, the corrected change in CAC score by dialysis type is shown in Table 6.5.

Table 6.5 Change in CAC score by dialysis type (weighted)

Dialysis group	Δtotal CAC (HU)	p value	95% CI range
Haemodialysis	137.67 ± 43.9	***0.011**	39.8 – 235.6
Nocturnal Haemodialysis	-143.29 ± 40.5	***0.005**	-233.5 - -53

CAC: coronary artery calcification, HU: Hounsfield units, CI: confidence interval

When analysed using weighted linear regression analysis a statistically significant difference in Δtotal CAC was seen between dialysis groups as shown in Table 6.6. Conventional dialysis subjects demonstrated significant progression in CAC 137.67 ± 43.9 HU, p=0.008 as compared to significant regression in CAC -143.29 ± 40.5 HU in the nocturnal group, although this did not reach significance.

For conventional haemodialysis there was very high correlation between progression of calcification and the severity of baseline calcification. Absolute change in calcification, as calculated by (CAC_{12} – $CAC_{baseline}$)/ $CAC_{baseline}$ (p=0.006, r=0.9) and annualised change (p=0.008, r=0.89). The change in calcification severity was not significant in the nocturnal group as compared to baseline. Suggesting that improvements in vascular calcification can be seen independent of the severity of calcification when starting extended hours therapy.

Table 6.6 Correlation of CAC progression with severity of baseline calcification

	Haemodialysis		**Nocturnal Haemodialysis**	
	p value	**r value**	**p value**	**r value**
Absolute Δ Total CAC	***0.006**	**0.9**	0.099	0.55
	All dialysis subjects: p=0.047, r value 0.487			
Relative Δ % change/ study	0.463	-0.34	0.573	-0.2
Δ Total change in CT-CAC/ year	***0.008**	**0.89**	0.233	0.42

*2 tailed correlation significant at 0.01 level, CAC: coronary artery calcification

6.7 Hokanson's method for analysis of change in CAC

By looking at the difference of the square root of two scores over time, Hokanson's method takes in to account a small or big baseline score when analysing a change in CACS as calculated by $\sqrt{CAC}_{follow\ up}$ - $\sqrt{CAC}_{baseline}$. Hokanson's square root method

was used to calculate CAC progression for each dialysis group. The individual results for each dialysis participant are shown in Table 6.7 and Table 6.8

Table 6.7 Hokanson's square root method for CAC progression for conventional haemodialysis group

$\sqrt{CAC_{baseline}}$ (HU)	$\sqrt{CAC_{follow\text{-}up}}$ (HU)	Hokanson's value	Significant > 2.5
19	22.44994	3.449944321	Y
19.94994	19.57039	-0.379551552	N
4.242641	5.830952	1.588311208	N
34.16138	44.69899	10.53761157	Y
4.358899	12.76715	8.408246391	Y
0	1	1	N

Table 6.8 Hokanson's square root method for CAC progression for nocturnal haemodialysis group

$\sqrt{CAC_{baseline}}$ (HU)	$\sqrt{CAC_{follow\text{-}up}}$ (HU)	Hokanson's value	Significant > 2.5
11.26943	10.0995	-1.169922731	N
9.165151	19.72308	10.55793153	Y
65.05382	63.06346	-1.990363767	N
35.14257	33.52611	-1.616457553	N
18.22087	12.4499	-5.77096756	N
73.25981	81.05554	7.795724887	Y
16.21727	16.91153	0.694259785	N
3.872983	5.196152	1.323169076	N
7.937254	8.660254	0.723000105	N
30.65942	31.36877	0.709354849	N

When analysing progression using the Hokanson's square route method, there was no difference in CAC progression between groups as compared by Mann-Whitney test ($p=0.079$) although this tended towards significance.

Table 6.9 Correlation of markers of bone mineralisation, oxidative stress and inflammation

Markers of bone mineralisation	Absolute change (Δ Total) CACS		Relative change (Δ percent change/ time) CACS		Δ change in CACS/ year	
	HD	NHD	HD	NHD	HD	NHD
ΔPO4-	0.215 (r=0.579)	0.865 (r=0.346)	0.535 (r=0.570)	0.265 (r=0.346)	0.215 (r=0.61)	1 (r=-0.415)
ΔCa2+	0.908 (r=0.032)	0.252 (r=0.108)	0.848 (r=0.880)	0.589 (r=0.108)	0.908 (r=0.45)	0.222 (r=0.378)
ΔPTH	0.253 (r=-0.244)	0.544 (r=0.365)	0.589 (r=-0.816)	0.637 (r=0.365)	0.253 (r=-0.249)	0.668 (r=0.225)
Markers of inflammation						
ΔCRP	0.215 (r=0.536)	0.260 (r=-0.30)	0.052 (r=0.750)	***0.021 (r=0.018)**	0.215 (r=0.536)	0.420 (r=-0.55)
ΔIL-6	0.589 (r=-0.339)	0.920 (r=-0.21)	0.879 (r=0.360)	0.276 (r=-0.28)	0.589 (r=-0.301)	0.777 (r=-0.28)
ΔIL-18	0.432 (r=-0.672)	0.154 (r=0.488)	0.76 (r=0.570)	0.244 (r=0.305)	0.432 (r=-0.649)	0.229 (r=0.305)
ΔBMP-6	***0.03 (r=-0.299)**	0.346 (r=-0.289)	0.562 (r=-0.271)	0.381 (r=-0.251)	***0.03 (r=-0.298)**	0.582 (r=-0.251)
ΔAGE	0.119 (r=-0.662)	0.265 (r=0.705)	0.879 (r=-0.123)	0.318 (r=0.625)	0.119 (r=-0.674)	0.275 (r=0.625)
Δhepcidin	0.535 (r=0.631)	0.973 (r=0.170)	0.383 (r=-0.150)	0.511 (r=-0.394)	0.535 (r=0.625)	0.582 (r=-0.394)
Markers of oxidative stress						
ΔTBARS	0.148 (r=-0.458)	0.354 (r=-0.231	***0.014 (r=-0.582)**	0.603 (r=-0.181)	0.148 (r=-0.473)	0.446 (r=-0.181)

P value: Spearmans correlation (p<0.05) Hb: haemoglobin, TSAT: transferrin saturation, Ret-He: reticulocyte haemoglobin equivalent, Ca^{2+}: serum calcium, BMP: bone morphogenic protein, IL-6: interleukin-6, TBARS: Thiobarbituric Acid Reactive Substances, AGE: advanced glycation end products, CRP: c reactive protein

Table 6.10 Correlation of CAC progression with significant baseline markers

	Absolute ΔTotal CACS		Relative (%change/ time) CACS	
Baseline:	**Haemodialysis**	**Nocturnal Haemodialysis**	**Haemodialysis**	**Nocturnal Haemodialysis**
Ca2+	*0.019 (r=-0.89)		*0.042 (r=-0.83)	
Hb	*0.005 (r=-0.94)			
Ret-He	*0.042 (r=-0.83)			
TSAT		*0.014 (r=0.74)		*0.025 (r=0.7)
Hepcidin		*0.024 (r=0.7)		*0.006 (r=0.8)
BMP-6	*0.03 (r=-0.8)			
IL-6	*0.023 (r=0.821)			
TBARS			*0.023 (r=0.821)	
AGE				*0.033 (r=-0.67)
Troponin	*0.003 (r=0.93)			

P value: Spearmans correlation (p<0.05). Hb: haemoglobin, TSAT: transferrin saturation, Ret-He: reticulocyte haemoglobin equivalent, Ca^{2+}: serum calcium, BMP: bone morphogenic protein, IL-6: interleukin-6, TBARS: Thiobarbituric Acid Reactive Substances, AGE: advanced glycation end products, CRP: c reactive protein

6.7.1 Analysis by CACS progression status

Progressor status was described by change in CACS. For this cohort, progressors were defined as an absolute increase in CACS >20HU and an annual relative increase >15%. Non-progressors did not meet both criteria, regressors had a reduction in absolute and relative CACS.

There is no consensus definition for CAC progression, Budoff et al., defined CAC progression by Hokanson's square root method: -

$$\sqrt{CAC}_{follow\ up} - \sqrt{CAC}_{baseline}$$

This method is not affected by the baseline score and an increase of >2.5 or a >15% annual increase is considered to reflect true change (Hokansen JE et al., 2004) The Multi-Ethnic Study of Atherosclerosis (MESA) study recognised progressors by i) an absolute increase in CACS >10HU and ii) an annual relative increase >10%. A linear relationship between CAC progression and risk of cardiovascular events was demonstrated. However coronary atherosclerosis and CAC progression are non-linear and unpredictable (Singh R et al.,1984).

In addition to CAC burden, CAC progression portends poor prognosis for all-cause mortality in incident dialysis patients. Bellasi et al., found vascular calcification progression modulated the risk associated with vascular calcification burden in incident dialysis patients. Mortality was associated with older age, diabetes, history of a previous atherosclerotic cardiovascular event and a high vascular calcification burden. Modulation of CAC progression with non-calcium-based phosphate binders attenuated the association of progression and outcomes (Bellasi A et al, 2021).

6.8 Discussion

CKD is associated with accelerated coronary calcification. The Chronic Renal Insufficiency Cohort (CRIC) study reported CKD to be associated with myocardial infarction, heart failure and stroke (Lash JP et al., 2009). CAC, as detected by cardiac computerised tomography is highly correlated with atherosclerotic plaque burden and risk of cardiovascular events in non-dialysis and dialysis dependent populations (Nelson AJ et al., 2020, Dilsizian V et al., 2021). Block et al., reported an independent association of CAC burden and all-cause mortality, advocating its use for risk-prognostication in the incident haemodialysis population (Block GA et al., 2007). Budoff et al., found that CAC progression analysis added incremental value to that of the baseline calcification score (Budoff MJ et al., 2010).

6.9 Limitations

CAC scores were analysed by change in score from baseline to follow up (ΔCACS). Several authors (Henein MY et al, 2011, Puri R er al., 2015, Andelius L et al., 2018, Lai R et al., 2020) chose not to analyse the change in CAC score due to concerns it does not control for baseline imbalance due to regression to the mean (Vickers AJ et al., 2001). Comparing the absolute or relative difference in CAC at baseline and follow up may not be accurate if CAC progression is non-linear (Schermund A et al., 2001).

6.10 Conclusion

Strong evidence exists to support the validity of CACS in CKD and ESRD, including those receiving haemodialysis. As a validated, independent prognostic tool associated with low dose radiation, CACS is advocated for cardiac risk stratification

within the CKD population. A zero score is associated with a high negative predictive value and a low risk of coronary artery disease and events. Jansz et al found median CACS to be higher in haemodialysis patients than those with CKD (210 [19 – 859] vs. 58 [0 – 254]) CAC predicts cardiovascular risk in CKD (Jansz TT et al., 2020). A score of >400 is highly predictive in identifying significant CAD in the CKD population. However, this does not extrapolate to patients receiving dialysis where hyperphosphatemia, deranged mineral bone profiles and accelerated vascular calcification occur (Jansz TT et al., 2021).

The Arterial Calcifications in Nocturnal Haemodialysis and Renal Transplantation Versus Conventional Dialysis (NOCTx) study assessed annualised CAC progression in patients receiving different renal replacement therapy modalities; - renal transplant, peritoneal dialysis, conventional and nocturnal haemodialysis. CAC progression was not significantly different between treatment groups with comparable progression seen in kidney transplantation, conventional and nocturnal haemodialysis over the 3 year follow up period (Jansz TT et al., 2020). Peritoneal dialysis was associated with more CAC progression than haemodialysis as analysed by the square root transformed volume score per year (ΔCAC SQRV) 92 vs 492mm^3 [adjusted difference 436, -47 – 919; p=0.08] (Jansz TT et al., 2018). Further standardised studies with extended follow up periods are required to assess cardiovascular outcomes for all RRT modalities.

CHAPTER 7

PLASMA MARKERS OF OXIDATIVE STRESS AND INFLAMMATION

7.1 Introduction

7.1.1 Oxidative stress and inflammation in ESRD

Oxidative stress and inflammatory pathways interlink, influencing CKD progression and thereafter, therapy response. An increase in pro-oxidants and impaired antioxidant capacity is associated with the uraemia of ESRD. This complex interplay, although not fully understood, is considered amongst other complications of CKD; - uraemic toxins, renal anaemia, disordered calcium-phosphate homeostasis, protein-energy malnutrition, endothelial dysfunction, impaired sympathetic regulation and impaired coagulation, to contribute to accelerated atherogenesis (Podkowinska A et al., 2020).

Haemodialysis, as a bio-incompatible renal replacement therapy further exacerbates the oxidative stress of ESRD where uraemic toxins promote the development of an inflammatory state. Complement activation, increased pro-inflammatory lymphocyte expression, platelet activation and neutrophil degranulation result in consequent cardiac remodelling and failure (Satta H et al., 2021). Low molecular weight antioxidants undergo haemofiltration, whilst the dialysis membrane and dialysate activate leucocytes and stimulate ROS production, augmenting inflammatory pathways (Sangeetha LB et al., 2018, Navarro-Garcia, JA et al., 2019).

Renal anaemia and oxidative stress are interrelated. Iron therapy is frequently used to treat renal anaemia in patients undergoing haemodialysis. The administration of IV iron results in the supersaturation of iron sequestration proteins transferrin and ferritin, with excess free iron exerting oxidative properties. Oxidative stress alters membrane properties of red blood cells, further worsening the iron deficiency

anaemia. Renal anaemia triggers the accumulation of oxidative products in haemodialysis patients, correction of anaemia improves oxidative stress status (Rysz J et al., 2020).

It is hypothesised that the extended hours' treatment of nocturnal haemodialysis ameliorates the impact of oxidative stress. Dialysis-related factors are known to include; - the biocompatibility of the dialyser membrane and its role in the development of endothelial dysfunction. Type and dosage of anticoagulant and its impact on oxidative stress products and polymorphonuclear degranulation; - for example citrate as a low molecular weight heparin (LMWH) substitute, which is regularly used for continuous veno-venous haemodiafiltration (CVVHDF) in critical care, is thought to significantly abrogate oxidative stress product release and degranulation, dependent upon divalent calcium cations. Haemodialysis with heparin or dalteparin circuit anticoagulation was accompanied by immediate degranulation at the start of haemodialysis (Gritters M et al., 2006). Medications administered, dialysate solution, use of an indwelling vascular catheter for access and duration of haemodialysis treatment (Liakopoulos V et al., 2017).

An increased inflammatory state is seen in low clearance patients (eGFR <15ml/min) approaching the need for RRT. The degree of eGFR impairment is a significant independent determinant of inflammatory activity and HRQoL (Pecoits-Filho R et al., 2003). Impaired residual renal function in ESRD patients is associated with depression, impaired HRQoL and fatigue. In terms of patient-reported outcomes fatigue is a well-reported complication of long-term haemodialysis alongside insomnia, muscle cramps and exhaustion, and affects both quality of life and survival

(Bossola M et al., 2015, Assad HN et al., 2022). The pathology of fatigue in haemodialysis patients is multifactorial, contributed to by anaemia, malnutrition, depression, ageing, inflammation and autonomic dysfunction (Ju A et al., 2018). Clinically relevant fatigue are subjective symptoms that reflect reduced activities of daily living (ADL).

The increase in post-dialysis fatigue experienced by patients undertaking conventional haemodialysis on the day of and after treatment, suggests a role for oxidative stress as a contributory factor. Symptoms are mediated by dialysis-induced changes in oxidative stress and inflammatory pathways and are reported in more than fifty percent of prevalent patients (Flythe JE et al., 2018). Patient-reported symptoms of fatigue and “wash-out” associated with conventional haemodialysis are not a feature of nocturnal haemodialysis.

More recently studies have shown that low free triiodothyronine (T3) levels are related to inflammatory status and endothelial activation in patients on haemodialysis. Netti GS et al., observed improved survival rates (88% vs 61.3%, p=0.001) and lower incidence of cardiovascular events (8% vs 40%, p=0.001) in patients undertaking nocturnal as compared to conventional haemodialysis after propensity score matching. Free T3 levels were maintained at normal levels in nocturnal as compared to conventional haemodialysis patients (Netti GS et al., 2020).

7.2 Aims of the chapter

The aim of the study was to compare and evaluate the cardiovascular impact of two forms of haemodialysis; conventional vs. extended hours nocturnal haemodialysis as compared with a matched control group. The aim of this chapter is to appraise the assessment of these dialysis modalities on oxidative stress and inflammation. The panel markers were chosen based on the existing knowledge base from current literature. Biomarkers selected to include on the oxidative stress panel were: - TBARS as a marker of lipid peroxidation, AGE as a marker of protein oxidation, BMP-6 an antioxidant and key regulator of hepcidin – the major regulator of iron metabolism and part of the TGF-β family, downregulated by oxidative stress and upregulated by iron. Serum markers of inflammation included hs-CRP, IL-6, IL-18, MCP-1 a chemokine for macrophage recruitment and VEGF; a proinflammatory cytokine stimulated for release by HIF on account of inflammatory stimuli or hypoxia triggered by oxidative stress.

A secondary aim was to establish whether there was any correlation between serum markers of oxidative stress and inflammation with biomarkers of cardiac strain: - cTnT and NT-proBNP.

7.3 Results

Markers of inflammation IL-6, IL-18 and VEGF were found to change with time within the healthy volunteer group as presented in Table 7.1. However, in this group no change was demonstrated for markers of oxidative stress or cardiac strain.

In the conventional haemodialysis group, a reduction in IL-6 (p=0.025) was demonstrated over the study period alongside an initial reduction in NT-proBNP (p=0.049) following dialysis initiation as presented in Table 7.2.

A significant reduction in TBARS (p=0.037) as a marker of oxidative stress and IL-6 (p=0.037) as a marker of inflammation was demonstrated in the nocturnal haemodialysis group as presented in Table 7.3. A significant reduction in IL-6 (p=0.037) and IL-18 (p=0.031) was seen in the healthy group at 12 months. This questions the validity of the control with a temporal change demonstrated. The same sampling approach was utilised for all tests and no issues were identified with freezer stability. One explanation may be the population-wide impact of COVID with a global significant change in social interaction and a subsequent change in the level of communicable disease.

A significant difference for IL-6 was seen between all groups at 0 (p=0.001) and 3 months (p <0.001) which was tending towards significance at 12 months (p=0.056) using Kruskal-Wallis test. Mann-Whitney test comparing the control group and NHD was significant for IL-6 at 0 (p=0.002), 3 (p<0.001) but not 12 months (p=0.075).

Kruskal-Wallis test between all groups showed a statistically significant difference for Troponin between the groups at 0, 3 and 12 months (p<0.001). Mann-Whitney test comparing the control group and NHD was significant for troponin at 0, 3 and 12 months (p<0.001).

However, no difference was demonstrated between conventional HD and NHD at 0, 3 or 12 months (Kruskal-Wallis and Mann-Whitney tests) for any marker of oxidative stress or inflammation.

Table 7.1 Oxidative stress and inflammatory markers within the healthy volunteer group, changes with time

Months	Baseline	3	12	$^{+}$p value^{a}	$^{+}$p value^{b}	$^{+}$p value^{c}
TBARS$^{\#}$ (µM)	5.07 [4.14 – 5.95]	4.37 [3.17 – 6.33]	4.21 [3.92 – 6.35]	0.721	0.721	0.285
AGE$^{\#}$ (AU/mg)	0.18 [0.09 – 0.33]	0.14 [0.03 – 0.33]	0.25 [0.05 – 0.62]	0.959	0.093	0.285
BMP-6$^{\#}$ (pg/ml)	0.2 [0.2 – 33.2]	0.2 [0.2 – 62.28]	0.93 [0.2 – 32.95]	0.465	0.345	0.686
Hepcidin$^{\#}$ (pg/ml)	342.79 [322.39 – 407.37]	362.4 [325.41 – 382.78]	520 [125.57 – 520]	-	0.575	0.721
IL-6$^{\#}$ (pg/ml)	2.45 [1.42 – 3.23]	2.14 [1.14 – 3.17]	0.5 [0.5 – 0.74]	0.594	0.066	***0.037**
IL-18 (pg/ml)	53.54 ± 36.86	54.26 ± 34.84	33.38 ± 30.59	0.856	0.059	***0.031**
MCP-1$^{\#}$ (pg/ml)	100.68 [75.31 – 261.31]	101.94 [70.48 – 257.58]	76.2 [53.73 – 200.85]	0.445	0.139	0.114
VEGF$^{\#}$ (pg/ml)	25.78 [1 – 241.57]	27.19 [1 – 165.05]	13.29 [1 – 140.91]	0.866	***0.028**	0.249
Troponin$^{\#}$ (ng/L)	6 [4-12]	8 [4.5 – 12.5]	7 [5-12]	0.458	0.739	0.809
NT-proBNP$^{\#}$ (pg/ml)	220.63 [180.9 – 6027.66]	267.76 [174.78 – 5161.13]	363.8 [163.99 – 6476.79]	0.241	0.508	0.445

Normally distributed data expressed as mean ± SD, $^{+}$p: paired samples t-test, ^{a}p value 0 – 3 months, ^{b}p value 3 - 12 months, ^{c}p value 0 – 12 months, $^{\#}$non-parametric data median [IQR], $^{+}$p: comparison of parameters at baseline, 3 and 12 months (Wilcoxon signed ranks test). IL-18: interleukin-18, IL-6: interleukin-6, BMP-6: bone morphogenic protein-6, AGE: advanced glycation end products, MCP-1: monocyte chemoattractant protein-1, VEGF: vascular endothelial growth factor, TBARS: thiobarbituric acid reactive substances, NT-proBNP: n-terminal pro b-type natriuretic peptide

Table 7.2 Oxidative stress and inflammatory markers in the conventional haemodialysis group, changes with time

Months	Baseline	3	12	+p value[a]	+p value[b]	+p value[c]
TBARS[#] (µM)	4.76 [3.28 – 8.24]	4.87 [3.52 – 6.33]	4.17 [3.27 – 4.78]	0.401	0.327	0.263
AGE[#] (AU/mg)	0.23 [0.18 – 0.36]	0.33 [0.16 – 0.55]	0.23 [0.16 – 0.3]	0.674	0.161	0.401
BMP-6[#] (pg/ml)	0.2 [0.2 – 0.26]	0.2 [0.2-0.2]	0.2 [0.2 – 0.38]	0.655	0.655	0.180
Hepcidin[#] (pg/ml)	377.1 [322.47 – 440.47]	325.74 [302.97 – 371.01]	336.53 [106.1 – 363.97]	-	0.779	0.123
IL-6[#] (pg/ml)	6.02 [4.24 – 17.9]	4.53 [3.46 – 6.75]	3.41 [0.5 – 4.3]	0.484	0.208	***0.025**
IL-18 (pg/ml)	94.89 ± 31.98	88.81 ± 20.06	76.13 ± 36.17	0.399	0.271	0.076
MCP-1[#] (pg/ml)	90 [85.23 – 108.41]	80.65 [71.85 – 96.84]	71.94 [53.06 – 79.07]	0.093	0.161	0.050
VEGF[#] (pg/ml)	6.24 [1 – 39.08]	7.64 [1.05 – 37.35]	7.01 [2 – 17.57]	0.463	0.237	0.345
Troponin[#] (ng/L)	64.5 [19.25 – 216]	103.5 [21 – 124]	51 [20 – 88]	0.271	0.123	0.233
NT-proBNP[#] (pg/ml)	294.47 [267.25 – 599.14]	280.25 [218.03 – 465.32]	265.83 [168.4 – 534.21]	***0.049**	1	0.093

Normally distributed data expressed as mean ± SD, +p: paired samples t-test, [a]p value 0 – 3 months, [b]p value 3 - 12 months, [c]p value 0 – 12 months, [#]non-parametric data median [IQR], +P: Wilcoxon signed ranks test. IL-18: interleukin-18, IL-6: interleukin-6, BMP-6: bone morphogenic protein-6, AGE: advanced glycation end products, MCP-1: monocyte chemoattractant protein-1, VEGF: vascular endothelial growth factor, TBARS: thiobarbituric acid reactive substances, NT-proBNP: n-terminal pro b-type natriuretic peptide

Table 7.3 Oxidative stress and inflammatory markers in the nocturnal haemodialysis group, changes with time

Months	Baseline	3	12	$^{+}$p value[a]	$^{+}$p value[b]	$^{+}$p value[c]
TBARS[#] (µM)	6.15 [4.1 – 7.3]	5.13 [4.89 – 5.55]	3.53 [3-3.7]	0.208	***0.036**	***0.037**
AGE[#] (AU/mg)	0.23 [0.20 – 0.39]	0.35 [0.22 – 0.43]	0.33 [0.15 – 0.42]	0.327	0.575	0.114
BMP-6[#] (pg/ml)	0.2 [0.2 – 0.2]	0.2 [0.2 – 0.2]	0.2 [0.2 – 0.2]	1	1	0.18
Hepcidin[#] (pg/ml)	370.48 [340.06 – 386.68]	367.23 [248.67 – 380.91]	349.72 [120.13 – 398.88]	-	0.263	0.333
IL-6[#] (pg/ml)	117.49 ± 58.67	105.43 ± 54.99	74.64 ± 30.18	0.195	0.187	***0.037**
IL-18 (pg/ml)	7.9 [5.14 – 22.62]	7.46 [5.16 – 17.56]	23.91 [0.5 – 83.73]	0.779	***0.036**	0.139
MCP-1[#] (pg/ml)	102.23 [88.5 – 123.33]	81.76 [61.85 – 95.13]	77.95 [74.2 – 95.98]	***0.012**	0.779	0.203
VEGF[#] (pg/ml)	8.4 [1.63 – 31.21]	4.45 [1.36 – 8.51]	5.16 [1 – 25.3]	0.612	0.612	0.889
Troponin[#] (ng/L)	36 [33 – 54]	50 [38 – 62]	41 [39 – 124]	0.507	0.594	0.374
NT-proBNP[#] (pg/ml)	249.53 [234.84 – 311.23]	253.3 [223.49 – 451.9]	255.27 [182.11 – 553.79]	0.674	0.674	0.959

Normally distributed data expressed as mean ± SD, $^{+}$p: paired samples t-test, [a]p value 0 – 3 months, [b]p value 3 - 12 months, [c]p value 0 – 12 months, [#]non-parametric data median [IQR], $^{+}$P: Wilcoxon signed ranks test. IL-18: interleukin-18, IL-6: interleukin-6, BMP-6: bone morphogenic protein-6, AGE: advanced glycation end products, MCP-1: monocyte chemoattractant protein-1, VEGF: vascular endothelial growth factor, TBARS: thiobarbituric acid reactive substances, NT-proBNP: n-terminal pro b-type natriuretic peptide

Table 7.4 Absolute Δ change in oxidative stress, inflammatory markers and markers of cardiac strain

Dialysis group	Healthy Volunteer	Haemodialysis	Nocturnal Haemodialysis	$^{+}$p value^{a}	$^{+}$p value^{b}	$^{+}$p value^{c}
ΔTBARS (μM)	-0.63 ± 2.33	-1.23 ± 3.05	-1.6 ± 1.87	0.652	0.301	0.748
ΔAGE (AU/mg)	0.12 ± 0.38	-0.06 ± 0.18	0.17 ± 0.18	0.212	0.787	0.107
ΔBMP$^{\#}$ (pg/ml)	0 [-3.2 – 1.04]	0 [0-0.12]	0 [0 – 0.25]	0.84	0.723	0.903
ΔHepcidin (pg/ml)	7.95 ± 188.37	-96.1 ± 205.95	-85.4 ± 171.47	0.287	0.262	0.908
ΔIL-6$^{\#}$ (pg/ml)	-1.59 [-2.58 - -0.06]	-3.3 [-8.8 - -0.46]	-10 [-4.93 – 37.2]	0.183	0.364	0.155
ΔIL-18 (pg/ml)	-20.16 ±24.94	-18.77 ± 25.54	-45.6 ± 58.8	0.909	0.232	0.217
ΔCRP (mg/L)		-4.62 ± 20.9	10.38 ± 16.23			0.131
ΔTroponin$^{\#}$ (ng/L)	0.5 [-1.25 – 1.25]	-4.5 [-136.8 – 5.5]	3 [-15.6 – 36.5]	0.325	0.676	0.197
ΔNTproBNP$^{\#}$ (pg/ml)	28.3 [-31.5 – 395.6]	-98.8 [-172.8 – 38.36]	-21.8 [-76.1 – 242.9]	0.110	0.450	0.183

Normally distributed data represented as mean ± SD, $^{+}$p value (independent samples t-test), p value$_a$: HV vs HD, p value$_b$: HV vs NHD, p value$_c$: HD vs NHD, $^{\#}$non-parametric data represented as median [IQR], p value (Mann-Whitney test), p value$_a$: HV vs HD, p value$_b$: HV vs NHD, p value$_c$: HD vs NHD. IL-18: interleukin-18, IL-6: interleukin-6, BMP-6: bone morphogenic protein-6, AGE: advanced glycation end products, MCP-1: monocyte chemoattractant protein-1, VEGF: vascular endothelial growth factor, TBARS: thiobarbituric acid reactive substances, NT-proBNP: n-terminal pro b-type natriuretic peptide

No significant change in oxidative stress or inflammatory marker was seen when comparing the interval change in parameters with time for dialysis groups or the healthy volunteers as presented in Table 7.4.

7.4 Correlation of markers of oxidative stress and inflammation

7.4.1 Healthy volunteers

Correlation for non-parametric data was assessed using Spearman's rank correlation. Baseline MCP-1 correlates with baseline VEGF (p=0.007, r=0.8) BMP-6 (p=0.001, r=0.9) hepcidin (p=0.047, r =-0.64) NT-pro-BNP (p=0.017, r=0.73) and VEGF at 12 months (p=0.005, r=0.81), BMP-6 at 12 months (p=0.01, r=0.77), Δhepcidin (p=0.02, r=0.72) but not IL-6, IL-18, TBARS, AGE or troponin. Baseline VEGF correlates with BMP-6 (p=0.001, r=0.87), hepcidin (p=0.012, r=-0.76) Δhepcidin (p=0.049, r=0.63) and NT-pro-BNP (p=0.014, r=0.74) and MCP-1 at 12 months (p=0.005, r=0.8), BMP-6 at 12 months (p<0.001, r=0.95), NT-proBNP at 12 months (p=0.002, r=0.84).BMP-6 correlates with baseline hepcidin (p=0.045, r=-0.64), Δhepcidin (p=0.023, r=0.7), baseline NT-proBNP (p=0.003, r=0.83), NT-proBNP at 12 months (p=0.002, r=0.85) and ΔNT-proBNP (p=0.046, r=0.64), MCP-1 at 12 months (p=0.001, r= 0.87) VEGF at 12 months (p<0.001, r=0.9).

Baseline IL-18 correlated with AGE at 12 months (p=0.048, r=-0.64), ΔAGE (p=0.048, r=-0.64) troponin at 12 months (p=0.034, r=-0.67) and ΔNTproBNP (p= 0.038, r=0.66). Baseline AGE/ IL-6 no correlation. Baseline TBARS correlates with IL-18 at 12 months (p=0.043, r=0.65), IL-6 at 12 months (p=0.031, r=0.68), and ΔIL-6 (p=0.038, r=0.66). Baseline hepcidin correlates with MCP-1 at 12 months (p=0.043, r=-0.65), VEGF at 12 months (p=0.005, r=-0.81), BMP-6 at 12 months (p=0.02, r=-

0.72), Δhepcidin correlates with Δtroponin (p=0.002, r=0.86). Baseline troponin correlates with 12-month hepcidin (p=0.016, r=-0.73). Baseline NT-proBNP correlates with MCP-1 at 12 months (p=0.033, r=0.67), VEGF at 12 months (p=0.014, r=0.74), BMP-6 at 12 months (p=0.002, r=0.85).

7.4.2 Conventional haemodialysis

MCP-1 baseline correlates with ΔIL-18 (p=0.045, r=0.7), MCP-1 at 12 months correlates with IL-18 at 12 months (p=0.047, r=0.7), ΔIL-18 (p=0.028, r=0.8), ΔNT-proBNP (p=0.047, r=0.7). Baseline VEGF correlates with baseline BMP-6 (p=0.022, r=0.8) and BMP-6 at 12 months (p=0.022, r=0.8). Baseline BMP-6 correlates with baseline troponin (p=0.039, r=-0.7), VEGF at 12 months (p=0.026, r=0.8), TBARS at 12 months (p=0.027, r=0.8). Baseline TBARS correlates with MCP-1 at 12 months (p=0.028, r=-0.8), ΔNT-proBNP (p=0.001, r=-0.9). Baseline AGE correlated with 12-month hepcidin (p=0.002, r=0.9). Baseline troponin correlates with 12-month BMP-6 (p=0.039, r=-0.7).

7.4.3 Nocturnal haemodialysis

Baseline MCP correlates with VEGF at 12 months (p=0.001, r=0.9), BMP-6 at baseline and 12 months (p=0.029, r=0.7), ΔBMP-6 (p=0.024, r=0.7). Baseline VEGF correlates with NT-proBNP (p=0.012, r=0.8) and BMP-6 at baseline and 12 months (p=0.029, r=0.7). Baseline BMP-6 correlates with VEGF at 12 months (p=0.027, r=0.7), baseline and 12-month NT-proBNP (p=0.029, r=0.7), Baseline TBARS correlates with IL-18 at 12 months (p=0.016, r=0.7). Baseline hepcidin correlates with NT-proBNP (p=0.033, r=-0.7). Baseline IL-6 correlates with 12-month TBARS (p=0.048, r=0.64). Baseline NT-proBNp correlates with ΔBMP-6 (p= 0.024, r=0.7).

7.5 Discussion

The kidneys are a vital source of vital antioxidants, the oxidative stress of uraemia and its ensuing cardiovascular complications are a well-recognised side-effect of the upregulation of inflammatory markers observed in CKD. Numerous studies indicate that this increased state of oxidative stress is exacerbated by haemodialysis (Russa D et al., 2019).

Haemodialysis clears the lower molecular weight antioxidants (Navarro-Garcia JA et al., 2019) in addition to the dialysis itself the oxidative state is affected by impaired residual renal function and subsequent uraemia. Levels of oxidative stress have been shown to be higher in ESRD patients receiving peritoneal dialysis than uraemic low-clearance CKD patients, but lower than patients receiving conventional haemodialysis (Rysz J et al., 2020). Nocturnal haemodialysis with its extended hours therapy normalises many physiological processes.

IL-18 levels reduced with conventional haemodialysis over time but were found to increase in the nocturnal haemodialysis group. Porazko et al., suggested that IL-18, but not IL-6 contributed to the development of vascular injury and arteriosclerosis in ESRD patients (Porazko T et al., 2009). Plasma IL-18 is a key factor in atherosclerotic plaque formation and rupture and its reduction may be associated with a reduction in cardiovascular events and an improvement in survival. Other recent studies have shown that elevated serum IL-18 concentrations are associated with proatherogenic lipid profiles and increased cardiovascular risk. Further larger powered studies are required to look at the impact of extended hours dialysis on markers of oxidative stress and inflammation.

A significant reduction in pro-inflammatory cytokine IL-6 was demonstrated in the nocturnal haemodialysis group (117pg/ml ± 59 to 75pg/ml ± 30, p=0.04). Given the importance of IL-6 as a pivotal cytokine within the inflammatory response this requires further study.

A significant change was seen in the control group for IL-6 and IL-18 over the full study period that was not present in the first 3 months, with a drop in all inflammatory cytokines in the control group at 12 months. This was not thought to be due to a sampling or processing error. The sample size was small, the control group may not have been as healthy as expected, however more likely these changes reflected the widespread behavioural changes and impact of the COVID-19 pandemic on the general population. The nocturnal haemodialysis group received treatment at home, unlike the conventional group who were required to attend in centre haemodialysis thrice weekly throughout the period of isolation for the population and thereafter as a vulnerable, high risk group. The reduction in inflammatory markers in the nocturnal population therefore needs to be considered in light of the changes seen in the control population, where population mixing was less than that of those patients who were required to attend hospital. This change is unexplained and unfortunately confounded by historic large scale population changes in behaviour outside of the control of the study environment.

CHAPTER 8

QUALITY OF LIFE ASSESSMENT MEASURES

8.1 Introduction

8.1.1 Quality of life assessment measures

The Short Form 36 (SF-36) is a multidimensional, self-reported mental and physical well-being scale, with 36 items from 10 sets of questions. Introduced in 1993 as part of the Medical Outcomes Study it is the most widely evaluated generic health measure (Ware JE et al., 1993). It is used to indicate the health status of a particular population and to appraise the impact of clinical interventions. It is not specific for dialysis patients and can therefore be used to compare ESRD patients with individuals with preserved renal function.

Normative population data is used to calculate SF-36 scores. Eight dimensions are covered by self-reported questions concerning physical functioning and role limitations, bodily pain, general health perceptions, energy/ vitality, social functioning, emotional role limitations and mental health. Each set varies in the number of questions and response options. A scoring algorithm converts the scores to a range of 0 – 100 where a score of 100 denotes the best possible health.

Regional differences in scores for physical function and bodily pain were reported in Wales (WHS 2011) as compared to the UK in the British ONS Omnibus survey (1992) and the Oxford Healthy Life Survey (1992) (Burholtt V et al., 2011).

Renal replacement therapy impacts HRQoL. Dialysis patients have reported poorer health than the general population (Merkus MP et al., 1997). A meta-analysis found patients receiving peritoneal dialysis had better HRQoL than conventional haemodialysis (Chuasuwan A et al., 2020). The FHN Nocturnal trial included a 12-

month change in SF-36 as one of its co-primary outcomes, a non-significant mean difference of 0.6 (-3.4 to 4.7, p=0.75) was demonstrated reproducing the non-significant findings of Manns BJ et al., where there was no significant difference in overall measures of quality of life with nocturnal as compared to conventional haemodialysis (Rocco MV et al., 2011). However, nocturnal haemodialysis was associated with clinically and statistically significant improvements in selected kidney-specific quality of life domains for burden and effects of kidney disease (Manns BJ et al., 2009).

Conventional haemodialysis is associated with reduced quality of life as well as high morbidity and mortality rates. Patients report feeling ‘washed out’ (Jhamb B et al., 2008) and fatigued after thrice weekly dialysis sessions and require a large pill burden in order to further treat blood pressure and mineral bone disease not corrected by the dialysis prescription.

8.2 Aims of the chapter

The aim of the study was to compare and evaluate the cardiovascular impact of two forms of haemodialysis; conventional vs. nocturnal haemodialysis. The aim of this chapter is to appraise and compare the HRQoL impact of the two dialysis modalities; utilising the SF-36 as a tool. In particular, the mental health and social function scores.

8.3 Results

The present analysis (Table 8.1) examines the changes in transformed mental and social function scores across the dialysis groups at different time points. We

undertook a mixed-effects linear regression interacting the fixed effects of dialysis group and time of measurement, with participant identification as the random effect; this allows the model to correct for the multiple observations from the same individual. Domains of particular interest for review were those of mental health and social function.

Table 8.1 Changes in transformed mental health and social function scores across dialysis groups over the 12-month study period

	Mental health		Social function	
	Coefficient	**95% CI**	**Coefficient**	**95% CI**
Dialysis group				
HV Control	Ref		ref	
Conventional HD	-6.64	-22.78, 9.49	-15.92[d]	-27.39, -4.46
Nocturnal HD	-28.09[a]	-42.98, -13.19	0.12	-10.08, 10.32
Time				
Baseline (0)	Ref		ref	
3 months (1)	4.8	-5.37, 14.98	-5.56	-15.48, 4.37
12 months (2)	5.85[b]	-4.68, 16.36	-1.11	-11.31, 9.09
Dialysis group*time				
HV Control*time 0	ref		ref	
Conventional HD*time 1	-18.65	-35.08, -2.23	12.03	-4.87, 28.42
Conventional HD*time 2	-12.73	-28.45, 4.08	-1.23	-17.89, 15.43
Nocturnal HD*time 1	15.73	-0.32, 31.79	13.45	-3.40, 10.31
Nocturnal HD*time 2	4.81[c]	-10.58, 20.20	-4.29	-20.41, 11.83
[Constant]	83.2	72.95, 93.45	45.56	37.93, 53.18

HV: healthy volunteer, HD: haemodialysis, CI: confidence interval, [a]Mental health coefficient at baseline, compared to control group, [b]effect unchanged with time, [c]change score after 3 months, [d]social function coefficient at baseline, compared to control group.

Other domains analysed in addition to mental health and social functioning scores were physical functioning, general health, vitality, role – physical, role – emotional and bodily pain, as displayed in Table 8.2).

Table 8.2 Changes in SF-36 scores across dialysis groups over the 12-month study period

	MH	PF	GH	VT	RP	SF	BP
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
Time							
Baseline (0)	ref	ref	Ref	ref	Ref	ref	ref
3 months (1)	4.8 (-5.37, 14.97)	-1 (-16.1, 14.1)	-3.5 (-14.12, 7.12)	6.5 (-3.53, 16.53)	0 (-20.96, 20.96)	-5.56 (-15.48, 4.37)	-4.44 (-15.92, 7.04)
12 months (2)	5.85 (-4.68, 16.39)	-0.11 (-15.76, 15.55)	-6.55 (-17.53, 4.43)	3.65 (-6.75, 14.06)	-3.7 (-25.41, 18.01)	-1.11 (-11.31, 9.09)	-4.29 (-16.21, 7.63)
Dialysis group							
HV control	ref	ref	Ref	ref	Ref	ref	ref
HD	-6.65 (-22.78, 9.49)	-43.72 (-67.7, -19.73)	6.43 (-7.92, 20.77)	-36.63 (-55.11, -18.14)	-54.82 (-86.37, -23.27)	-15.93 (-27.39, -4.46)	18.41 (-3.61, 40.42)
NHD	-28.09 (-42.98, -13.2)	-43.17 (-65.3, -21.03)	**13.06 (0.12, 25.99)**	-37.56 (-54.95, -20.17)	-51.85 (-80.75, -22.96)	0.12 (-10.08, 10.32)	**31.85 (11.05, 52.65)**
Dialysis group*time							
HV control*time 0	ref	ref	Ref	ref	Ref	ref	ref
HD*time 1	-18.65 (-35.08, -2.23)	10.68 (-13.72, 35.09)	5.36 (-11.62, 22.34)	5.29 (-11, 21.57)	**39.87 (6.1, 73.64)**	12.04 (-3.53, 27.6)	-1.62 (-20.28, 17.05)
HD*time 2	-12.19 (-28.45, 4.08)	0.11 (-24.06, 24.27)	4.84 (-12.02, 21.7)	9.87 (-6.23, 25.97)	10.38 (-23.09, 43.84)	13.46 (-2.07, 28.98)	7.86 (-10.6, 26.31)
NHD*time 1	15.74 (-0.32, 31.79)	-4.26 (-28.11, 19.6)	-3.41 (-20.05, 13.24)	11.74 (-4.16, 27.65)	-0.82 (-33.86, 32.21)	-1.23 (-16.58, 14.11)	-4.34 (-22.56, 13.89)
NHD*time 2	4.81 (-10.57, 20.2)	7.79 (-15.07, 30.65)	-1.53 (-17.52, 14.47)	8.7 (-6.51, 23.92)	**32.05 (0.37, 63.73)**	-4.29 (-19.14, 10.56)	-3.7 (-21.13, 13.73)

HV: healthy volunteer, HD: haemodialysis, CI: confidence interval, MH: mental health, PF: physical functioning, GH: general health, VT: vitality, RP: role functioning – physical, RE: role emotional, SF: social functioning, BP: bodily pain, text: significantly worse than control, **text**: better than control

Table 8.3 Changes in SF-36 domain scores across dialysis groups over the 12-month study period

Groups	Mental health	Physical functioning	General health	Vitality	Role physical	Role emotional	Social functioning	Bodily pain
HD vs control	-16.93 (-29.37, -4.48)	-40.12 (-58.63, -21.62)	9.83 (0.14, 19.52)	-31.58 (-46.99, -16.16)	-51.67 (-75.56, -27.78)	-38.07 (-61.53, -14.62)	-7.43 (-13.68, -1.18)	20.49 (1.84, 39.13)
NHD vs control	-21.24 (-33.74, -8.74)	-41.99 (-60.58, -23.4)	11.41 (1.68, 21.14)	-30.74 (-46.21, -15.27)	-52.13 (-76.13, -28.13)	-41.44 (-65.01, -17.88)	-1.72 (-7.97, 4.53)	29.17 (10.46, 47.89)
NHD vs HD	-4.31 (-17.28, 8.66)	-1.86 (-21.15, 17.42)	1.58 (-8.59, 11.76)	0.84 (-15.15, 16.83)	-0.46 (-25.46, 24.54)	-3.37 (-27.87, 21.13)	5.71 (-0.93, 12.35)	8.69 (-10.64, 28.01)
Time								
1 vs 0	3.83 (-3.04, 10.69)	1.14 (-9.06, 11.34)	-2.85 (-9.94, 4.24)	12.18 (5.37, 18.99)	10.13 (-5.15, 25.4)	13.02 (-1.1, 27.13)	-1.95 (-8.45, 4.54)	-6.43 (-14.24, 1.38)
2 vs 0	3.4 (-3.19, 9.98)	2.52 (-7.26, 12.31)	-5.44 (-12.27, 1.38)	9.84 (3.32, 16.36)	11.65 (-3.02, 26.33)	10.44 (-3.11, 23.99)	1.94 (-4.36, 8.25)	-2.9 (-10.37, 4.57)
2 vs 1	-0.43 (-7.04, 6.18)	1.38 (-8.44, 11.21)	-2.6 (-9.47, 4.28)	-2.34 (-8.87, 4.2)	1.53 (-13.23, 16.28)	-2.58 (-16.19, 11.04)	3.9 (-2.46, 10.26)	3.53 (-3.96, 11.02)
Groups*time[e]								
control 0 vs 1	4.8 (-5.37, 14.97)	-1 (-16.1, 14.1)	-3.5 (-14.12, 7.12)	6.5 (-3.53, 16.53)	0 (-22.74, 22.74)	853 (-20.96, 20.96)	-5.56 (-15.48, 4.37)	-4.44 (-15.92, 7.04)
control 0 vs 2	5.85 (-4.68, 16.39)	-0.11 (-15.76, 15.55)	-6.55 (-17.53, 4.43)	3.65 (-6.75, 14.06)	639 (-23.53, 23.53)	-3.7 (-25.41, 18.01)	-1.11 (-11.31, 9.09)	-4.29 (-16.21, 7.63)
control 2 vs 2	1.05 (-9.48, 11.59)	0.89 (-14.76, 16.55)	-3.05 (-14.03, 7.93)	-2.85 (-13.25, 7.56)	539 (-13.13, 43.93)	-3.7 (-25.41, 18.01)	4.44 (-5.76, 14.65)	0.16 (-11.76, 12.08)
HD 0 vs 1	**-13.85 (-26.76, -0.95)**	9.68 (-9.48, 28.85)	1.86 (-11.39, 15.11)	11.79 (-1.04, 24.62)	12.81 (-15.81, 41.44)	**39.87 (13.39, 66.35)**	6.48 (-5.51, 18.47)	-6.06 (-20.78, 8.66)
HD 0 vs 2	-6.33 (-18.72, 6.06)	0 (-18.41, 18.41)	-1.71 (-14.5, 11.09)	**13.52 (1.23, 25.8)**	-7.76 (-35.32, 19.81)	6.67 (-18.8, 32.14)	**12.35 (0.64, 24.05)**	**3.57 (-10.52, 17.65)**
HD 1 vs 2	7.52 (-3.64, 18.68)	-9.68 (-26.26, 6.89)	-3.57 (-15.19, 8.05)	1.73 (-9.29, 12.75)	-20.57 (-45.48, 4.35)	**-33.2 (-56.18, -10.21)**	5.86 (-4.92, 16.65)	9.63 (-3, 22.26)
NHD 0 vs 1	**20.54 (8.11, 32.97)**	-5.26 (-23.72, 13.21)	-6.91 (-19.72, 5.91)	**18.24 (5.9, 30.59)**	17.56 (-10.06, 45.18)	-0.82 (-26.36, 24.71)	-6.79 (-18.49, 4.91)	-8.78 (-22.94, 5.37)
NHD 0 vs 2	10.67 (-0.54, 21.88)	7.68 (-8.97, 24.34)	-8.08 (-19.71, 3.56)	**12.35 (1.26, 23.45)**	**42.72 (17.72, 67.71)**	**28.34 (5.27, 51.41)**	-5.4 (-16.19, 5.39)	-7.99 (-20.71, 4.73)
NHD 1 vs 2	-9.87 (-22.44, 2.7)	12.94 (-5.73, 31.61)	-1.17 (-14.2, 11.86)	-5.89 (-18.33, 6.55)	25.15 (-2.86, 53.16)	**29.17 (3.3, 55.03)**	1.39 (-10.6, 13.38)	0.8 (-13.46, 15.06)
Comparison[f]								
NHD 0 vs HD 0	**-21.44 (-37.94, -4.95)**	0.56 (-23.96, 25.07)	6.63 (-8.02, 21.27)	-0.93 (-19.84, 17.98)	-18.87 (-52.62, 14.88)	2.97 (-29.27, 35.21)	**16.05 (4.35, 27.75)**	0.8 (-13.46, 15.06)
NHD 1 vs HD 1	12.95 (-3.87, 29.76)	-14.39 (-39.38, 10.61)	-2.14 (-17.12, 12.84)	5.53 (-13.68, 24.74)	-14.12 (-48.59, 20.36)	**-37.73 (-70.63, -4.82)**	2.78 (-9.21, 14.77)	13.45 (-9.08, 35.97)
NHD 2 vs HD 2	-4.44 (-20.07, 11.19)	8.24 (-14.99, 31.47)	0.26 (-13.39, 13.9)	-2.09 (-20.25, 16.07)	31.61 (-0.08, 63.29)	24.64 (-5.74, 55.02)	-1.7 (-12.49, 9.09)	10.72 (-12.13, 33.58)

HV: healthy volunteer, HD: haemodialysis, CI: confidence interval, 0: baseline, 1: 3 month study visit, 2: 12 month study visit, [e]change in scores by time within groups, [f]comparison of dialysis modalities at 3 time points

8.4 Discussion

8.4.1 Mental health

The analysis in Table 8.1 shows that those in the nocturnal dialysis group reported significantly worse mental health than the controls [a] and that overall the mental health scores did not vary with time [b]. The interaction compared the differences in dialysis groups with the healthy controls at baseline. In the conventional unit haemodialysis group, we can see that although reporting lower scores than the controls at baseline, these differences were not significant. The nocturnal haemodialysis group, however, demonstrated positive change scores that were improved [c] after 3 months (p=0.55), though this improvement was not carried on to 12 months. One explanation for the non-sustained improvement in scores may be the global COVID19 pandemic which occurred between time points 1 and 2. The uncertainty surrounding this, in addition to the burden of chronic disease placing patients into a vulnerable category may well have significantly impacted on individuals' overall mental health and general well-being.

8.4.2 Social functioning.

Those attending in-centre for unit haemodialysis had a significantly reduced score[d], indicating that the patients attending conventional haemodialysis in hospital or at a satellite haemodialysis unit had a lower social functioning, e.g. an ability to fulfil their role within environments such as work, social activities or family roles.

The interaction terms suggest that the unit haemodialysis group improved over time, but not significantly. Interestingly the nocturnal haemodialysis group, overall and over time appear to have reported levels of social function similar to the controls,

which may suggest that nocturnal dialysis does not impact patients social functioning.

8.4.3 Domain analysis SF-36

In order to examine the effects of the changes in time across the groups the estimated marginal mean score differences were calculated between the groups and a series of pairwise comparisons performed (Table 8.3). From the interpretation of this analysis by group; both dialysis groups were significantly different from the control group for all the domains and were not substantially different. From the interpretation of this analysis by time; there was only a significant improvement in vitality.

The groups*time interaction looks first at the changes in scores by time within the groups[e]. Firstly, there was no change in the control group over time. The conventional haemodialysis group saw a decrease in mental health and an increase in role emotional from baseline to the 3 months study visit, but this was reversed between the 3 and 12 month study visits. From baseline to the end of the study period, they saw an increase in vitality, social functioning and bodily pain. The nocturnal group saw an increase in mental health and vitality (this increase was maintained to the end) between baseline and 3 months and an increase in role physical and role emotional between baseline and study completion and 3 month study visit and study completion for role emotional, suggesting a sustained increase. The conventional and nocturnal haemodialysis scores were compared at the three-time points[f]. The nocturnal group was lower in mental health and higher in social functioning at baseline when compared to the conventional group. The nocturnal

group was lower in role emotional at the 3-month time point however the dialysis groups were the same at the end.

8.5 Conclusion

It is well known that functional status and quality of life are strong independent risk factors for increased hospitalisation and subsequent mortality in incident dialysis patients (McClellan WM et al., 1991). Many methods exist for assessing HRQoL including the renal-specific Kidney Disease Quality of Life Short Form and the preference-based EuroQol EQ5D-5L questionnaire. Various methodologies have reported a patient preference for nocturnal rather than conventional haemodialysis (McFarlane PA et al., 2007).

Conventional haemodialysis is an inadequate treatment for ESRD. Ineffective clearance is inherently associated with a significant symptom burden (cramps, fatigue, dizziness etc.) and a necessary requirement for polypharmacy. ESRD patients are recognised to have one of the highest pill burdens of any chronic disease state (Chiu YW et al., 2009). Nocturnal haemodialysis is recognised to offer improved quality of life and patient outcomes.

A study by Dumaine et al., found in centre nocturnal haemodialysis to improve HRQoL for patients with ESRD. A significant improvement ($p=0.01$) was seen after 12 months conversion from conventional haemodialysis in mental component score. Regarding patients with reduced HRQoL and baseline scores below the median; improvements were also reported in symptoms/ problems of kidney disease

(p=0.003), effects of kidney disease (p=0.026) and physical component score (p=0.018) (Dumaine CS, 2022).

Singh et al., found nocturnal patients to score higher in both the physical component summary and mental component summary of the KDQOL:SF-36. The study also found that nocturnal patients felt the burden of kidney disease less than those patients receiving conventional haemodialysis. This was associated with a reported reduction in levels of middle molecules PTH and β2-microglobulin (Singh K et al., 2020).

Value based healthcare seeks to provide improved health care outcomes for patients within a cost-effective, sustainable model (Apel C, 2021). Patient reported outcome measures (PROMs) are constructs designed to assess the quality of care delivered from a patient's perspective; in particular, those outcomes most meaningful to patients. Their significance as a clinical outcome assessment method beyond those of biomarkers, morbidity measures or survival is increasingly recognised.

Going forwards, the inclusion of PROMs as standard in clinical studies will be paramount, particularly when assessing chronic disease treatments with a high symptom burden such as haemodialysis. The UKRR routinely collect information concerning patient activation measures (PAM) and PROMs as part of the 'Your Health Survey' for patients with CKD and ESRD requiring RRT. Data collected includes; - renal unit, treatment modality, sex, ethnicity, patient name/NHS number/postcode and date of birth, health literacy, EQ5D-5L (as a quality of life measure), Palliative care Outcome Scale-Symptoms Renal (POS-S Renal) as a

symptom burden measure and PAM (to assess knowledge, skills and confidence in self-management).

HRQoL is an important outcome measure in patients with ESRD for all renal replacement therapy modalities. Jansz et al found that after kidney transplantation, recipients scored higher on the ‘effects of kidney disease’ domain as compared to nocturnal haemodialysis (Jansz TT et al., 2018). This is a useful consideration when it comes to discussing modality choices with advanced CKD patients.

CHAPTER 9

GENERAL DISCUSSION

9.1 Change in baseline characteristics and biochemical parameters

A statistically significant difference was observed between baseline urine output between patients starting conventional and nocturnal haemodialysis as tabulated in Table 3.1 (p=0.011). A loss of baseline residual renal function was observed in individuals commencing nocturnal haemodialysis. This was likely due to the increased dialysis vintage associated with individuals commencing nocturnal haemodialysis training (p=0.004) and the increased number of previous RRT modality switches or failures; where there was a significant history of conventional haemodialysis treatment (p<0.001). The FHN trial found frequent nocturnal haemodialysis to accelerate the decline of residual kidney function when studied in prevalent patients, the affect was sustained at 1 year (Daugirdas JT et al., 2013). A significant decline in 48-hour urinary volume was also observed in another study in the nocturnal haemodialysis arm as compared to conventional haemodialysis [2794 ± 1662 mL to 601.7 ± 315.3 mL vs. 2399 ± 950 mL to 1943 ± 1087.0 mL respectively, (p=0.01)] (Skeat L et al., 2020). These findings were reflected in our study where participants in the NHD group were anuric as compared to individuals undertaking conventional HD (1000 [400 – 1550ml] after 12 months treatment (p=0.001) and also had a significant loss of residual renal function (p=0.012) as is expected in the first 12-18 months of incident haemodialysis.

Pre-dialysis urea measurements were significantly lower in the nocturnal haemodialysis group as compared to the conventional haemodialysis group (p=0.008) in Table 3.2. This is on account of the increased hours and frequency of nocturnal dialysis (average total 40 hours/ week as compared to 12 hours/ week with thrice weekly conventional haemodialysis.

There was a significant difference in anti-hypertensive requirement between conventional HD and NHD groups (p=0.043) after 12 months extended hours dialysis, with a reduction in the number of anti-hypertensives prescribed for nocturnal participants from a median average of two, to a single agent as shown in Table 3.4. A reduction in blood pressure and the associated requirement for anti-hypertensive therapy has been consistently demonstrated in extended hours treatments with in-centre and home-based nocturnal haemodialysis (Culleton BF et al., 2007, Rocco MV et al., 2011). This is thought to be achieved by several postulated mechanisms; a reduction in sympathetic activity and peripheral resistance, reduction in nocturnal hypoxaemia due to amelioration of obstructive sleep apnoea and improved vagal modulation along with improved endothelial function (Koh TJK, 2019).

Haemoglobin (Hb) levels (g/L) were slightly lower in the NHD group than the conventional HD group (98 ± 18 vs. 115 ± 14, p=0.038). Serum ferritin levels (ug/L) were much lower in NHD than conventional HD participants (162 ± 151 vs. 582 ± 179, p<0.001, there was no statistical difference in serum ferritin levels between NHD and the control group (p=0.638). The haemoglobin content of reticulocytes (Ret-He) used as a marker of iron depletion, was lower in the NHD group as compared to conventional HD but still within the normal range 28 – 36pg (30.1 [29 – 34.9] vs. 36.8 [34.2 – 39.1], p=0.012 as outlined in Table 3.5. The mean average IV iron dose administered for nocturnal haemodialysis patients was lower than the conventional group although not statistically significant (p=0.1) due to a change in practice in response to the COVID-19 pandemic in an attempt to mitigate the risk of transmission and potential complications. In line with this rationale the administered

iron dose correlated with the prescribed ESA dose for conventional HD (p=0.001, r =0.9) and ESA dose/ week (p=0.004, r=0.89) but not for NHD (p=0.159, r=0.5).

The average ESA dose in units/week was lower in the NHD group, although this did not reach statistical significance (p=0.315). There was no statistical difference between groups in terms of the ESA resistance index (p=0.360) as demonstrated in Table 3.6. An improvement in haemoglobin and reduction in Epo requirement has not been consistently demonstrated in the literature. In a crossover study there was a significant improvement in haemoglobin in individuals switching to nocturnal from conventional haemodialysis 115±2 g/L to 122±2 g/L at 6 months and 124±2 g/L at 12 months (p=0.03) with no change in the conventional haemodialysis group. (Schwartz DI et al., 2005). The proportion of patients not requiring ESA therapy also was significantly reduced (24% in NHD vs. 9% in conventional HD, p=0.01). However, no significant impact on haemoglobin or Epo requirement was demonstrated by Culleton et al., 2007 or in the FHN nocturnal trial (Rocco MV et al., 2011).

A significant improvement in serum phosphate was also demonstrated in the nocturnal haemodialysis group (p=0.016). It is well recognised that an early reduction is seen in serum phosphate within 2 months of starting extended hours treatment as demonstrated by the Alberta group (Walsh M et al., 2010). The associated change in binder prescription was significant between conventional HD and NHD groups (p<0.001), with an associated significant reduction in pill burden seen in the NHD group; accounting for MBD and anti-hypertensive prescriptions (p=0.004). This study adds to the evidence base for an improvement in biochemical parameters, however

the apparent contrast between obtaining euvolaemia and its benefits contrasts with the associated loss of RRF, which requires further study.

9.2 Quantitative measures of left ventricular dysfunction

Negative cardiac remodelling associated with haemodialysis treatment results in cardiovascular morbidity and mortality which is well-described in the literature. Chronic fluid overload associated with hypertension causes LVH, impaired cardiac filling and relaxation results in diastolic dysfunction leading to impaired LV systolic dysfunction. Coronary artery disease causes myocardial ischaemia, remodelling and fibrosis with reduced contractility and impaired cardiac output. Conventional haemodialysis results in myocardial stunning, with regional wall motion abnormalities, a reduction in contractile function and subsequent LV dysfunction in over 50% of dialysis patients (McIntyre et al., 2008, Burton JO et al., 2009). Frequent haemodialysis avoids the associated haemodynamic compromise of large volume ultrafiltration (Jefferies HJ et al., 2011) with a lower incidence of myocardial stunning, improved LV mass and quality of life (Chertow GM et al., 2010).

9.2.1 Global longitudinal strain

Ejection fraction % has been traditionally used by nephrologists as an approximation of reduction in LV function in CKD/ ESRD. However, given the high incidence of LVH in this population, the presence of which impairs assessment of systolic function, measurement by LVEF may underestimate LVSD. GLS is a more sensitive measure of strain as reduction in GLS precedes reduction in LVEF and is present in roughly a third of CKD stage 3B – 5 patients with preserved LVEF ≥50% (Ernande L et al., 2014, Hensen LC et al., 2018). GLS is superior to LVEF in the dialysis population in

terms of its sensitivity to LVSD and its incremental ability to predict cardiovascular outcomes (Kalam K et al., 2014,).

Conventional HD patients had consistently impaired GLS (consistent with reported -13.4 ± 3.5%, Chiu D et al., 2016), NHD patients showed an absolute improvement of 2% (15% as compared to baseline) from a more impaired baseline figure of -13.8 to -15.8, returning towards the normal range with extended hours treatment (p=0.04967). This became non-significant if crossover patient included in analysis for NHD group (p=0.260). There was no difference in ΔGLS between groups p=0.743 as presented in Table 4.4. Albeit a non-significant improvement in GLS, this study adds to evidence base for improved outcomes with extended hours haemodialysis. As a pilot study, it was not adequately powered to detect a significant effect as N was small. However, given that an improvement was seen in a group with loss of residual renal function and a longer dialysis vintage the trend warrants further investigation with a multi-centre study.

9.2.2 Left ventricular mass

LVM is a strong and independent predictor of survival and cardiovascular events in patients undergoing dialysis and is known to increase progressively with ESRD and haemodialysis. A 6% regression in LV mass was seen in the NHD group, although this didn't reach significance, p=0.730. Regression of LV mass has been reported in patients converting from conventional to in-centre nocturnal haemodialysis (Wald R et al., 2012) findings that were reproduced with the FHN group (Rocco MV et al., 2011). A non-significant deterioration in LVMi was seen in male individuals in the conventional haemodialysis group (p=0.463), a non-significant improvement in LVMi

was seen in female individuals in both groups as demonstrated in Table 4.9; from moderately to mildly abnormal in conventional HD participants (p=0.593) and an improvement from severely abnormal to mildly abnormal for NHD participants (p=0.180). Combined analysis indexed by height (to correct for malnutrition and body fluid status) for gender trended towards significance (p=0.083) as outlined in Table 4.11. Further study looking at these differences is warranted.

9.3 Quantitative measures of left atrial dysfunction

Left atrial strain plays a pivotal role in modulating LV performance and has proven diagnostic and prognostic value in a variety of clinical scenarios. In the CKD population impaired eGFR is independently associated with a reduction in LA reservoir strain (Unger ED et al., 2016). LA volume and LVMI are known to increase in patients with ESRD along with a decline in diastolic function (Li C et al., 2019). Alterations in left atrial reservoir strain (LASr) occur before changes in LA volume (Vianna-Pinton R et al., 2009). In a prospective study of 243 stage 3/4 CKD patients LASr was found to be an independent predictor of cardiovascular death and MACE; superior to traditional echocardiography measures of LV function or LA volume. This pilot study was however not adequately powered to identify a difference in LA strain measures. Utility of LA strain is largely confined to research at present, future evaluation of LA phasic function by strain analysis may provide an accessible, reproducible method of assessing diastolic dysfunction (Santos ABS et al., 2016) and functional capacity in a multi-morbid, frail ESRD population (Gan GCH et al., 2021).

9.4 Assessment of CACS

CAC as a representation of total coronary plaque burden is a well-established powerful predictor of cardiac events and an independent predictor of death (Matsuoka M et al., 2004). Rapid progression of vessel calcification is seen with chronic haemodialysis. A significant difference in CACS was seen in the conventional haemodialysis group in calcification of the right coronary artery (p=0.028) and total CAC (p=0.043). A significant increase was not seen in the nocturnal haemodialysis group. A statistically significant difference was seen in CAC progression across the study period between the conventional dialysis group and the extended hours nocturnal haemodialysis group; with a 71.2% and 6.7% respective increase in calcification (p=0.043). A median increase in CACS of 62HU [1 – 152] was observed in the conventional dialysis group as compared to 9HU [-138 – 91] in the nocturnal haemodialysis group.

In order to clinically appraise the change in CACS the data was assessed to look at progression, non-progression and regression of calcification. In addition to CAC burden, CAC progression portends poor prognosis for all-cause mortality in incident dialysis patients. Conventional dialysis subjects demonstrated significant progression in CAC 137.67 ± 43.9 HU, p=0.008 as compared to significant regression in CAC -143.29 ± 40.5 HU in the nocturnal group, although this did not reach significance. For conventional haemodialysis there was very high correlation between progression of calcification and the severity of baseline calcification. Absolute change in calcification, as calculated by (CAC_{12} – $CAC_{baseline}$)/ $CAC_{baseline}$ (p=0.006, r=0.9) and annualised change (p=0.008, r=0.89). The change in calcification severity was not significant in the nocturnal group as compared to baseline. Suggesting that

improvements in vascular calcification can be seen independent of the severity of calcification when starting extended hours therapy. Strong evidence exists to support the validity of CACS in CKD and ESRD, including those receiving haemodialysis. As a validated, independent prognostic tool associated with low dose radiation, CACS is advocated for cardiac risk stratification within the CKD population. A zero score is associated with a high negative predictive value and a low risk of coronary artery disease and events. Further standardised studies with extended follow up periods are required to assess cardiovascular outcomes for all RRT modalities.

9.5 Plasma markers of oxidative stress and inflammation

Oxidative stress and inflammatory pathways interlink, influencing CKD progression and thereafter, therapy response. An increase in pro-oxidants and impaired antioxidant capacity is associated with the uraemia of ESRD and its inherent cardiovascular complications.

Hs-CRP, IL-6, IL-18, MCP-1 and VEGF were chosen as plasma markers of inflammation, TBARS, AGE, BMP-6 and hepcidin as biomarkers of oxidative stress and cTnT and NT-proBNP as markers of cardiac strain. In the conventional group a reduction in IL-6 ($p=0.025$) was demonstrated over the study period alongside an initial reduction in NT-proBNP ($p=0.049$) following dialysis initiation as presented in Table 7.2. A significant reduction in TBARS ($p=0.037$) as a marker of oxidative stress and IL-6 ($p=0.036$) and IL-18 ($p=0.037$) as markers of inflammation was demonstrated in the nocturnal haemodialysis group. Levels of IL-18 follow a similar trend to the control population in nocturnal haemodialysis with a statistically significant reduction in pro-inflammatory levels between 0 – 12 months, this was not

demonstrated in the conventional haemodialysis group. A statistically significant difference for IL-6 was seen at 0 ($p=0.001$) and 3 months ($p<0.001$) which was tending towards significance at 12 months ($p=0.056$) between all groups. A statistically significant difference for Troponin was demonstrated between all groups at 0, 3 and 12 months ($p<0.001$). No statistically significant difference was consistently demonstrated between conventional HD and NHD at 0, 3 or 12 months for any marker of oxidative stress or inflammation. This was likely due to the small sample size.

9.6 Study limitations

9.6.1 Sample size

This study was a pilot study and therefore representative of results from a single centre. The study was non-randomised, the NHD cohort were therefore from a selected population introducing sample bias. Data was assumed to be normally distributed, but when assessed by 1-KS the majority of the study data was non-parametric due to the small sample sizes and the skewed distribution; results were therefore a function of the sample not the population. The feasibility study was underpowered to detect an effect, which partly explains the non-significance of some results.

9.6.2 Recruitment limitations

Study recruitment to the nocturnal haemodialysis arm was limited by the training capacity of the self-care unit. As each patient takes a minimum of 12-weeks to train in order to safely dialyse at home, new patients on the waiting list could not start the programme until space was available. This meant that only 6-8 patients could train at

a time, some were not eligible to enrol in the study on account of inclusion/ exclusion criteria and were unable to commit to participating in the study. Screening for nocturnal haemodialysis participants as the rate limiting recruitment factor commenced in November 2018 and continued through until January 2020. Participants were matched in triplets with individuals on conventional haemodialysis and a control group participant. Groups were matched for age, gender and socioeconomic status (by postcode). Aetiology of ESRD, co-morbidities and dialysis vintage was similar between dialysis groups as previously described in chapter 2. The final study visits for participants completing the study were conducted in May 2021. A successful Welsh Government Transformational Fund project was borne out of the recruitment limitations, the work for which and the outputs are described in chapter 10.

9.6.3 COVID-19 global pandemic

Initial recruitment and ongoing study visits were impacted by the global coronavirus pandemic. This also heavily impacted standardised haemodialysis care i.e. the frequency of IV iron administration, as discussed in Chapter 3. A non-typical deterioration in haemoglobin was observed in the nocturnal haemodialysis arm ($p=0.039$) which was likely due to the COVID effect where there was a planned reduction in IV iron administration to avoid patients attending health care centres and the associated risk of COVID-19 transmission. A formal hold on study visits lasted about 7 months which impacted the duration of the study. Participants in all groups, including the healthy controls, were apprehensive with regards to attending hospital sites for research investigations given the risk and potential consequences of contracting COVID-19.

9.6.4 Dialysis vintage

In clinical practice it is extremely rare for truly incident dialysis patients to commence nocturnal haemodialysis as their chosen RRT modality, for reasons described in chapter 1. One of the main limitations of the study concerned the dialysis vintage of the nocturnal arm patients, who with their extended history of ESRD had undertaken various renal replacement therapy modalities (i.e. PD, failed transplant). With a difference in urine output at baseline (p=0.011) and 12 months (p=0.001) due to loss of residual renal reserve, they were not a true 'incident' cohort.

Finally, there was no difference demonstrated in previously widely documented BP control (Jansz TT et al., 2018) between groups (p=0.796), the small sample size was likely underpowered to detect a statistically significant effect.

9.6.5 USCOM data

Due to the breadth of cardiovascular data collected, the decision was made following an interim VIVA not to analyse the USCOM data for inclusion into this thesis.

9.7 Discussion

ESRD is associated with an excessively high cardiovascular mortality accounting for 30-40% deaths on dialysis. Concentric LVH and systolic failure present in 41% and 16% of incident dialysis patients respectively. Cardiovascular calcification affects 60-90% people with CKD. This thesis concerns the results of a single-centre prospective feasibility study, investigating the cardiovascular outcomes of 12 months conventional haemodialysis vs extended hours nocturnal haemodialysis and the correlation with markers of oxidative stress, inflammation, calcification and cardiac

strain. Non-traditional risk factors driven by the uraemic state complicate appropriate risk stratification and management. LVH, dilatation and systolic/diastolic dysfunction are common due to chronic volume and pressure overload. Studies have shown that conventional haemodialysis induces global and segmental cardiac ischaemia, with an impaired haemodynamic response to dialysis, elevations in cardiac troponin T, reductions in segmental and global contractile function due to 'cardiac stunning' and an elevated mortality risk.

9.7.1 Primary endpoint – LV GLS as assessed by STE, correlation with plasma markers of oxidative stress, inflammation and cardiac strain

The study was powered for the primary endpoint; GLS as measured by 2D STE. STE is a sensitive marker of LV systolic function incorporating multidirectional assessment of myocardial deformation. LV GLS has been shown to have a significant role in predicting cardiovascular outcomes as compared to LVEF. It is a measure of longitudinal shortening of the myocardium, relative to its original length/thickness which can be impaired despite a normal LVEF. Impairment to longitudinal functional usually precedes circumferential and radial dysfunction in pressure overload, with resultant LVH. A GLS >-15% is a predictor of all-cause mortality, including in those with LVH. GLS is reported to maintain intra and inter-dialytic consistency, therefore is not affected by load manipulation as with most ECHO measurements. Abnormal GLS thought to be a precursor of uraemic cardiomyopathy (interstitial fibrosis and myocyte hypertrophy) reflective of haemodialysis-related myocardial stunning. A reduction in GLS is a significant risk factor for all-cause mortality in adults with ESRD and has been shown to be impaired after a single haemodialysis session. A 1% deterioration in GLS has been reported

to be independently associated with a 12% increased risk of a composite cardiac endpoint (Romano S., et al 2018).

The primary objective was to compare the effect of NHD versus conventional HD on myocardial strain. The primary endpoint was mean change in LV GLS over time. Measurements were all obtained pre-dialysis by the same cardiac physiologist to account for changes in fluid status and intraobserver bias. Conventional haemodialysis patients exhibited consistently impaired GLS, consistent with previously reported data -13.4 ± 3.5% (Chiu D et al., 2016). Whereas extended hours nocturnal haemodialysis patients improved from a more severe baseline towards the normal range with extended hours treatment. The improvement was significant if analysed as intention to treat (-13.8 [-15.475 - -12.475] to -15.8 [-17.2 - -6.26], p=0.04967), however despite a more marked improvement in median GLS became non-significant if the crossover patient was included (-13.9 [-16.1 - -12.85] to -16.2 [-17.2 - -12.25] p=0.260). GLS strongly correlated with baseline (p=0.038, r=0.7) and 12-month troponin (p=0.049, r=0.7) levels in the conventional but not the nocturnal haemodialysis group. ΔGLS correlated with baseline TBARS p=0.01 (r=0.83) as a measure of reduced oxidative stress and final hepcidin level as a marker of inflammation p=0.01 (r=-0.83), lower hepcidin levels were associated with improved GLS. GLS is a sensitive marker of cardiac strain enabling early detection of LV systolic dysfunction and heart failure in haemodialysis patients, that is more accessible than cardiac MRI in clinical practice. A larger, more highly powered study is needed to assess the favourable effect of extended hours haemodialysis on myocardial structure and function.

9.7.2 Secondary endpoint – CT CACS, correlation with plasma markers of oxidative stress, inflammation and cardiac strain

CACS, as a representation of total coronary plaque burden, is well established as a powerful predictor of cardiac events. Every 100 unit increase in CACS is suggested to be associated with a 20% increase in relative risk of a coronary event. Inflammation and deranged bone mineralisation may contribute to atherogenesis and arterial calcification. We compared progression of CAC in conventional and nocturnal haemodialysis patients. Groups were well matched for age, gender, aetiology of ESRD and cardiovascular risk factors. Significant progression of CT-CAC in the conventional haemodialysis group (not reproduced in the nocturnal group), which exceeded the 20-25% annual progression expected in a non-dialysis patient of average Framingham-risk. Relative interscan CACS (as calculated by % change/ time) was significantly elevated in conventional haemodialysis (71.2%) vs nocturnal haemodialysis (6.7%) p=0.043. Absolute progression (as calculated by ΔCAC) correlated with baseline calcification (p=0.006, r=0.9) for conventional, but not nocturnal haemodialysis. Over the study there were no significant changes in markers of bone mineralisation regarding inflammation. Both dialysis groups demonstrated a reduction in IL-6 (117pg/ml ± 59 to 75pg/ml ± 30, p=0.04). Elevated serum IL-18 is known to be associated with all-cause mortality in conventional haemodialysis patients, independent of cardiac dysfunction (Liu YW et al., 2014). Baseline Hepcidin strongly correlated with absolute (p=0.024, r = 0.7) and relative CACS progression (p=0.006, r =0.8) for nocturnal haemodialysis. TSAT%, as a marker of iron status, also correlated with absolute (p=0.014, r = 0.74) and relative CACS progression (p=0.025, r=0.7). Further sub-group analysis concerned patients in both haemodialysis groups as determined by their progressor status. Progressors

were defined as those where there was an absolute increase in CAC >20HU and a relative progression >15%/ year. Non-progressors did not meet both criteria, classification for regression required a reduction in absolute and relative CACS.

Hepcidin was the only biomarker associated with CAC progression. Higher serum hepcidin levels (370pg/ml [321-398pg/ml] were observed in the progressor group, (non-progressors 352pg/ml [297-374pg/ml]) than those with regression of CACS (243pg/ml [138 – 348pg/ml], p=0.045, r=0.51). Significant correlation of baseline hepcidin with relative CACS (p=0.037, r=0.9) was observed in the regression group. Baseline serum hepcidin may be useful as a predictor of accelerated atherosclerosis with CAC progression and risk stratification for cardiovascular mortality in haemodialysis patients.

Doubling of CACs in CKD patients has been reported to increase the estimated probability of CV mortality by approximately 43% in a 10-year period (Cano-Megías M et al., 2019). Other studies reported a 20% increase in the risk of a major coronary event: - myocardial infarction or death from coronary heart disease (Detrano R et al., 2008). Extended hours treatment with nocturnal haemodialysis significantly decreased progression of CAC compared with conventional haemodialysis. Progression appeared to be more dependent on levels of inflammation than deranged bone mineralisation with hepcidin the best predictor of CAC progression, but larger scale adequately powered studies are required.

9.8 Conclusion

This study adds to the evidence base in support of extended hours haemodialysis as a therapy for ESRD and its associated reduction in cardiovascular risk. The demonstrated reduction in polypharmacy, improvement in phosphate control are well recognised benefits. Lower ESA doses and improved blood pressure control are widely reported however were not found to be statistically reproduced in this study. Despite the impact of the novel coronavirus COVID-19 on the study, this itself highlighted infection-control benefits, in that patients undertaking nocturnal haemodialysis could continue to do so in the relative safety of their own homes.

CHAPTER 10

OTHER OUTPUTS ARISING FROM WORK

10.1 Introduction

A key limitation impacting upon participant recruitment to the study was the training capacity and time taken to train individuals for nocturnal haemodialysis in the self-care department. 6 training spaces were available, and patients required an average of 12 weeks training in order to meet the competencies to safely dialyse at home.

A co-ordinated MDT effort was made, to review the patient journey for individuals undertaking home haemodialysis training, with a view to streamline the process and make efficiencies where possible. The MDT consisted of myself, Dr Ashraf Mikhail (Consultant Nephrologist and Clinical lead for Nocturnal Haemodialysis), Christopher Brown (Consultant Renal Pharmacist & Head of Renal Pharmacy), the lead nurse for self-care, a band 3 health care support worker and representation from the renal technical services.

A successful bid was submitted to the Welsh Government Transformational Fund programme and was successfully awarded a total funding of £343,000 including the COVID-19 extension (see Appendix). As a truly co-productive service development, Helen's story was at the heart of the project and the project aim; to improve the uptake and positive delivery of nocturnal haemodialysis:

10.2 Helen's story

"My kidney failure has been a real challenge. Almost 20 years ago I started dialysis and I made many sacrifices. Strict restriction to my diet and measuring every drop of fluid I drunk was a daily routine. I had to take many medicines every day and attend hospital 3 times every week for dialysis. I scheduled my dialysis so I could continue

my career as a staff nurse for the NHS. After 6 years on dialysis I experienced the freedom that a transplant kidney offers. This amazing gift allowed me to enjoy 10 years of a normal life. My transplant failed. I had to return to dialysis but this time it is very different. I now have dialysis in my own home. I do it 5 nights a week as I sleep. I chose when I do it, and after a good night's sleep I wake up having done 8 hours of dialysis. This means I am free to eat and drink what I wish, I do not need a cocktail of drugs and I feel well. Me and my smart phone manage my own condition. I am supported by the team in the renal unit to care for myself. I access my blood test results and changes to my dialysis treatments and medicines on my phone or tablet. I can change my dialysis days, or hours or my drugs depending on my results. I am in control and able to keep myself well. My renal unit sends me text reminder for blood test, medicines supplies or changes I need to make. I attend hospital once a month for a blood test, my drugs and a review of my health; and of course, a cup of tea and a couple of biscuits (which I am free to eat). Everything is done in single visit; no waiting or delays. After that I have all I need at home and all the information at my fingertips to care for myself. I am in control of my own treatments. I understand my condition and how to manage it. With digital access to my own records and support when I need it from the renal unit I am well; I have an active and fulfilled life. I am even free to have short holidays abroad now and then."

10.3 Methods

As an innovative and collaborative project focused on patient centred outcomes, the bid was developed as an MDT. It was developed for patients, by patients - who are the key stakeholders. In order to scope out the required project content, regular patient focus groups, captured by infographic artist (see appendix) were facilitated.

The inter-regional, interprofessional project team, were supported nationally by the WRCN. As a national scale up of innovation, the primary aim is to meet an outcome target of 30% of RRT patients receiving a home therapy as stipulated by NICE/ RA. The outputs through this will be achieved include: - the production of patient stories contained within a digitalised patient education and support package including a renal website, CKD education videos, promotional patient stories and training materials. These materials will be championed by supportive home therapy link nurses and educational events to complement regional programme delivery. The project was presented at a directorate departmental business meeting, underwent financial review, was appraised and supported by the WRCN and is now an interprofessional, nationally focused, patient-centred project following regional partnership board sanction and receipt of Welsh Government funding.

10.4 Results: examples of patient education material outputs

10.4.1 Meet the Expert videos:

Compilation: The benefits of home HD - https://youtu.be/kYXB_aIR4zM

[redacted]: Relationships and home HD - https://youtu.be/Eaypn9DQgrk

[redacted]: Dialysis partner - https://youtu.be/i1-iimPLVjY

10.4.2 Animations

- “What is Chronic Kidney Disease?” (English) https://youtu.be/zcrXw_U_1YA
- “Paratoi eich cartef ar gyfer haemodialysis” (“Preparing your home for haemodialysis”) (Welsh) https://youtu.be/D4LeY8SomwM
- “The Kidneys and bone, heart and blood vessel health” (English) https://youtu.be/cHON6qYnJdU

10.4.3 Patient information leaflets

10.4.4 Home haemodialysis: Frequently Asked Questions (FAQs)

(Welsh) – “A yw haemodialysis yn y cartref yn anodd i’w ddysgu?” (Is home haemodialysis difficult to learn?) https://youtu.be/G6CdXuZKHEI

(English) – “Will my home look too much like a hospital?”

https://youtu.be/HGnxsdZJElw

Helen’s story: https://youtu.be/BjGTb_jy8Cg

10.4.5 Home dialysis e-learning platform and resources

The following resources will soon be available to patients in training for and established on home dialysis. They will be available on our new kidney pages on the Learning@Wales platform:

Our patient tutorials include “Meet Your Machine”, “Diasafe”, “Filter Board” and “Decalcification”. The latter is shown here: https://youtu.be/itk7y0-Iztg

Our first home HD problem solving module: “Low arterial pressure alarm” is below:

https://community-portal-prod-previewdata.s3.us-west-2.amazonaws.com/files/2022/03/ce3ef032714052565c76/index.html

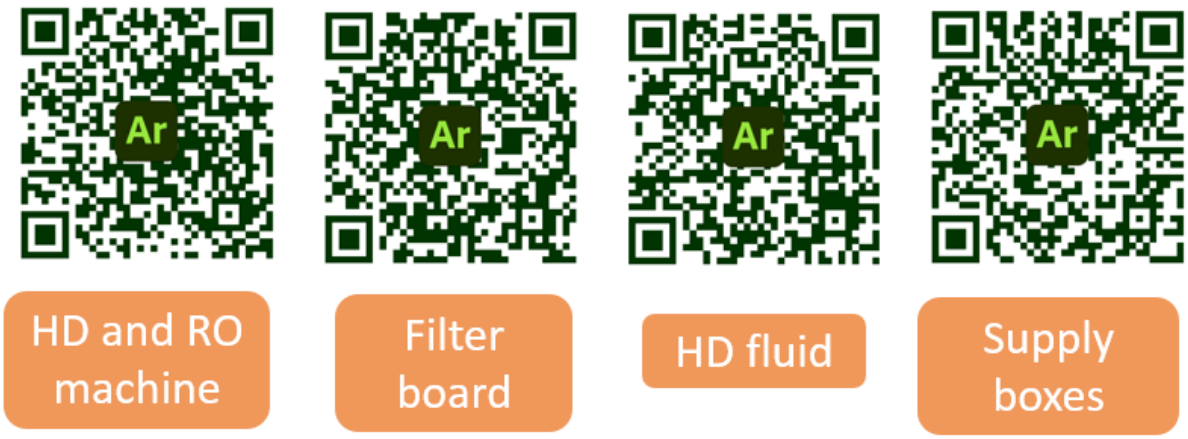
10.4.6 360° Virtual Tours

Please follow this link to explore one of the dialysis units in Morriston Hospital, including the home dialysis self-care training area, and patients’ homes with the dialysis machine and equipment in place. This is a demonstration of a resource that will soon be available for people to navigate themselves:

https://youtu.be/a1UpIgU-oa4

10.4.7 Augmented Reality app

Download the free Adobe Aero app on your Apple device (not currently available on Android) and scan the QR codes below to experience HHD in augmented reality:



The Minister for Health and Social Services in Wales visited the renal department in May this year and used the app. Please follow links below to see what the Minister said:

Welsh:
https://twitter.com/LlCIechydaGofal/status/1527944803232669696?t=aJx4nWMSmrClCFZBQuLJqA&s=08

English:
https://twitter.com/WGHealthandCare/status/1527944791757139969?t=vXjztW4Gu8HMC5bzlf6oFQ&s=08

The patient facing multimedia content from the transformation fund project won the Swansea Bay Living Our Values (LOV) award for “Using multimedia to improve kidney health literacy”, September 2022 and was a finalist for the NHS Wales award for empowering people to co-produce their care, October 2022.. The co-productive materials produced will be used to improve patient journeys for people living with kidney disease on a national basis across Wales.

APPENDICES

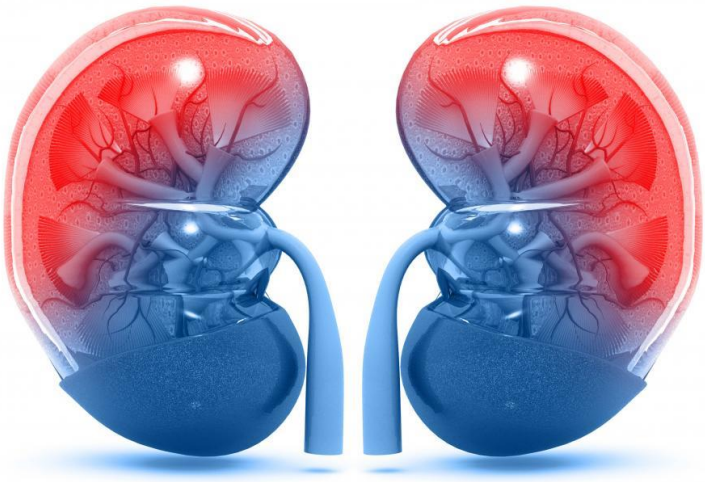
Swansea University
Prifysgol Abertawe

GIG CYMRU NHS WALES
Bwrdd Iechyd Prifysgol Abertawe Bro Morgannwg University Health Board

IRAS no: 250304

HEALTHY VOLUNTEERS WANTED

Morriston Hospital Renal Unit is looking for healthy volunteers to take part in a research study in Swansea.



The study, lasting 9 to 12 months is looking at the impact of kidney failure on the heart. As a healthy volunteer you would be required to have several blood tests and scans at Morriston Hospital to look at the health of your heart over the study period.

Transport can be arranged if required and you may be compensated £50 for your time and inconvenience if you are eligible.

Contact: Dr Karen Brown [redacted] or

Dr Ashraf Mikhail [redacted] or

call [redacted] to find out more

CARDIOVASCULAR OUTCOMES IN NOCTURNAL VS. UNIT HAEMODIALYSIS

Investigating the impact of nocturnal haemodialysis on cardiac function and markers of inflammation and oxidative stress in patients with end stage renal disease.

DIALYSIS PARTICIPANT INFORMATION SHEET

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully over the next 3 to 7 days and discuss it with others if you wish. If you decide not to participate in the study it will not affect the standard of medical care that you would otherwise receive. Thank you for reading this.

What is the purpose of this research?

Nearly half of patients with end stage kidney disease receive haemodialysis in hospital three times a week on an outpatient basis; currently only 4 in 100 patients in the UK do their own haemodialysis at home either as short daily dialysis or longer hours overnight (nocturnal).

Nocturnal patients report freedom to eat and drink freely, need to take less tablets, are less symptomatic, have more spare time as they dialyse overnight and are not constrained to hospital transport or schedules. Research shows that nocturnal patients have fewer chronic illnesses and better survival rates than those receiving haemodialysis in hospital. NICE (The National Institute for Health and Care Excellence) and the Renal Association aim to expand the provision of home therapies up to 30 in 100 people doing their own dialysis in the comfort of their own home.

Heart disease is common in end stage kidney disease patients and the leading cause of death. High blood pressure and excess fluid in dialysis patients impairs heart function. The build-up of toxins and other metabolic effects of kidney failure cause additional damage to the blood vessels.

The aim of this study is to assess both the inflammatory state of kidney failure and impact of haemodialysis by measuring a profile of blood tests over the first year of treatment. The effect of dialysis on the heart will be assessed by performing a series of scans before and after starting haemodialysis; comparing conventional hospital dialysis and longer hour's nocturnal dialysis.

Why have I been invited?

You have been invited because you are a patient with established chronic kidney disease and are due to commence/ have started long-term haemodialysis within the last 6 months in a unit where we are conducting this study.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, we will describe the study and ask you to sign a consent form. If you decide not to take part, you do not have to explain your reasons and it will not affect your medical treatment or legal rights.

You are free to withdraw your consent at any time, without giving a reason, even after signing the consent form. Any unused data will be destroyed. Any results that have been used prior to the withdrawal of consent will continue to be used in this study.

What will happen to me if I take part?

The study will last 9 to 12 months from enrolment. A routine physical examination, blood pressure reading and ECG will be performed as part of the screening process. If you are eligible to participate you will be asked to undergo two scans to look at the health of your heart; upon enrolment and again at the end of the study to look for any changes to your heart function after a year of haemodialysis.

1. ECHO – this will be performed at the Cardiac Outpatients Department, Morriston Hospital.
It is a jelly scan similar to that used for pregnant women that uses sound waves (ultrasound) to produce pictures of your heart; it tells us how well your heart is pumping and whether your heart valves are working properly. It takes about 30 minutes, is painless and doesn't have any side effects. You will be asked to undress to the waist, but you'll be covered up appropriately.

2. CT scan – this will be performed at Swansea University, Institute of Life Sciences (ILS2).
The CT scan is an open-ring structure resembling a 'giant doughnut' which uses x-rays to take detailed cross-sectional pictures of your heart. You will be asked to change into a hospital gown, the scan will take approximately 15 minutes and no contrast will be required.

This study will look to assess whether nocturnal dialysis reduces the build-up of plaque in the coronary arteries compares to conventional dialysis. If nocturnal dialysis leads to a slower built of coronary plaque than conventional dialysis then it may lead to fewer heart attacks in the future. The amount of coronary plaque will be assessed at the start of the study and after 1 year using coronary artery calcium scoring. Coronary artery calcium scoring is a widely used and well validated tool to estimate the amount of coronary plaque. The score is calculated following a low dose CT scan of the heart. The x-ray dose of 2 coronary calcium scores at the ILS2 is usually less than the x-rays received from 1 year of background radiation in the UK. This gives a lifetime risk of cancer of roughly 1 in 10,000.

3. USCOM – sequential ultrasound readings using a small probe placed near the breastbone each lasting about 5 minutes will be taken on three dialysis sessions at enrolment, after 3 months and upon completion at 9 – 12 months. The readings will be repeated over the course of a haemodialysis session. We aim to take readings just before connection, 15 minutes pre-washback and just after haemodialysis. The probe does not disturb the haemodialysis process and does not require it to be stopped at all.

Three blood tests (10ml) will be taken as part of routine haemodialysis sessions/ clinical visits where possible at enrolment, 3 months and 9 – 12 months. Samples will be stored with your consent at the Welsh Kidney Research Unit biobank and may be used for future research projects including genetic research.

A short form health survey questionnaire (SF-36) is a validated, patient-reported survey of health. It is used to monitor and compare a patient's perception of their disease. Participants will be asked to complete the SF-36 at enrolment, after 3 months and upon completion of the study (9-12 months).

Will I be paid anything for taking part?

Any data collected will be as a gift and you will not benefit financially at the time of donation or in the future should this research lead to the development of a new treatment or medical test. You will not incur any extra costs by participating in the study; all transportation to scan appointments will be arranged by the research team.

We will provide a self-addressed envelope, which you can use to return the questionnaires.

What will my data be used for?

Our research uses the blood test profiles and imaging of the heart that you have provided to improve our understanding of the stress of haemodialysis on the circulation. Your data will be used to help us better understand what is happening during in-centre and nocturnal haemodialysis and may be available for larger similar studies if they plan to include and combine such information.

Will you analyse my DNA?

No, this study will not involve the analysis of DNA. If you consent to your samples being stored for future research these may be included in genetic studies.

What are the possible benefits of taking part?

Your contribution will help us understand more about the symptoms, progression, and circulatory (blood vessel) changes occurring during haemodialysis. The intention in this study is that the information obtained will not immediately alter your care in any way but will help us understand the changes in the circulation during haemodialysis. The scans of your heart will give information about the health and function of your heart. Although, there is no immediate benefit to you from taking part in the trial, if major changes are observed then they may affect your treatment in the future. This will be left to the treating clinician to decide, any decision he or she makes is not considered part of this study. The information that we get from this study will help us to improve treatment for patients undergoing haemodialysis in the future.

What are the possible risks of taking part?

Your haemodialysis procedure and any risks associated with it will already have been explained to you. Trained clinicians will take the ECHO, CT and USCOM measurements. This study is non-invasive, the dose of x-ray from the CT scan is less than the x-rays received from 1 year of background radiation in the UK. This gives a lifetime risk of cancer of roughly 1 in 10,000.
The collection of the data will not involve any discomfort and will only take a short amount of time at each of the three study visits, as far as possible these will correlate with planned hospital visits.

Will my GP or other health/ care professional be told I am taking part in the study?

Yes, your GP will be notified of your involvement in the study.

Will anyone look at my medical records?

Relevant sections of your medical notes will be accessed for the purposes of this study. Clinical notes, patient data and clinical investigation results will be kept in a confidential manner and stored only on NHS computers. All personal data will be treated as strictly confidential and only those on the research team will be able to link this data to your pseudonymised samples and other research data.

What happens if I am no longer able to participate in the study?

Identifiable data or samples already collected with your consent would be retained and used in the study. No further data or samples would be collected or any other research procedures carried out on or in relation to you.

Will my taking part in this study be kept confidential?

All information collected during the study will be kept strictly confidential in accordance with the Data Protection Act. Your name, address, NHS number or any other identifying information will not be passed onto anyone and your data will be assigned an anonymous identification code. You will not be identified in any published study results. Only the research team will have access to the information that can identify you and link you to your data. Abertawe Bro Morgannwg University Health Board is the sponsor for this study based in the United Kingdom. We will be using information from your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Individuals from ABMU Health Board and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The only people in ABMU Health Board who will have access to information that identifies you will be people who need to contact you or audit the data collection process. Abertawe Bro Morgannwg University Health Board will keep identifiable information about you for five years after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible

You can find out more about how we use your information at
http://www.wales.nhs.uk/sitesplus/documents/863/Research%20privacy%20notice%20-%20final.pdf
You can find out more with regards to how we will use your data and your rights under the law here
https://www.hra.nhs.uk/information-about-patients/
https://understandingpatientdata.org.uk/what-you-need-know

What happens to my data at the end of the study?

Your data may be retained at the end of this study for use in future research within the UK and abroad. At this stage we do not know what the research will involve. On the consent form you will be given the option to exclude your data from future research. Your data will not be sold for profit.

What will happen to the results of the study?

It is our intention to publish the results of this study in academic journals and present findings at conferences. Participants will not be identified in any report, publication or presentation.

What if there is a problem?

If you are harmed by taking part in this research study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action, but you may have to pay for it.

If you wish to complain, or have grounds for concerns about any aspect of the way you have been approached or treated during the course of this research; the normal National Health complaints procedure is available to you. The PALS team can be contacted on [redacted] or [redacted].

Who is organising and funding this research?

The research is organised by Dr Ashraf Mikhail, Dr Daniel Obaid and Dr Karen Brown; Morriston Hospital, Abertawe Bro Morgannwg University Health Board and Professor Jeffrey Stephens and Dr Sarah Prior, Institute of Life Sciences, Swansea University. The study is being carried out by Dr Ashraf Mikhail and Dr Karen Brown using their own charitable kidney research funds. The study is forming the basis for a postgraduate research qualification (MD) for Dr Karen Brown.

Who has reviewed this study?

This study has been reviewed and given favourable opinion by the Joint Scientific Research Committee and associated external reviewers. All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests.

Further information and contact details

Should you have any questions relating to this study, you may contact us during normal working hours:

Dr Karen Brown
[redacted]

Dr Ashraf Mikhail
[redacted]

If you would like to discuss this study with someone independent of the study please contact:

[redacted]

We would like to thank you for considering taking part in this study. If you decide to participate you will be given a copy of the information sheet and a signed consent form to keep

CARDIOVASCULAR OUTCOMES IN NOCTURNAL VS. UNIT HAEMODIALYSIS

Investigating the impact of nocturnal haemodialysis on cardiac function and markers of inflammation and oxidative stress in patients with end stage renal disease.

CONSENT FORM – NHD PARTICIPANT

Name of Researcher(s): Ashraf Mikhail, Karen Brown, Jeffrey Stephens, Daniel Obaid, Sarah Prior

	Please initial
I confirm that I have read and understood the patient information sheet version 4.0 dated 10th October 2018 for the above study and have had the opportunity to ask questions and these have been answered satisfactorily	
I understand that my participation is voluntary and I am free to withdraw at any time without giving a reason and without my medical care or legal rights being affected	
I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from Swansea University, regulatory authorities or the NHS ABMU Health Board, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records	
I agree to provide cardiac imaging (ECHO/ USCOM/ CT measurements) for the above study	
I agree to provide blood samples as specified for the above study, these will be stored at the Welsh Kidney Research Unit (WKRU) once the study has completed and may be used in future research	
I give consent to the samples provided being used in future studies including genetic research	
I agree for my data to be used for future use by researchers in the UK and abroad, I understand (the research may involve use by the commercial sector and) that researchers will not be able to identify me from my data.	
I consent to my GP being notified of my participation and agree to take part in this study	

Name of participant (print)	Date	Signature
Name of person taking consent (print)	Date	Signature

THANK YOU FOR PARTICIPATING IN OUR RESEARCH
YOU WILL BE GIVEN A COPY OF THIS FORM

ADRAN ARENNEG
DEPARTMENT OF NEPHROLOGY

Participant GP address

Dr Ashraf Mikhail [redacted]

Today's Date:

Participant details

Dear Colleague,

The above named patient has given consent to participate /as a control in a single-centre, observational study within ABMU Health Board. The study, looking at cardiovascular outcomes in end stage renal disease (ESRD); nocturnal vs. in-centre haemodialysis is expected to last 9 – 12 months. Following baseline screening, if enrolled, the participant will undergo a physical examination, ECG, blood pressure reading and a profile of blood tests to look at inflammation and oxidative stress in ESRD. The blood test profile will be repeated 3 months into the study and upon completion at 9 – 12 months. Participants will undergo several scans to assess cardiac function at the beginning and completion of the study:

1. Echocardiogram (Cardiac Outpatients, Morriston Hospital)
2. CT Coronary Artery Calcification Scoring (Institute of Life Sciences 2, Swansea University) n.b. this will not be performed for healthy control participants.

Serial USCOM (ultrasound cardiac output monitor) readings will be taken (on dialysis) at baseline, 3 and 9 – 12 months.

If you would like a copy of the patient information sheet or have any questions regarding the study please contact one of the investigators; Dr Ashraf Mikhail (Chief Investigator) or Dr Karen Brown (Principal Investigator).

Yours sincerely

Dr Karen Brown
Senior Clinical Research Fellow


HOME THERAPIES
PATIENT FOCUS GROUP
HEARING THE PATIENT & FAMILY VOICE
PROF Shaldon!
MARCH 12th
WORLD KIDNEY DAY!
STAGE 1+2
90%
HOW CAN WE MAKE SHARED DECISION MAKING BETTER FOR PATIENTS & FAMILIES?
PROVIDE MORE INFO WITHOUT BEING ALARMIST!
NOT WORRYING PEOPLE
YOU'RE AT STAGE 1
BLOOD TEST
CKD
MONITOR
STAGE 3
30%
THIS STAGE COULD BE UNPACKED A BIT MORE
PATIENT STORIES
MORE EDUCATION ON WHAT KIDNEYS DO & WHAT HAPPENS TO YOU PHYSICALLY
CREATE VIDEOS
AWARENESS IN SCHOOLS
STAGE 4
15%
IS IT IMPACTING ON YOUR SOCIAL LIFE?
SUPPORT FROM NURSES & EMOTIONAL SUPPORT
HOW DO YOU FEEL?
Holistic APPROACH
INCLUDE FAMILIES IN DISCUSSIONS
VIDEOS FOR THIS STAGE. FOR ANAEMIA, PHOSPHATE MANAGEMENT, ETC.
WEBSITE MY EXPERIENCE
WHAT IS IMPORTANT TO YOU?
STATE OF ACCEPTANCE
STAGE 5
-15%
-COMPLETELY DIFFERENT TO THE OTHER STAGES
WHY ME?
You're 1 of 1
VIRTUAL SUPPORT
SIARAD I BOBL SYN CAEL DIALYSIS YN BAROD
VISUALISE GFR'S FOR PEOPLE
AGES
RESEARCH IS NEEDED FROM STAGE 1→3
MAJORITY OF CARE IN PRIMARY
MORE INFORMATION ON FOOD
GET THE INTERVENTIONS RIGHT AT THIS STAGE
PEER SUPPORT
TRAJECTORY TOWARDS HOME
YOU NEED THE LIGHT AT THE END OF THE TUNNEL
DIABETIC CLINIC
INFORMATION AVAILABLE AT CLINICS
50% OF PUBLIC ARE NOT AWARE THEIR KIDNEYS MAKE URINE!
UPSKILL NURSES & MDT
HANDS ON HELP WITH MACHINES
PATIENT EXPERT
BLUE LIGHT
HOME 1ST FOR YOU
ASPIRATIONS
WRCN
NICE
RA
30% OF PATIENTS SHOULD BE AT HOME
WE WANT TO SMASH THROUGH THIS NUMBER!!
Benefits of Home Therapies
PERITONEAL DIALYSIS
NOCTURNAL DIALYSIS
I don't feel sick anymore
Helping me to be as well as I can be
BRINGING YOUR CARE HOME
BENEFITS OF NOCTURNAL
I CAN EAT WHAT I WANT
"I've had my life back"
"I CAN GO AND DO WHAT I WANT TO DO"
"I feel normal"
I HAVE FREEDOM & ENERGY!
LIVE LONGER!
I CAN CARRY ON WITH LIFE AS NORMAL (ALMOST)
IM NOT IN HOSPITAL, GREAT TO BE AT HOME
GOOD FOR YOUR HEART
VISUAL COPYRIGHT ELEANORBEER.COM 2020

Home Dialysis Transformation Fund Bid
Authors: • Dr Karen Brown, ST6 Renal Medicine/Senior Clinical Research Fellow • Dr Clare Parker, Clinical Lead and Consultant Renal Physician • Dr Ashraf Mikhail, Consultant Renal Physician (Project Lead) • Mr Christopher Brown, Consultant Renal Pharmacist • Mr Gareth Cottrell, Associate Service Director – Medicine • Mrs. Tracy Owen, Assistant Service Group Manager – Renal Medicine
Delivery Organisation: Swansea Bay University Health Board
Regional Partnership Board: West Glamorgan
Project Funding: A funding of £271,419 is required to develop a patient education programme for home dialysis, and develop a digital platform to host the material to be available to all patients of Wales
Purpose/key points: • The Welsh Renal Clinical Network (WRCN), NICE and the Renal Association stipulate that 30% of dialysis patients should receive a home therapy. Currently the figure within SBUHB is 23% • The TF bid, which is aligned with the Renal Delivery plan, is a core component of the department's vision to further expand home therapy supported by a digitised patient education programme • The digitised patient education programme will encompass the different patient options for home dialysis, and will be hosted on a digital platform that will be available to all people with kidney disease in Wales. Mindful of digital inclusion, the material will aim to improve the digital and health literacy for people with CKD and will be available, bilingually, in other formats

INTRODUCTION/BACKGROUND

Kidney disease is common, affecting up to 1 in 10 of the adult population, and the numbers are expected to rise significantly over the next decade, driven by the increase in diabetes and obesity. Once kidney function falls below around 15%, most patients start to develop symptoms related to their kidney disease. Without treatment these symptoms are likely to progress and can become life-threatening (established renal failure–ERF).The three main treatment options available to patient with ERF are transplantation, dialysis and supportive care without dialysis. Dialysis can occur in a dialysis unit (UHD) or in a patient's home.

Currently 23% of patients with ERF receive a home dialysis in SBU HB, of which a third are on haemodialysis. This is higher than the Welsh and UK national average. NICE and the UK Renal Association stipulate that 30% of dialysis patients would be suitable for and should receive home dialysis. The WRCN is committed to achieving this standard; aligning the department's vision for further expansion and service development with the network's Renal Delivery plan and the commissioning of specialised services in Wales.

This bid will benefit from work already ongoing in Wales regarding patient choice and education. Understanding the reasons behind patient choice towards a particular mode of renal replacement therapy will enable us to provide all options in an appropriately balanced way to help patients make fully informed decisions, e.g. which factors attract patients towards a unit based therapy rather than a home based therapy. Peer to peer information generated within Wales may positively inform patients about a home therapy that they may not have considered previously.

In March 2019, Vaughan Gething (Minister for Health and Social Services) and David Rees (Assembly Member) attended the World Kidney Day awareness and educational event at Ysgol Cwm Brombil, Neath Port Talbot. On hearing A Patient's story, they expressed a view that the provision for home haemodialysis should be expanded across Wales. This gave rise to the idea for an application to the Welsh Government's Transformation Fund.

A patient's story

My kidney failure has been a real challenge. Almost 20 years ago I started dialysis and I made many sacrifices. Strict restriction to my diet and measuring every drop of fluid I drunk was a daily routine. I had to take many medicines every day and attend hospital 3 times every week for dialysis. I scheduled my dialysis so I could continue my career as a staff nurse for the NHS.

After 6 years on dialysis I experienced the freedom that a transplant kidney offers. This amazing gift allowed me to enjoy 10 years of a normal life.

My transplant failed. I had to return to dialysis but this time it is very different.

I now have dialysis in my own home. I do it 5 nights a week as I sleep. I chose when I do it, and after a good night's sleep I wake up having done 8 hours of dialysis. This means I am free to eat and drink what I wish, I do not need a cocktail of drugs and I feel well.

Me and my smart phone manage my own condition. I am supported by the team in the renal unit to care for myself. I access my blood test results and changes to my dialysis treatments and medicines on my phone or tablet. I can change my dialysis days, or hours or my drugs depending on my results. I am in control and able to keep myself well.

My renal unit sends me text reminder for blood test, medicines supplies or changes I need to make. I attend hospital once a month for a blood test, my drugs and a review of my health; and of course a cup of tea and a couple of biscuits (which I am free to eat). Everything is done in single visit; no waiting or delays. After that I have all I need at home and all the information at my fingertips to care for myself.

I am in control of my own treatments. I understand my condition and how to manage it. With digital access to my own records and support when I need it from the renal unit I am well; I have an active and fulfilled life. I am even free to have short holidays abroad now and then.

Home dialysis embodies the concepts outlined in 'A Healthier Wales'. Multidisciplinary support allows people with ERF to manage their own health and wellbeing; dialysing at home. In spite of these benefits, the majority of patients continue to choose and start UHD when for many, home therapy may be more appropriate. The rapid increase in the prevalence of diabetes and obesity means that the number of patients developing kidney failure is likely to increase significantly over the next decade. Continuing to expand UHD capacity is not a sustainable option for the NHS.

Empowering patients to experience self-care through co-production, allows individuals to regain control and manage their chronic illness, promoting well-being and dispelling traditional 'institutionalisation' with direct reliance for provision of care. Improved patient accessibility to treatment, allows patients to re-engage in society and possibly return to work.

As a therapy for ERF, home dialysis offers better clinical and patient centred outcomes. Home dialysis allows better health related quality of life, reduction in hospitalisation, greater independence, increased freedom and reduced travel times. It also has the potential to reduce symptom and tablet burden, relaxation of strict fluid and dietary restrictions as well as improved recovery time following dialysis sessions. Home dialysis also offers patient choice; patients may choose to dialyse during the day or night, and may choose to undertake more regular or longer times on dialysis that can help liberate lifestyle, or dietary and fluid restrictions. Home dialysis promotes

‘health and wealth’ benefits for the individual that reduces the impact of illness on society as a whole.

Expanding the home dialysis population is a cost-effective means of reducing the demand on in-centre dialysis (hospital-based and associated satellite dialysis units). This is an important consideration for delivering future services since there are significant challenges ahead. The demand for kidney care is unprecedented and is growing. With a growing elderly and frail population the demand for dialysis is and will increase. By ensuring those who can care for themselves at home are enabled to do so, resource can be utilised for the increase in volume and complexity of all dialysis provision.

Patient transport is a costly element of in-centre dialysis due to the frequency of dialysis treatment (at least three times per week for the majority of patients). Due to the rurality of Wales, these journeys can often be lengthy and time consuming for patients. Alternative health care models must be championed in an environment of austerity, healthcare staff shortages and inequitable access to care.

SBUHB and the South West Wales region is well equipped to lead a paradigm shift in the approach to dialysis provision given the geographical challenges inherent in delivering a regional service. Realisation of this innovative digital educational project regionally, with collaboration from colleagues across Wales, would enable national scale-up, adoption or adaption.

The objective of this transformational bid is bold and ambitious. Requiring changes to staff engagement and streamlining training procedures in line with the long-term vision and aspirations for home dialysis. As well as a change in mind-set, a change in process and structure will springboard SBUHB and Wales to a deserved position as a UK exemplar of home dialysis. Developed with patients, for patients, a supportive self-care treatment, centred on co-production importantly puts patients back in control.

CURRENT EDUCATION PROGRAMME

The way pre-dialysis education is delivered differs across the country varies. Some areas have a dedicated pre-dialysis clinic, other areas have multidisciplinary team meetings whilst others have home visits. The content of the education programme also differs according to local unit policy. These differences across the region are likely to influence patient decisions. The treatments discussed during education also vary according to who delivers the patient education, this could reflect underlying clinician bias (both conscious and unconscious) towards various treatment options.

GOVERNANCE AND RISK ISSUES

No increased levels of risk have been identified for the Health Board as significant. If successful the bid may help to reduce other risks on the register such as 1582 (overcapacity in unit haemodialysis at Morriston hospital), by allowing proportions of staff to move between unit and home dialysis.

If anything, the current bid will reduce the risk rating because it will streamline the training process and thereby allow staff to dedicate more time to direct patient care.
Any increase in the numbers of patients choosing a home therapy will reduce the pressure on unit haemodialysis capacity at Morriston.

No other governance or risk issues have been identified.

FINANCIAL IMPLICATIONS

The TF bid is seeking a total of £271,419 which will be drawn down over a 16 month period from Qtr 4 Fiscal 2019/20 to Qtr 4 Fiscal 2020/21. The funding will establish the infrastructure required to create an innovative digital educational resource. The team are optimistic that this investment will translate into a greater uptake of home dialysis therapies, help maximise current resource and staff time, to provide patients a modern resource for improving health literacy to make informed choices about the treatments they choose. It will tap into and record years of experience and expertise of our excellent renal nurses ensuring that vital skills and knowledge are recorded for the use of our patients now and in the future. This innovation in training will benefit patients in need across Wales.
If successful, the bid will fund the employment of key personnel to deliver the project on a fixed term contract for 12 months (breakdown of costs - appendix 1). It plans to deliver digital patient educational material, available via a digital platform to include web access and via an app. It will be developed in collaboration with patients to ensure that it meets their needs.
There would be no ongoing costs to SBU HB following the completion of the project.

MOVING FORWARD

In order to achieve a patient education programme that fulfils the needs of all renal patients across Wales, we plan to use data collected already from patient focus groups to re-design the education programme around what patients and carers are saying i.e. co-produce a bespoke education programme so information is delivered in a format and manner that actually enables patients/carers to understand and process complex information so they can make a truly informed choice.

A programme timeline is included in appendix 2.

RECOMMENDATION

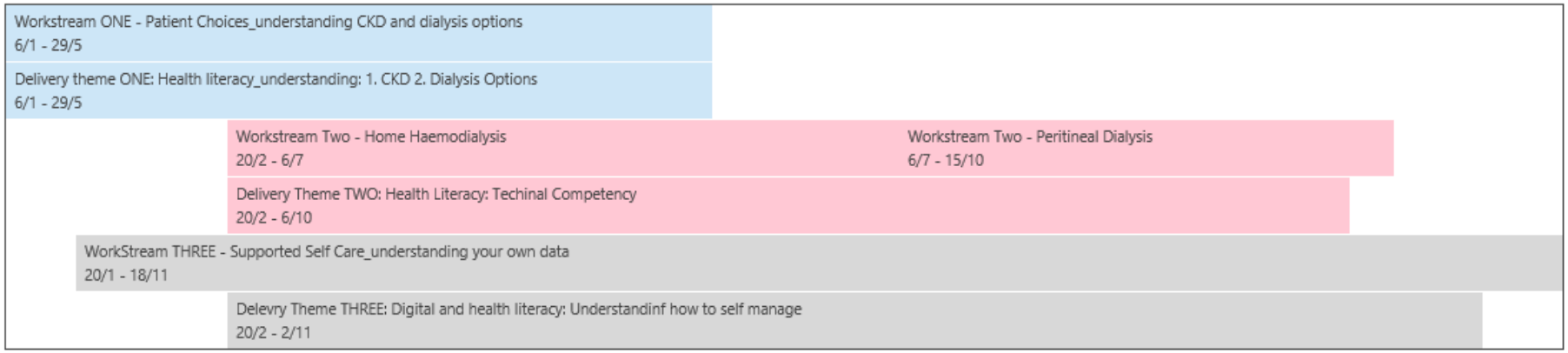
The WRCN is asked to support the bid, in order for the Welsh Glamorgan Regional Partnership Board to be asked to approve the bids' submission to Welsh Government.

Appendix 1 - Costings

Item	Description	Category	Cost (inc VAT)
	Development of patient education package for home dialysis		£271,419

[redacted]

Appendix 2 – Programme timeline



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