Studies of the vasculopathy of Chronic Kidney Disease using iron-enhanced and cardiac Magnetic Resonance Imaging

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Summary

Use of conventional contrast agents, both iodinated or gadolinium-based, in patients with late-stage chronic kidney disease (CKD) are limited by the risks for additional acute kidney injury and nephrogenic systemic fibrosis (NSF), respectively, that must be balanced by the critical nature of the radiologic study for the well being of the patient. In addition, current techniques have reduced accuracy for arterial diagnosis in the presence of arteriosclerotic calcification or have limitations in assessing peripheral and central vein patency. To overcome these challenges we examined whether ferumoxytol-based vascular magnetic resonance imaging (MRI) can offer a practical solution to both gadolinium-based and iodinated contrast agents when assessing vessel anatomy. We focused on two district groups of patients: a) kidney transplant candidates and b) patients requiring vascular access creation for haemodialysis.

Kidney transplantation is the treatment of choice for suitable patients with end-stage renal disease (ESRD) with around 90 000 kidney transplants performed every year worldwide. Approximately 25% of patients with CKD have evidence of peripheral arterial disease (PAD) on non-invasive studies. Even though PAD does not preclude transplantation, revascularisation procedures may be required before listing. Characterisation of PAD in kidney transplant candidates relies on history, physical examination and imaging studies. Imaging studies with vascular mapping, including computed tomography angiography (CTA), provide precise preoperative anatomy of vascular and extravascular systems allowing the surgeon to determine if kidney transplantation is possible, whether presurgical procedures are necessary, and the best surgical technique for each candidate. Until now the widespread use of CTA in the workup of potential kidney transplant recipients has been limited because of the perceived increased risk of nephrotoxicity in patients with residual renal function.

Preoperative sonographic mapping of arm vessels is essential for creating permanent haemodialysis access and used for arterial and venous evaluation to optimise arteriovenous fistula (AVF) placement. But Duplex ultrasound (US) is limited by an inherent operator-dependence, the inability to provide direct evidence of central stenosis and the lack of image manipulation and reconstruction to inform the surgeon about vascular anatomical course and tortuosity. Contrast-enhanced MR angiography provides excellent visualisation of both central and upper extremity vessels. However, the risk of NSF in advanced CKD

has curtailed its use in arteriovenous access planning. The alternative option of traditional iodinated contrast-based CT angiography risks nephrotoxicity in patients with residual renal function.

Arteriovenous fistula is considered the preferred type of access for maintenance haemodialysis, however it may contribute to maladaptive cardiovascular remodelling. The creation of an AVF leads to a localised area of high flow shunting of blood from the arterial to venous circulation, and exposes the low pressure, high capacitance venous system to the high pressure, low capacitance arterial system. Immediately following creation, AVF is associated with an increase in cardiac output, predominantly as a consequence of reduced systemic vascular resistance, increased myocardial contractility, and an increase in stroke volume and heart rate. Over time, because of the increase in blood volume, the right atrial pressure, pulmonary artery pressure, and left ventricular (LV) end-diastolic pressure gradually increase until the myocardium decompensates, the LV dilates, the ejection fraction declines, and the patient has symptoms of heart failure.

Ferumoxytol has been increasingly used for MR angiography, particularly for patients with CKD. Ferumoxytol is a carbohydrate-coated ultra-small paramagnetic iron oxide approved for intravenous treatment of iron deficiency anaemia. However, ferumoxytol was originally designed as an intravascular contrast agent for MRI, and therefore, has powerful imaging attributes not present in other intravenous iron products nor the extracellular gadolinium-based contrast agents. A large molecular weight of 750 kD for ferumoxytol delays contrast extravasation, allowing slow administration or application before the patient is transferred to the MRI suite. The glomerulus does not filter ferumoxytol. Removal of ferumoxytol occurs via circulating macrophages with the remaining iron oxide particles taken up by the reticuloendothelial system of the liver, spleen and bone marrow. Given its half-life of approximately 15 hours, ferumoxytol allows enhancement of both the arterial and venous vasculature without the need for bolus timing.

As part of this thesis, we have applied novel techniques using ferumoxytol-enhanced MR angiography (FeMRA) whilst planning transplantation or haemodialysis in two comparative cohort studies. To optimise our MRI protocol and ferumoxytol dosing regime, we also performed preliminary feasibility and dose-finding studies. The first cohort included patients undergoing CTA of iliac vasculature prior to listing for kidney transplantation. The second cohort included patients undergoing US vascular mapping

prior to upper limb AVF creation for haemodialysis. A third cohort consisted of study participants in the second cohort who underwent cardiac magnetic resonance imaging (CMR) at baseline and 6 weeks after AVF surgery to assess changes in cardiovascular anatomical and functional parameters. We compared outcomes of interest including quality of image and diagnostic accuracy in a head-to-head design between CTA or Duplex US and FeMRA. For the CMR study, changes in outcomes of interest from baseline to follow-up scans were assessed. All three studies are briefly discussed below.

In a prospective study of 36 kidney transplant candidates, FeMRA was compared with CTA for assessment of arterial and vein diameter, calcification, and signal. FeMRA was comparable to CTA for evaluating arterial diameter and calcification and offered improved venous depiction. Two transplant surgeons identified vein abnormalities critical to venous anastomosis planning in 11% of patients with FeMRA. These findings favor FeMRA and could improve clinical practice.

In a prospective study of 59 participants with CKD requiring upper limb vascular mapping, FeMRA identified 15 central vessel stenoses and characterised 37% of arterial sections as unsuitable for AVF creation compared with 26% for Duplex US ($p = 0.01$). Ferumoxytol-enhanced MR angiography independently predicted successful fistula outcome for models including and excluding central vasculature. Compared with Duplex US, FeMRA had superior detection of central vein stenosis and arterial disease that correlated with outcomes of arteriovenous fistula surgery for haemodialysis.

In a prospective study of 40 participants who underwent CMR imaging before and an average time of 6.4 weeks after AVF creation, a mean increase of 7.4 g ($p = 0.02$) was observed in LV myocardial mass. The changes were more pronounced in high blood flow arteriovenous fistulas (15.5 g, $p = 0.003$). Significant increases in LV end-diastolic volumes, cardiac output, and cardiac index were also seen after AVF creation ($p < 0.04$). These data support further investigation of the impact of routine AVF creation in CKD patients on clinical outcomes.

Our results demonstrate that ferumoxytol-enhanced MR angiography is a robust method for vascular mapping of patients with advanced CKD with similar or higher yield compared with the currently employed imaging techniques. Ferumoxytol's favorable pharmacodynamics allows imaging of predialysis patients without concerns for iodine or gadolinium contrast toxicity.

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Authors Declaration

The work presented in this thesis was that of the author and his supervisors, Professor Patrick Mark and Mr David Kingsmore. All experimental work was carried out by the Author unless otherwise stated.

More specifically, I have obtained sponsor and ethical approvals, study funding and contrast supply free of charge, performed patient screening and recruitment, supervised MRI scans, performed all the ultrasound scans, analysed MRI scans, and drafted all published manuscripts.

This thesis has been composed by myself and is a record of work performed by myself. It has not been previously submitted for a higher degree.

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List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
AA	Abdominal aorta
ABI	Ankle-brachial index
ACCF	American College of Cardiology Foundation
AHA	American Heart Association
AKI	Acute kidney injury
ALARA	As low as reasonably achievable
AV	Arteriovenous
AVF	Arteriovenous fistula
AVG	Arteriovenous graft
BA	Brachial artery
BMI	Body mass index
b-SSFP	Balanced steady state free procession
BV	Basilic vein
CAC	Coronary artery calcification
CCI	Charlson comorbidity index
CE-MRA	Contrast-enhanced MRA
CHF	Congestive heart failure
CI	Confidence interval

CI-AKI	Contrast-induced acute kidney injury
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMR	Cardiac magnetic resonance imaging
CNR	Contrast-to-noise ratio
CRP	C-reactive protein
CT	Computed tomography
CTA	Computed tomography angiography
CV	Cephalic vein
CVC	Central venous catheter
CVD	Cardiovascular disease
CVS	Central vein stenosis
DSA	Digital subtraction angiography
DUS	Duplex ultrasound
DVT	Deep vein thrombosis
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
ESVS	European Society for Vascular Surgery
FDA	Food and Drug Administration

FeMRA	Ferumoxytol-enhanced magnetic resonance angiography
FLASH	Fast low-angle shot
FMD	Flow-mediated dilatation
FTM	Failure to mature
GBCAs	Gadolinium-based contrast agents
HD	Haemodialysis
HFpEF	Heart failure with preserved ejection fraction
HR	Hazard ratio
HRRS	High-resolution steady-state
hs-CRP	High sensitivity C-reactive protein
ICAM-1	Intercellular adhesion molecule 1
ICC	Interclass correlation coefficient
IL-1	Interleukin-1
IL-6	Interleukin-6
IVC	Inferior vena cava
KDIGO	Kidney Disease: Improving Global Outcomes
KDOQI	Kidney Disease Outcomes Quality Initiative
KTR	Kidney transplant recipient
LV	Left ventricular
LVH	Left ventricular hypertrophy
MCP-1	Monocyte chemoattractant protein-1

MDRD	Modification of Diet in Renal Disease
MED	Minimum effective dose
MI	Myocardial infarction
MIP	Maximum intensity projection
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
NO	Nitric oxide
NSF	Nephrogenic systemic fibrosis
NT-proBNP	N-Terminal-pro B-type Natriuretic Peptide
PACS	Picture Archiving and Communication System
PAD	Peripheral artery disease
PIS	Patient information sheet
PTH	Parathyroid hormone
PVR	Pulse volume recording
QISS	Quiescent interval single-shot
RA	Radial artery
RCIA	Right common iliac artery
RCIV	Right common iliac vein
REC	Research Ethics Committee
REIA	Right external iliac artery
REIV	Right external iliac vein

ROI	Regions of interest
s-IL2R	Soluble interleukin-2 receptor
SBP	Systolic blood pressure
SD	Standard deviation
SI	Signal intensity
SMC	Smooth muscle cells
SNR	Signal-to-noise ratio
SSFP	Steady-state free procession
TGFß	Transforming growth factor beta
TLR-4	Toll-like receptor 4
TNF-α	Tumor necrosis factor-a
TOF	Time of flight
U	Units
US	Ultrasound
USPIO	Ultrasmall superparamagnetic iron oxide
USRDS	United States Renal Data System
VCAM-1	Vascular cell adhesion molecule 1
VSMC	Vascular smooth muscle cells

Chapter 1. INTRODUCTION

1.1 Vasculopathy in chronic kidney disease

1.1.1 Epidemiology and pathophysiology

Reduced kidney function is a risk factor for cardiovascular disease (CVD) in the general population, in part reflecting the close association of CVD risk factors and glomerular filtration rate. Population data (Fellström et al., 2005) suggest that even minor kidney dysfunction is associated with increased CVD risk.

Cardiovascular disease is the most common cause of death in patients with chronic kidney disease (CKD). The risk of CVD death gradually rises during a renal patient's timeline from the development of CKD to progression to end-stage renal disease (ESRD) and is dramatically increased during dialysis (Figure 1-1) (Turin et al., 2012). Cardiovascular disease mortality in haemodialysis (HD) patients is 10–20 times greater than in the general population (Foley et al., 1998; Levey et al., 1998), whilst transplantation confers the highest survival benefit among all the different renal replacement therapies (Figure 1-2).

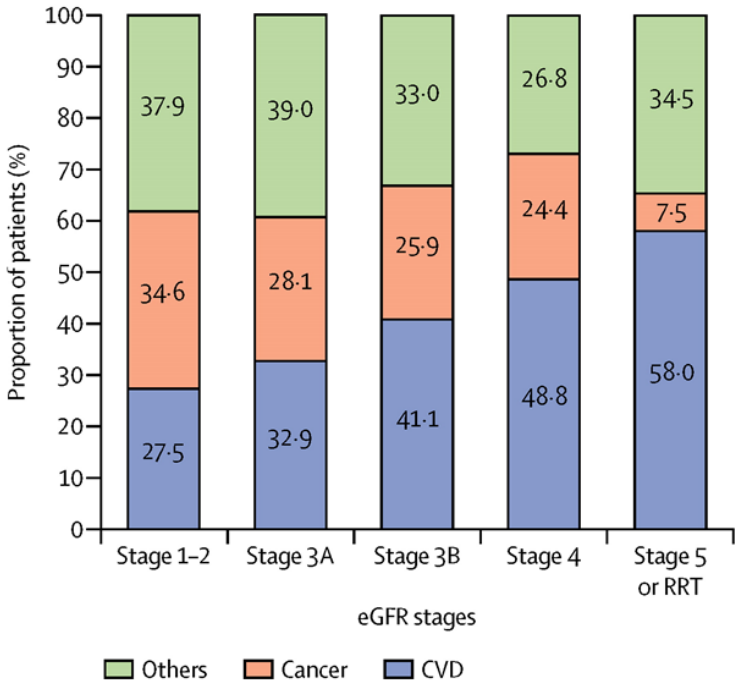


Figure 1-1 Causes of death per eGFR stages.

Data are adjusted per eGFR stage for age and sex to the WHO world averages in 2000–05.

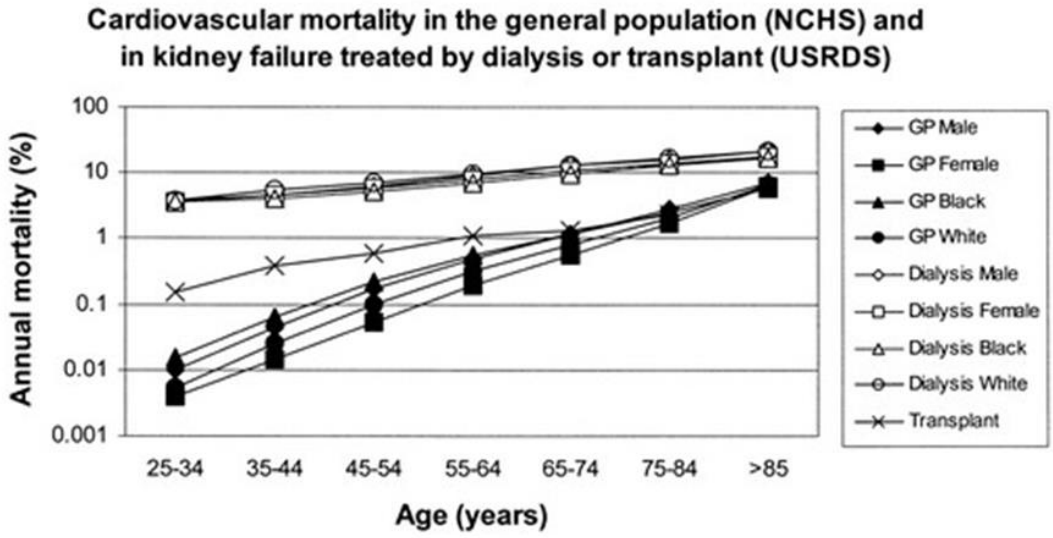


Figure 1-2 Cardiovascular mortality.

Defined by death due to arrhythmias, cardiomyopathy, cardiac arrest, myocardial infarction, atherosclerotic heart disease, and pulmonary oedema in general population (GP; National Center for Health Statistics [NCHS] multiple cause of mortality data files International Classification of Diseases, 9th Revision [ICD 9] codes 402, 404, 410 to 414, and 425 to 429, 1993) compared with kidney failure treated by dialysis or kidney transplant (United States Renal Data System [USRDS] special data request Health Care Financing Administration form 2746 Nos. 23, 26 to 29, and 31, 1994 to 1996). Data are stratified by age, race, and sex. CVD mortality is underestimated in kidney transplant recipients owing to incomplete ascertainment of cause of death.

In the general population, CVD predominantly relates to underlying coronary artery atherosclerosis and is associated with conventional cardiovascular risk factors such as diabetes mellitus, hypertension, dyslipidaemia, cigarette smoking and family history. This paradigm does not hold true for CKD patients who exhibit a number of risk factors associated with pre-existing renal disease. In patients with ESRD sudden, presumed arrhythmic, cardiac death rather than myocardial infarction is the predominant mode of cardiovascular mortality. Despite the high incidence of sudden cardiac death, surprisingly little is known about arrhythmias in ESRD. This reflects the difficulty in capturing short-lived arrhythmic episodes in asymptomatic patients.

The mechanisms underlying the high cardiovascular risk in CKD patients involve various pathogenetic mechanisms including excess vascular calcification, endothelial dysfunction, and inflammation.

1.1.1.1 Vascular calcification

Vascular calcification is observed even in very young patients with CKD, who lack the typical cardiovascular risk factors of hypertension, dyslipidaemia, and smoking (Goodman et al., 2000; London et al., 2003; Sigrist et al., 2007). All large and medium-sized muscular arteries and arterioles can calcify. Although veins hardly ever calcify (unless injured or arterialised), calcification has been described within veins used to create new dialysis vascular access in patients with CKD, and it is located predominately within the neointimal and medial layers (Lee et al., 2012). This difference is probably due to differences in mechanical forces and in histologic structure between arteries and veins.

Vascular calcification is characterised by deposition of calcium phosphate within vessels, and is now understood to be an active, cell mediated process, whereby vascular smooth muscle cells (VSMC) convert to an osteoblast-like phenotype, releasing matrix and inflammatory chemokines. Phosphate is transported into VSMC by sodium dependent phosphate co-transporter, Pit-1, and causes osteogenic differentiation by activation of transcription factors such as core binding factor a1 (cbfa-1) (Steitz et al., 2001). Uraemic serum also causes VSMC osteoblastic differentiation independently of phosphate concentration however, and this might be mediated through oxidative stress. For example, H_2O_2 was shown to induce an osteogenic phenotype in VSMC, signalling via Runx2, Msx2-wnt, and NOX (Byon et al., 2008). Indeed, even the calcific effects of hyperphosphataemia are mediated in part through redox signalling. In a model of uraemic vascular calcification using bovine aortic smooth muscle cells, calcium deposition was abrogated by inhibition of mtROS production (Zhao et al., 2011). As well as these biochemical, hormonal, and iatrogenic elements contributing to vascular calcification in CKD, there is deficiency of a number of protective mechanisms. Circulating regulators of extracellular calcium such as fetuin A and matrix GLA protein are reduced in CKD (Luo et al., 1997), and patients with the lowest levels of these inhibitors have worse cardiovascular outcomes. Pyrophosphate depletion causes massive arterial calcification in mice, and levels of this inhibitor are reduced by HD.

Among CKD patients, there are two types of vascular calcification, with different pathogeneses: medial and intimal calcification. Medial calcification seems to be more closely associated with HD treatment and its duration and is a powerful and independent prognostic marker of all-cause and CV mortality, while intimal calcification is associated with generalised atherosclerosis, which is not specifically attributable to HD (London et al., 2003). The two processes can coexist in the same patient, and indeed the same vessel, and both are associated with CV mortality. In a study of patients with pre-dialysis CKD, vascular calcification was assessed by CT of the abdominal aorta and superficial femoral artery, and found to be associated with poor renal function and higher pulse wave velocity (Toussaint et al., 2008).

Medial calcification occurs as a result of both a phenotype switch of vascular smooth muscle cells to osteoblast–like cells and local inflammation (Vervloet & Cozzolino, 2017) (Cozzolino et al., 2006). A number of elements of the uraemic milieu have been shown to promote the phenotype change, such as hyperphosphatemia, hypercalcemia, and, possibly, high concentrations of parathyroid hormone (PTH). Hypercalcemia and hyperphosphatemia both increase the release of matrix vesicles, resulting in the deposition of hydroxyapatite. The molecular mechanisms regulating these processes have not been completely defined but likely involve the inhibition of target genes by microRNA (Fakhry et al., 2018). Medial calcification decreases vascular distensibility leading to increased vessel stiffness and an increased pulse pressure. This contributes to the risk of heart failure, stroke, or myocardial infarction. Medial calcification also worsens the progression of intimal lesions.

Intimal calcification is secondary to established atherosclerosis. The pathogenesis of atherosclerosis appears to be the same in CKD as in non-CKD patients. However, mechanisms that contribute to intimal calcification, such as shear stress, local inflammation, and the calcification of macrophage and vascular smooth muscle cell-derived microvesicles are amplified in CKD patients. In addition, the arterial stiffness caused by medial calcification likely directly contributes to the shear stress, atherosclerosis, and calcification of the intima (Huveneers et al., 2015). The major clinical effect of intimal calcification is in the formation and progression of atherosclerotic lesions resulting in coronary artery disease, cerebrovascular disease, and peripheral arterial disease (PAD).

1.1.1.2 Endothelial dysfunction

The endothelium is the single cell luminal lining of the vascular system and releases a variety of factors, which play an important role in regulation of VSMC tone and proliferation, inflammatory cell chemotaxis and activation, and platelet activation and aggregation. In particular, nitric oxide (NO) produced by endothelial cells diffuses freely into VSMC where it activates guanylate cyclase and causes endothelium dependent vasodilatation (Figure 1-3) (Ignarro, 1990).

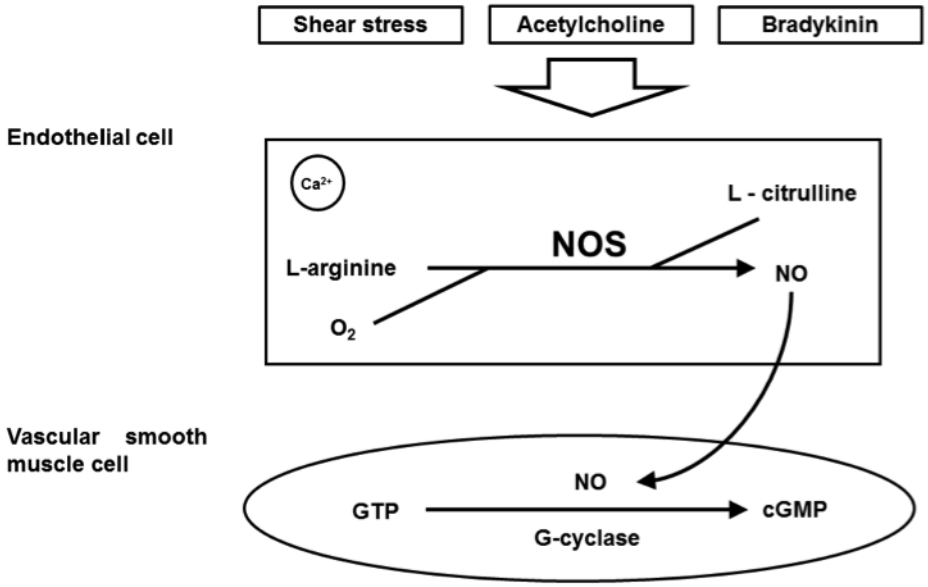


Figure 1-3 Vascular smooth muscle cell relaxation in response to nitric oxide.

NO is generated from NOS also utilising molecular oxygen whilst producing the by-product L-citrulline. NO is freely diffusible through cell membranes, and moves from the endothelial cell to the vascular smooth muscle cell where it activates G-cyclase. The cGMP which is produced activates protein kinases which ultimately lead to release of intracellular calcium and smooth muscle relaxation. NO = Nitric oxide, NOS = Nitric oxide synthase, G-cyclase = Guanylyl cyclase, cGMP = cyclic guanosine monophosphate.

Endothelial dysfunction is the earliest step in the cascade of events leading to atherosclerosis, and the fundamental feature of this condition is impaired NO bioavailability. Endothelial dysfunction is associated with renal failure and contributes to the accelerated atherosclerosis in patients with CKD. If perpetuated long enough, dysfunction of endothelial cells is followed by their apoptosis, which can finally result in functional and structural disintegration of the endothelial cell layer. In patients with CKD, ongoing endothelial damage in the capillary system of the renal medulla and accompanying vascular rarefaction are thought to be central processes toward progressive kidney damage.

Exposure of endothelial cells in culture to uraemic serum results in switching to a pro-atherogenic phenotype. For example, a proteomic analysis showed increased expression of proteins relating to inflammation and oxidative stress, such as proteasome components, superoxide dismutase and glutathione peroxidase, which probably occurs via NFκB signalling (Carbo et al., 2008). Similarly, rabbit aortic endothelial cells cultured in uraemic serum show increased NFκB nuclear translocation and DNA binding, reduced NO production and increased TNFα production (Feng et al., 2011). In some studies uraemic serum was shown to increase endothelial cell proliferation (Monroy et al., 2015; Serradell et al., 2003) whereas in other studies reduced proliferation, and rather apoptosis was observed (García-Jérez et al., 2015). The effect may depend on the concentration of uraemic serum, with proliferation seen at lower concentration, and apoptosis at higher concentrations; or to draw a clinical correlation, the effect of uraemia on the vascular endothelium may depend on the severity of renal disease. Patients with CKD also show reduced differentiation of endothelial progenitor cells (Goligorsky et al., 2010), which may reflect reduced capacity for vascular repair.

Moreover, uraemia and endothelial damage have been shown to up-regulate several markers of coagulation, fibrinolysis and endothelial adhesion molecules that enhance platelet binding. Finally, damage and subsequent activation of the vascular endothelium initiates a cascade of molecular and cellular events that lead to neointima formation and stenosis, including vascular inflammation, dedifferentiation of quiescent smooth muscle cells (SMC) and increased deposition of extracellular matrix. This is shown in *in vivo* vascular function studies such as flow mediated dilatation (FMD) and venous occlusion plethysmography. In one study of 105 patients with CKD, FMD was reduced to 3.8% compared to 5.7% in controls (Dogra et al., 2006). In another study of 304 patients with CKD not on dialysis, FMD was reduced in a stepwise manner with increasing severity of renal impairment (Yilmaz et al., 2011). Similarly, endothelial function measured using plethysmography was shown to be reduced in CKD; brachial artery blood flow showed a lesser response to metacholine infusion in CKD as compared to controls, whilst response to nitroprusside infusion was the same in both groups (Morris et al., 2000).

Taken together, it has been postulated that endothelial dysfunction represents the earliest stage of the development of atherosclerosis and cardiovascular disease, as well as a final common mechanism by which conventional and non-conventional cardiovascular risk factors exert pathophysiological effect.

1.1.1.3 Inflammation

Chronic low-grade inflammation, as evidenced by increased levels of pro-inflammatory cytokines and C-reactive protein (CRP), is a common feature of CKD and may cause atherosclerotic CVD through various pathogenetic mechanisms. Evidence suggests that persistent inflammation may also be a risk factor for progression of CKD, which may result in a vicious inflammation-driven circle. The causes of inflammation in CKD are multifactorial. The influence of various comorbidities may contribute to inflammation in the setting of progressive loss of renal function.

Cytokines and pro-inflammatory factors have been shown to play central roles in the activation of acute and chronic vascular responses to injury (Igata et al., 2005). For example, thrombin secreted by activated platelets adhering to the injured endothelium triggers the release of fibroblast growth factors, stimulating SMC mitogenesis and chemotaxis. Transforming growth factor beta (TGFß), a pleiotropic cytokine, promotes intimal hyperplasia by augmenting neointimal cell proliferation, inducing SMC migration and stimulating the secretion of fibrotic extracellular matrix proteins (Pardali et al., 2010). Patients with renal disease undergoing HD have a raised inflammatory profile with significantly increased high sensitivity C-reactive protein (hs-CRP), serum tumor necrosis factor-a (TNF-α), interleukin-1 (IL-1), soluble interleukin-2 receptor (s-IL2R), interleukin-6 (IL-6), monocyte chemoattractant protein-1 (MCP-1), vascular cell adhesion molecule 1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1), as well as increased expression of the pro-inflammatory receptor Toll-like receptor 4 (TLR-4) (de Graaf et al., 2006; Lobo et al., 2013; Milburn et al., 2013; Papayianni et al., 2002; Smits et al., 2000).

In addition, inflammation plays a crucial role in calcification. Infiltrating macrophages release pro-inflammatory cytokines that drive the influx of lymphocytes and smooth muscle cells(Tabas & Bornfeldt, 2016). Cellular microvesicles released from macrophages form a nidus for calcification, and macrophage-derived inflammatory regulators contribute to the disintegration of elastic fibers and matrix components in the vessel wall, all which may promote calcification.

1.2 Imaging studies to assess vasculopathy in CKD

Traditional imaging methods to assess the vasculature may be challenging to apply in patients with CKD as they have a higher risk of complications or suboptimal performance. These patients may require vascular imaging for various indications similar to the general population, but also for indications that are unique in the CKD group. For example, vascular imaging is integral part of the evaluation for kidney transplant candidacy evaluation and suitability for vascular access creation.

Evaluation of the aortoiliac vasculature prior to kidney transplantation with CT or MRI can be challenging due to the risk of precipitating worsening of the kidney function with iodine-based contrast agents, systemic toxicity with GBCAs, poor diagnostic yield with non-contrast techniques or blooming artifacts from extensive calcification with contrast-based techniques.

Inadequate anatomy of peripheral vessels (smaller arterial diameter, small draining vein) before access creation is a risk factor for arteriovenous fistula (AVF) failure. Equally, central vein stenosis (CVS) is a complication of dialysis central venous catheters due to stagnation of blood, turbulent blood flow during HD and repeated catheterisations (Oguzkurt et al., 2004; Schwab et al., 1988) and can compromise AVF maturation. Nearly 100% of AVFs that fail to mature have an anatomic problem of some type (Beathard, Arnold, Jackson, Litchfield, & Lifeline, 2003; Beathard et al., 1999; Nassar et al., 2006) and more than one lesions are frequently present when an AVF fails (Beathard, Arnold, Jackson, Litchfield, & Physician Operators Forum of, 2003; Nassar et al., 2006). Duplex ultrasound (US) is routinely performed for vascular mapping pre-operatively, however it cannot directly assess for the presence of CVS.

1.2.1 Evaluation of the potential kidney transplant recipient

Kidney transplantation is the treatment of choice for most patients with ESRD. As well as improving quality of life, successful transplantation accords major benefits by reducing cardiovascular risk in these patients. Despite the drop in the waiting time to a kidney transplant over the last decade to an average of two and a half years in the UK, there is still a significant shortage of donated organs. This creates a need for thorough assessment of potential kidney transplant recipients (KTRs) to optimise usage of the offered kidneys.

A large number of potential KTRs with established renal failure have peripheral arterial disease and need additional tests to characterise the vessels before placement of a kidney graft. Among dialysis patients, 24% have clinical evidence of PAD (e.g., claudication, rest pain, or tissue loss), 35% have evidence of an abnormal ankle-brachial index (ABI), and nearly 46% have health care claims related to PAD (Jones et al., 2016). Mild claudication is typically caused by single-segment disease with development of collateral circulation. Severe claudication and critical limb ischemia are associated with multilevel disease. Overall survival among ESRD patients who develop critical limb ischemia is less than 23% at 5 years. PAD was a risk factor for waitlist mortality (HR 1.47, $p < 0.001$) and subsequent allograft loss (HR 2.01, $p < 0.001$)(Brar et al., 2013). Patients with progressive peripheral arterial occlusive disease experience markedly lower post-transplant survival (5-year survival 26% vs 80%) and may not benefit from transplantation (Sung et al., 2000). Furthermore, the degree of iliac artery calcification increases with length of dialysis prior to evaluation and listing (Kahn, Ram, Eberhard, Groselj-Strele, Obermayer-Pietsch, & Müller, 2017). However, when compared to remaining on dialysis, kidney transplant in patients with PAD was associated with 50% reduction in mortality at 5 years (68.1% vs 34.5%, $p < 0.0001$).

Advanced aortoiliac disease is a relative contraindication to kidney transplantation. Aortoiliac disease includes the infrarenal segment of the abdominal aorta, common iliac arteries, internal iliac arteries, and external iliac arteries, proximal to the inguinal ligament or deep circumflex iliac artery. High-grade, calcific stenosis precludes kidney transplant in the ipsilateral iliac fossa, if there is an insufficient length of soft artery to allow safe clamp placement and anastomosis. Peripheral arterial disease is not only a marker for general cardiovascular morbidity but also a risk factor for technical complications. Imaging studies with vascular mapping can assess arterial and venous anatomy, thereby establishing whether kidney transplantation is possible, whether presurgical procedures are necessary, and which is the best surgical technique for each candidate.

Guidelines in the assessment of potential KTRs with peripheral arterial disease emphasise the significance of identification of arterial or venous disease before proceeding to transplantation. This is highlighted in the recent Kidney Disease: Improving Global Outcomes (KDIGO) guideline on the evaluation of candidates for kidney transplantation (Chadban et al., 2020), where they recommend assessment of vascular anatomy and patency for these patients. Characterisation of PAD in transplant candidates relies on

history, physical examination and imaging studies. History and physical examination will identify high-risk patients that warrant further investigations. Potential KTRs with clinically apparent PAD should undergo imaging and management of their vasculature in consultation with a vascular surgeon before considered for transplantation. For candidates without clinically apparent PAD, the ones with risk factors for PAD (e.g., diabetes, tobacco use, history of CVD and long-term dialysis dependence) or clinical evidence of limb ischemia (e.g., claudication, rest pain, or prior amputations) should be screened for PAD.

Historically, abdominal radiograph of the abdomen and pelvis to examine for iliac calcification is the initial test to assess the burden of arteriosclerosis. A great deal of calcification may be indicative of a widespread atheromatous process within the arteries and is commonly followed by further imaging studies. Assessment of the severity of PAD can be accomplished through lower extremity segmental flow and pressure studies and non-invasive duplex evaluation (Chen et al., 2016). Non-contrast computed tomography (CT) can provide important information on the degree of proximal iliac artery and aortic calcification, which assists with pre-operative planning (Kahn, Ram, Eberhard, Groselj-Strele, Obermayer-Pietsch, & Müller, 2017). However, CT has reduced accuracy for arterial diagnosis in the presence of arteriosclerotic calcification, which is extremely common in these patients. Computed tomography angiography (CTA) entails the use of iodine-based contrast that may precipitate deterioration in kidney function or even the need for renal replacement therapy (Davenport et al., 2013; Parfrey et al., 1989). Similarly, in patients receiving maintenance HD, contrast administration has the potential risk of accelerating a decline in residual kidney function. Magnetic resonance angiography (MRA) in patients with advanced kidney disease using linear chelate gadolinium-based contrast agents (GBCAs) has been associated with the rare disease ‘nephrogenic systemic fibrosis’ (NSF) (Collidge et al., 2007). Non-contrast-enhanced MRA (CE-MRA), such as time-of-flight or phase-contrast techniques, is very time consuming for assessment of multidirectional flow with poor signal from deep vascular structures and at the sites of flow disturbance. Alternative imaging methods also have drawbacks: for example, Duplex US is a potentially useful modality but can be difficult to interpret and is vulnerable to high inter- and intra-operator variability and patient habitus. Lastly, this patient group has a higher risk of complications from conventional catheter-based x-ray angiography, which is usually reserved for use in the setting of possible endovascular intervention or targeted angiography when lower volumes of iodine-based contrast medium can safely be used in patients with CKD.

1.2.2 Vascular mapping before vascular access creation

The goal of vascular access is to provide reliable, safe, repeated access to the circulation with minimal complications. Arteriovenous fistulas are preferred to grafts and central venous catheters (CVC) given their long-term patency and lower rate of complications. Once a fistula is created, it must develop to the point that it is of adequate size and depth to allow successful repetitive cannulation, and that it can provide adequate blood flow to support the HD prescription. Arteriovenous fistula maturation is a complex vascular remodeling process that requires vessel dilation, marked increases in blood flow rates in the feeding artery and draining vein, and structural changes in the vessel walls (Dixon, 2006). Successful maturation and use of a newly created AVF relies on multiple factors including demographic and clinical parameters, anatomical characteristics pre- and post-operatively, biological predictors of outcome, and practices associated with surveillance. It is generally apparent at four to six weeks following creation whether an AVF will mature without additional intervention (Asif et al., 2006; Ferring et al., 2014).

Evaluation of the advanced CKD patient in preparation for the placement of a dialysis access is extremely important. Proper patient selection will enhance the opportunity to place the proper access type in the proper patient. A major problem with AVFs is the high frequency of primary failure as a result of either poor maturation or early thrombosis. Thereafter, maintaining AVF patency may be compromised by emergent structural or functional problems that may develop during routine use (Badero et al., 2008; Sivanesan et al., 1999). Their durability is far from optimal with 1-year primary patency rates of 60–65% (Tordoir et al., 2003). In a multicentre, observational cohort study of 582 new AVFs in 537 patients, only 116 (37.3%) pre-dialysis and 131 (48.3%) dialysis patients were using the AVF for HD 1 year after creation (Figure 1-4) (Stoumpos, Traynor, et al., 2019). In this study primary patency was defined as the interval from the time of access placement until any type of intervention to maintain or to restore patency, access thrombosis, or time of measurement of patency; primary assisted patency was defined as the interval from the time of access placement until access thrombosis or the time of measurement of patency; and secondary patency was defined as the interval from the time of access placement until access abandonment, thrombosis, or time of measurement of patency (Sidawy et al., 2008). The primary patency at 1 year was 48% (95% CI, 44-52; n=234/582), primary assisted patency was 67% (95% CI, 63-71; n=322/582), and secondary patency was 69% (95% CI, 65-73; n=331/582) (Figure 1-5). In two meta-analyses of AVF patency reports covering

>20 years of AVF creation, when primary failure was included in the calculation of patency rate, the primary and secondary patency rates were 60-64% and 71-79% at 1 year, respectively (Al-Jaishi et al., 2014; Bylsma et al., 2017). As such, AVF dysfunction is one of the leading causes of morbidity and mortality among ESRD patients (Bray et al., 2012; Feldman et al., 1996).

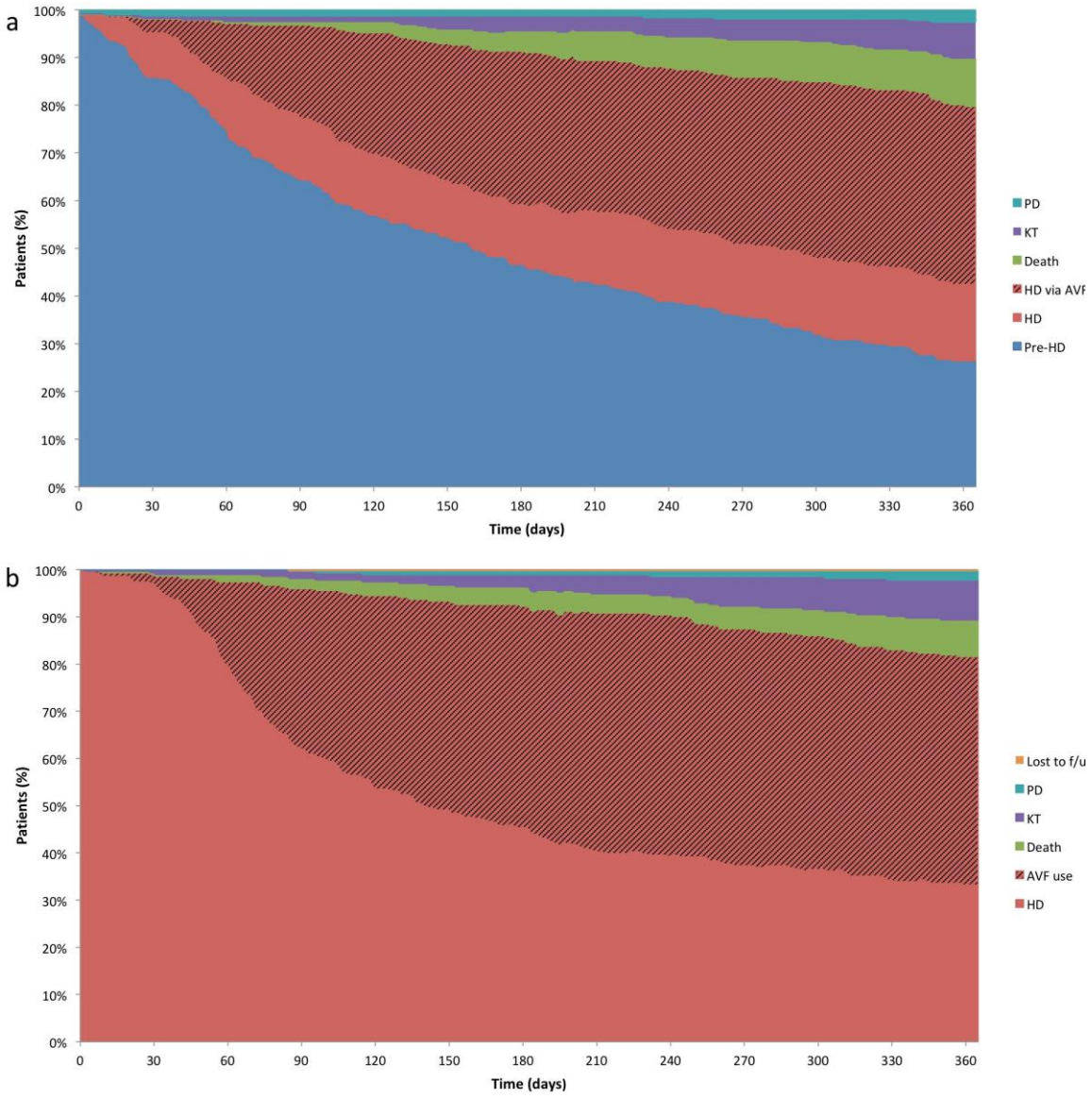


Figure 1-4 A graph chart displaying the natural history of patients' status.

Patients' status from the time of AVF creation and up to 1 year of follow-up divided by patients' status at time of AV access creation. A. Predialysis patients. B. Dialysis-dependent patients.
AVF, arteriovenous fistula; f/u, follow-up; HD, haemodialysis; KT, kidney transplantation; PD, peritoneal dialysis. Reproduced with permission from J Vasc Surg. 69(6):1889-1898 (2019). Copyright 2018 Society for Vascular Surgery.

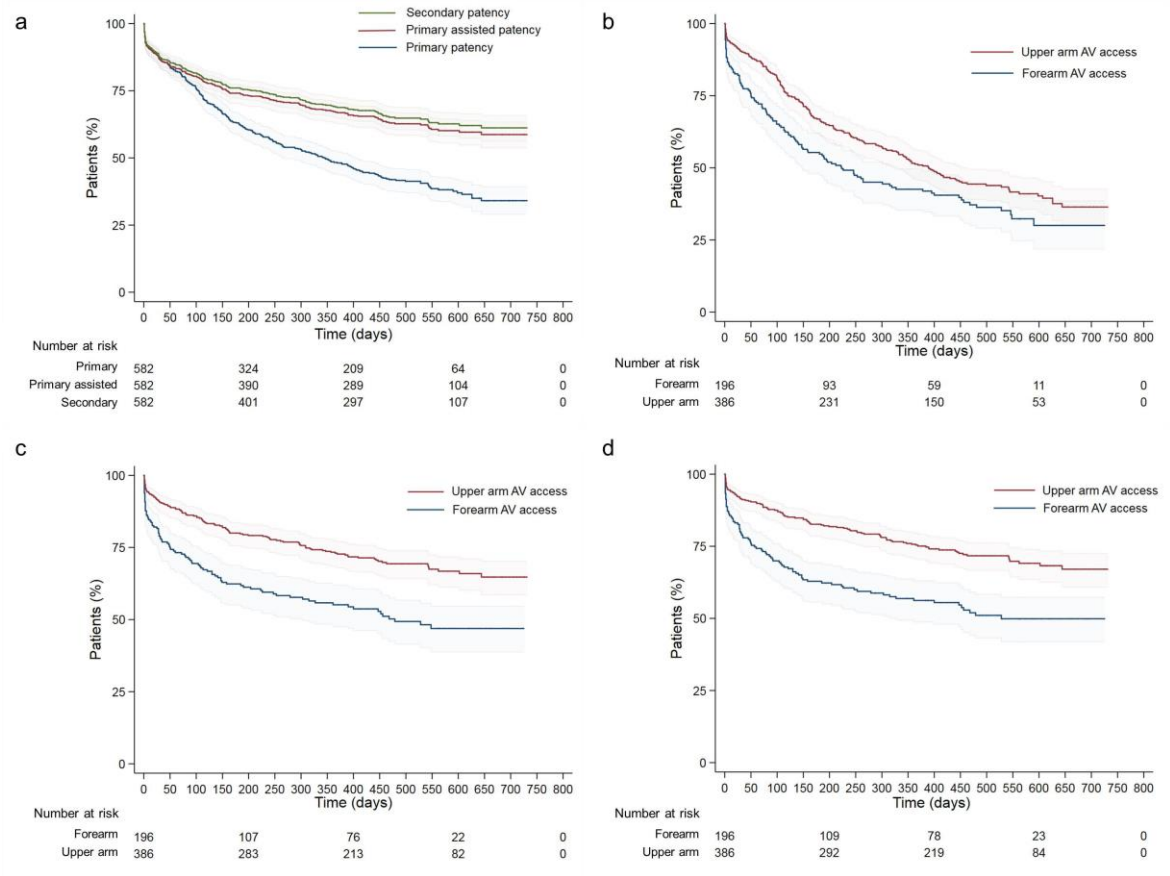


Figure 1-5 Kaplan-Meier curves for AVF patency.

A. Primary, primary assisted, and secondary patency of all AVFs. B-D. Patency by AVF type (upper arm vs forearm): primary patency (B), primary assisted patency (C), and secondary patency (D). Reproduced with permission from J Vasc Surg. 69(6):1889-1898 (2019). Copyright 2018 Society for Vascular Surgery.

The exact pathophysiology of AVF failure is unclear, although the cellular mechanisms leading to increased proliferation, migration, and eventually stenosis have common pathways including inflammation, uremia, hypoxia, sheer stress, and increased thrombogenicity. These pathways work synergistically through shared molecular messengers causing excessive intimal hyperplasia and eventually narrowing of the venous outflow, ultimately leading to AVF thrombosis (Rothuizen et al., 2013). The stimuli responsible for the formation of intimal hyperplasia in AVFs are triggered by vascular access surgery as well as trauma of repeated cannulation (MacAskill et al., 2015).

The term vascular mapping refers to the study and evaluation of the vessels (both arterial and venous) in preparation for the creation of a vascular access. Vascular mapping should be performed in all patients prior to the placement of an access. Routine preoperative mapping results in a marked increase in placement of arteriovenous fistulas (AVF), as well as an improvement in the adequacy of forearm fistulas for dialysis (Allon et al., 2001;

Ilhan et al., 2013; Silva et al., 1998). Arterial anatomy is of obvious importance; however, if there is a vascular problem that is going to interfere with the creation of an AVF, it is more likely to be venous than arterial. Evaluation of both is important to success.

The goals of the arterial evaluation are to identify an artery for the inflow of the AV access that is capable of delivering blood flow at a rate adequate to support haemodialysis. With the increasing age of the dialysis population and the frequency of diabetes and hypertension as comorbidities, arterial occlusive disease is commonly encountered in the patient being evaluated for haemodialysis AV access. The use of the chosen artery must not jeopardize the viability of the digits and hand. A generally recognised standard for arterial diameter does not exist. A minimum arterial diameter threshold of 2 mm is the most commonly quoted based on a landmark publication on this subject (Silva et al., 1998) showing an increased rate of AVF creation (63 vs 14%) with a lower primary failure rate (8 vs 36%) using a radial artery diameter threshold of 2 mm.

Detailed evaluation of the venous anatomy is an important aspect of vascular mapping in preparation for haemodialysis AV access placement. Vascular problems affecting access creation are more likely to be venous than arterial. The veins of the extremity are frequently the object of the iatrogenic injury as a result of venepuncture or central venous access. As with arterial size, a generally recognised standard for vein size does not exist. The minimum venous diameter threshold most often quoted is 2.5 mm at the point of the anastomosis (Silva et al., 1998). Interestingly, one report involving small groups of patients suggests that forearm venous distensibility rather than luminal diameter is a predictor of AVF success (van der Linden et al., 2006).

Different methodologies are currently being used for vascular mapping depending upon local practice and expertise. Ultrasound is the most commonly used imaging modality for evaluating the vessel anatomy prior to AV access placement and has become the standard of practice. It is non-invasive, it has the ability to perform dynamic studies and it does not require administration of intravenous radiocontrast. The main disadvantage of US is an inability to evaluate the central veins. Angiography may be the preferred method in selected patients (those with risk factors for central stenosis, patients with previous failed attempts for AV access creation, obese patients, and patients with severe PAD) as it can accurately assess central and peripheral vasculature. A disadvantage of angiography lies in the need to initiate an intravenous access in the hand to do an optimal study, which is

challenging given the lack of intravenous access sites in CKD patients. Also its use has been limited, primarily due to concern over the use of radiocontrast in patients with residual renal function.

1.2.3 Vascular access surveillance

All arteriovenous fistulas should be evaluated after their creation for appropriate fistula maturation. The newly created AVF should be examined by an experienced clinician no later than four to six weeks after creation to determine if the AVF is clinically usable (Saran et al., 2004). As a general rule, at 6 weeks following fistula creation it is generally apparent whether a fistula will mature without additional intervention (Asif et al., 2006; Ferring et al., 2014). Fistula non-maturation is the most common cause of early fistula failure; 30%–60% of newly created fistulas are abandoned because of maturation failure (Biuckians et al., 2008; Stoumpos, Traynor, et al., 2019). The most common abnormality identified is a juxta-anastomotic stenosis (within 2 cm of the anastomosis), which can usually be treated with balloon angioplasty. Occasionally, ligation of collateral veins can help mature the fistula by redirecting all the arterial blood into a single venous channel.

Once matured, AVFs should be examined at each dialysis session and monitored for any problems with dialysis. Vascular stenosis is common and can lead to inadequate HD or fistula thrombosis if not identified and treated in a timely fashion. Although venous stenotic lesions in a mature AVF can develop anywhere within the access circuit, there are certain unique sites of predilection, including swing points, the cephalic arch, and at vein valves (Badero et al., 2008; Beathard et al., 1999; Hammes et al., 2008). Outflow lesions are found almost exclusively in mid-forearm and elbow/upper arm AVF. The development of collateral veins is frequent and often preserves flow in the access (Manninen et al., 2008).

Swing points are best described as accentuated curves in the AVF or its drainage, natural or artificially created (Falk et al., 2003). In a study of 127 cases, the distribution of swing-point stenosis was equivalent among the various fistulas (brachiocephalic 35.4%, radiocephalic 33.9%, and brachiobasilic 30.7%) (Badero et al., 2008).

The cephalic arch is a unique vascular structure, anatomically and haemodynamically, and a particularly problematic area (Kian & Asif, 2008; Rajan et al., 2003). Problems in this location are more commonly seen with brachiocephalic AVF than with radiocephalic. In

one report (Rajan et al., 2003), a differential of 39 to 2% was documented. This has been attributed to differences in flow through the cephalic arch with these two types of access. A radiocephalic AVF has less flow through the cephalic arch with the double drainage offered by both the basilic and cephalic veins plus the fact that this access tends to have a lower flow rate than does an upper arm AVF. Angioplasty of these lesions is associated with a high incidence of recurrence, which has been treated with stenting, or alternatively, for refractory lesions, surgery.

Inflow lesions (anastomotic and juxta-anastomotic) affecting the feeding artery are commonly encountered in distal radiocephalic AVFs. In a report dealing with a cohort of 101 dysfunctional AVFs (Asif et al., 2005), 8% were found to have lesions in the feeding artery and 21% had stenosis of the arterial anastomosis. There was a higher incidence of inflow stenosis for forearm as compared with upper arm AVFs. Others have reported the incidence of arterial stenosis in these cases at 6 to 18%. These lesions result in decreased blood flow in the access leading to inadequate dialysis (Romero et al., 1986).

Clinical monitoring and surveillance are currently used to screen for vascular stenotic lesions. Clinical monitoring includes routine examination of the fistula, monitoring for problems with dialysis and monitoring of Kt/V. Surveillance methods include measurement of intra-access flow, assessment of access flow using duplex ultrasound (DUS) and measurement of static dialysis venous pressure.

Because of insufficient evidence, there are no specified recommendations on how often the fistula should be evaluated or which additional examinations should be performed. The timing and modality of surveillance during the early postoperative period vary greatly from centre to centre depending primarily on the centre’s preference and capacity. Angiography is the most sensitive and specific imaging modality to identify and characterise stenotic vascular lesions, however it is expensive and invasive (Schwab et al., 1988; Windus et al., 1990). For screening, non-invasive assessment is preferred to first identify fistulas with a high likelihood of stenosis. Arteriovenous fistulas with sufficiently abnormal screening tests would then undergo diagnostic angiography and, if indicated, treatment. Some centres rely on physical examination only, whereas others use DUS to assess maturation status. Duplex ultrasound is a simple, non-invasive method to assess the functional and anatomic characteristics of a maturing AVF. Theoretically, DUS surveillance has the advantage of identifying the causal lesion that leads to AVF maturation failure and assessing its severity.

Data suggest that duplex flow measurements may be useful for patients with AVFs (Tonelli et al., 2008; Tonelli et al., 2001). However, in a systematic review of four randomised trials evaluating access flow-based monitoring in native AVFs (Tonelli et al., 2008), although DUS surveillance prevented access thrombosis in AVFs (relative risk 0.45, 95% CI 0.28-0.77), it failed to reduce the rate of access loss.

1.2.4 Associations between cardiac function and vascular access

Cardiovascular disease is a well-known predictor of fistula failure to mature (FTM) (Lok et al., 2006) but the role of a low cardiac output state before fistula creation has not been investigated sufficiently. An inability of the heart to increase the cardiac output following fistula creation may lead to hypotension, reduced fistula flow and subsequent failure of maturation.

On the other hand, the creation of an AVF has deleterious cardiac effects (Iwashima et al., 2002). It is well established that creation of arteriovenous access for dialysis has significant effects on both systolic and diastolic function. The AVF adds a low resistance, high-compliance venous compartment to the central arterial system. It is associated with increased blood flow, pulmonary hypertension, and cardiac output. Although usually clinically insignificant, the increased cardiac output and blood flow may be so great at times that they result in overt cardiac failure (Pandeya & Lindsay, 1999; Sandhu et al., 2004). This is particularly true if the patient has underlying heart disease and/or the access has flows greater than 2,000 mL/min (Basile et al., 2008). Factors associated with AV access precipitating heart failure include development of right ventricular dilatation, left atrial dilatation, development of atrial fibrillation, male sex, prior vascular access surgery, and high AV access flow rate (Reddy et al., 2017).

1.3 Imaging studies to assess kidney transplant recipient candidates

1.3.1 Abdominal XR

Plain films of the lower extremity may demonstrate arterial calcification in locations consistent with PAD, such as at arterial branch points, or along the mid to distal thigh along the course of the superficial femoral artery, or distally in the distribution of the tibial

vessels. Aortic calcification is associated with an increased risk for CV events in kidney transplant recipients. Studies assessing vascular calcification using lumbar X-ray found significant associations of vascular calcification with CV events in KTRs.

In a retrospective study of 701 KTRs, a high abdominal aortic calcification score acquired on dual-energy X-ray absorptiometry (DXA) for routine clinical evaluation of bone density was associated with both CV events and overall survival (Benjamens et al., 2018). Similar findings were shown in a prospective study of 253 KTRs, where lumbar X-ray was performed to score aortic calcifications, which were found to be strongly predictive of future CV events (Claes et al., 2013).

Abdominal X-ray is a useful first step in the imaging workup. However, the images are not as detailed and X-ray is inferior in terms of sensitivity and specificity compared to other approaches such as CT or MRI. Further imaging studies may be necessary to clarify the results of an abdominal x-ray or to look for abnormalities not visible on the abdominal X-ray.

1.3.2 Non-invasive vascular function tests

Non-invasive physiologic vascular studies play an important role in the diagnosis and characterisation of PAD of the lower extremity. These studies evaluate the physiologic parameters of blood flow through ankle-brachial index, segmental arterial pressures, and pulse volume recordings (PVR). Collectively, they comprise a powerful toolset for defining the functionality of the arterial system, localising the site of disease, and providing prognostic data. Although they do not employ imaging, they remain a critical component for a comprehensive radiologic vascular laboratory.

1.3.2.1 Ankle-brachial index (ABI)

Calculation of the ABI is a relatively simple and inexpensive method to confirm the clinical suspicion of lower extremity arterial occlusive disease. The ABI is the ratio of the systolic blood pressure (SBP) measured at the ankle to that measured at the brachial artery. Originally described by Winsor (WINSOR, 1950) in 1950, this index was initially proposed for the non-invasive diagnosis of lower extremity PAD (Yao et al., 1969). Later, it was shown that the ABI is an indicator of atherosclerosis at other vascular sites and can

serve as a prognostic marker for cardiovascular events and functional impairment, even in the absence of symptoms of PAD (Criqui et al., 1992; McDermott et al., 2009).

To obtain an accurate ABI, the patient should rest for 15 to 30 minutes prior to measuring the ankle pressure. The study starts with measuring the dorsalis pedis and posterior tibial artery pressures at the ankle. To calculate the ABI for each lower extremity, the higher pressure measured in the lower extremity (dorsalis pedis or posterior tibial artery) is divided by the brachial pressure of the arm with the higher pressure. According to the 2011 American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines, ABI values >1.40 are suggestive of non-compressible calcified vessels, 1.00 to 1.40 are normal, 0.91 to 0.99 borderline, and <0.90 abnormal (Sibley et al., 2017) (Figure 1-6).

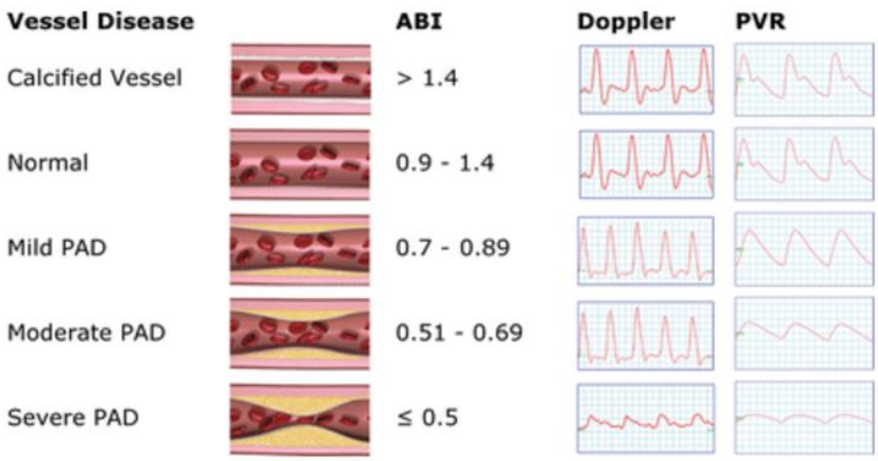


Figure 1-6 Non-invasive vascular function tests.
Graphic for interpreting ABI, Duplex waveforms, and PVR waveforms in PAD.

In a study examining the relationship of ABI with CVD and all-cause mortality among CKD patients, a U-shaped association was observed with ABI <1.0 related to risk of PAD, MI, composite CVD, and all-cause mortality whereas ABI ≥1.4 was related to clinical

PAD (Chen et al., 2016). ABI has been demonstrated to be reliable and correlate with post-transplant outcomes (Wu et al., 2014).

1.3.2.2 Segmental arterial pressures

Once arterial occlusive disease has been verified using the ABI measurements, the level and extent of disease can be determined non-invasively and relatively inexpensively using segmental limb pressures. Specialized equipment in the vascular laboratory is used to obtain blood pressures at successive levels of the extremity, allowing for localisation of the level of disease fairly accurately.

For estimation of lower extremity segmental pressures, the patient is placed in a supine position and rested for 15 minutes. Three or four standard-sized blood pressure cuffs are placed at several positions on the extremity (Figure 1-7). The pedal vessel (dorsalis pedis, posterior tibial) with the higher systolic pressure is used, and the pressure that occludes the pedal signal for each cuff level is measured by first inflating the cuff until the signal is no longer heard and then progressively deflating the cuff until the signal resumes. The pressure at each level is divided by the higher systolic arm pressure to obtain an index value for each level.

A 20 mmHg or greater reduction in pressure is indicative of a flow-limiting lesion if the pressure difference is present either between segments along the same leg or when compared with the same level in the opposite leg (ie, right thigh/left thigh, right calf/left calf). Well-developed collateral vessels may diminish the observed pressure gradient and obscure a haemodynamically significant lesion. Successive significant (>20 mmHg) decrements in the same extremity indicate multilevel disease.

As with ABI measurements, segmental pressure measurements in the lower extremity may be artifactually increased or not interpretable in patients with non-compressible calcified vessels. Patients with diabetes (who have medial sclerosis) or patients with CKD often have non-occlusive pressures with ABIs >1.4, limiting the utility of segmental pressures in these populations. Pulse volume recordings (which are independent of arterial compression) or arterial duplex are preferentially used to evaluate these patients instead.

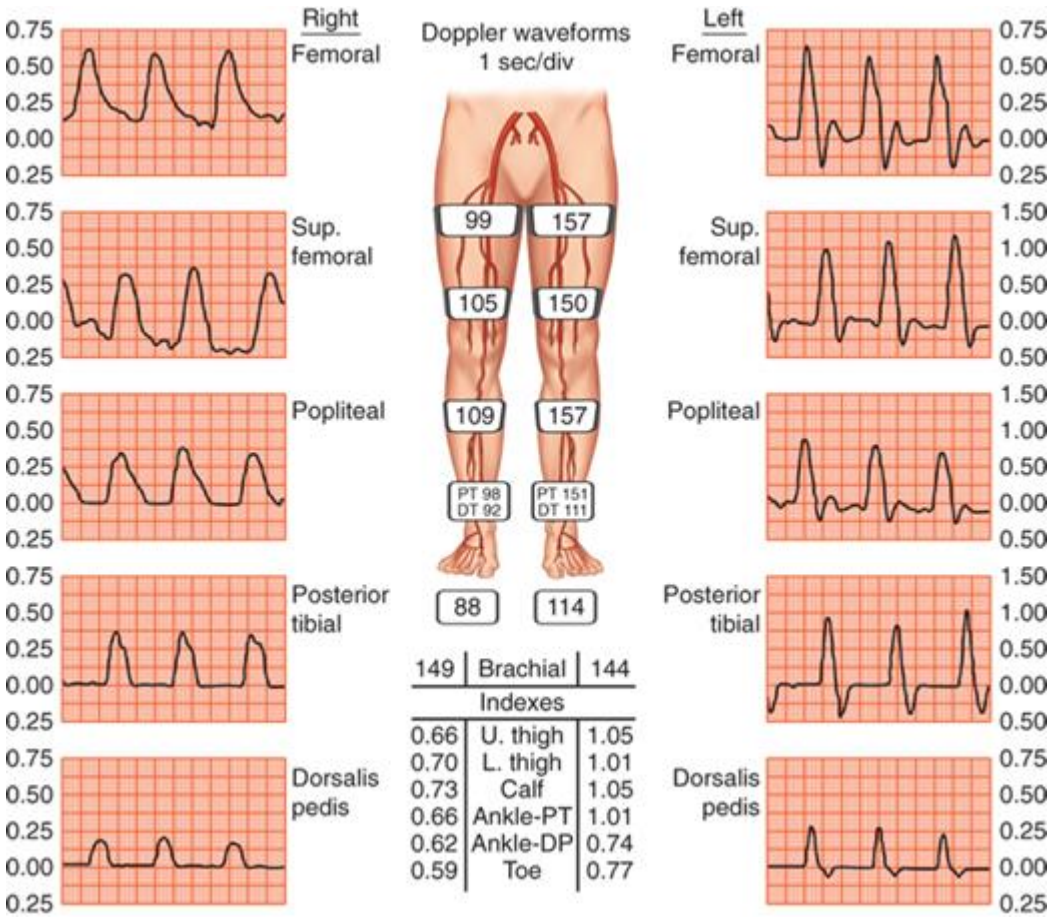


Figure 1-7 Typical report of peripheral vascular study.

Segmental arterial pressure measurement plus Duplex evaluation of the lower extremity.

1.3.2.3 Pulse volume recordings (PVR)

A PVR is a graph of the pulsatile change in limb volume from blood flow using constant standard pressure. Modern vascular laboratories acquire these tracings using the same pressure cuffs used for segmental limb pressure measurement. Volume changes in the limb segment beneath the cuff are reflected as changes in pressure within the cuff, which is detected by a pressure transducer and converted to an electrical signal to produce an analog pressure pulse contour known as a PVR.

A normal PVR is composed of a rapid upstroke with a sharp peak, a dicrotic notch, and a concave-up late diastolic component. Abnormal PVR findings include decreased amplitude, a flattened peak, and an absent dicrotic notch (Figure 1-8). Amplitude of less than 5 mm from trough to peak has been used as a criterion for diagnosing vascular claudication. Abrupt changes in amplitude and contour indicate occlusion between the two

levels. Since cardiac output, vasomotor tone, patient movement, and aortic stenosis influence PVRs, interpretation of these measurements should be limited to the comparison of one extremity to the other in the same patient and not between patients.

Interpretation of PVRs in combination with Duplex waveforms can also help diagnose chronicity of arterial occlusive disease. In acute thrombosis, both the Duplex waveform and the PVR waveform are absent or decreased. With the development of arterial collaterals, as is seen with chronic occlusive disease, the PVR waveform may be relatively preserved compared with the Duplex waveform.

1.3.3 Ultrasound (US)

Ultrasound is the mainstay for non-invasive vascular imaging and has gained a prominent role in the assessment of the peripheral vasculature. It is used to evaluate the location and extent of vascular disease, arterial haemodynamics, and lesion morphology. Ultrasound is commonly used in the setting of renal transplantation to evaluate the vasculature pre-operatively, in the first few hours or days post-renal transplantation, in routine post-transplant surveillance, and when there is a need for evaluation of graft dysfunction. A meta-analysis of 14 studies found that sensitivity and specificity of Duplex US for ≥50% stenosis or occlusion were 86 and 97% for aortoiliac disease and 80 and 98% for femoropopliteal disease(Koelemay et al., 1996).

Real-time ultrasonography uses reflected sound waves (echoes) to produce images and assess blood velocity. Two US modes are routinely used in vascular imaging: the B (brightness) mode and the Doppler mode (B mode imaging + Doppler flow detection = duplex ultrasound). The B-mode provides a grayscale image useful for evaluating anatomic detail. The quality of a B-mode image depends upon the strength of the returning sound waves (echoes), which are attenuated and scattered as the sound wave moves through tissue. The identification of vascular structures from the B-mode display is enhanced in the color mode, which displays movement (blood flow) within the field. The shift in sound frequency between the transmitted and received sound waves due to movement of red blood cells is analysed to generate velocity information (Doppler mode). Flow toward the transducer is standardised to display as red, and flow away from the transducer is blue; the colors are semiquantitative and do not represent actual arterial or venous flow. The ratio of the velocity of blood at a suspected stenosis to the velocity

obtained in a normal portion of the vessel is calculated. Velocity ratios >4.0 indicate a >75% stenosis in peripheral arteries.

A normal lower extremity arterial Doppler velocity tracing is triphasic (waveform A, Figure 1-8), with a sharp upstroke and peaked systolic component, sharp downstroke, an early diastolic component with reversal of flow, and a late diastolic component with forward flow. The biphasic arterial Doppler velocity waveform (waveform B**,** Figure 1-8) has a rapid upstroke, sharp peak, and fairly rapid downstroke, with a short period of antegrade flow in diastole. Flow is not seen below the baseline. As atherosclerosis develops, the elastic and muscular recoil of the vessel wall is lost, resulting in loss of forward flow during late diastole, creating a biphasic waveform. A biphasic signal is considered abnormal if there is a clear transition from triphasic signal along the vascular tree and is seen with single-level arterial occlusive disease. The monophasic arterial Doppler velocity waveform (waveform C, Figure 1-8) has a slow upstroke, rounded peak, slow downstroke, no flow reversal, and is non-pulsatile. The loss of vascular resistance in severe PAD results in the loss of reversal of flow and in the monophasic waveform. Monophasic waveforms are always considered abnormal and are seen with multilevel obstructive arterial disease.

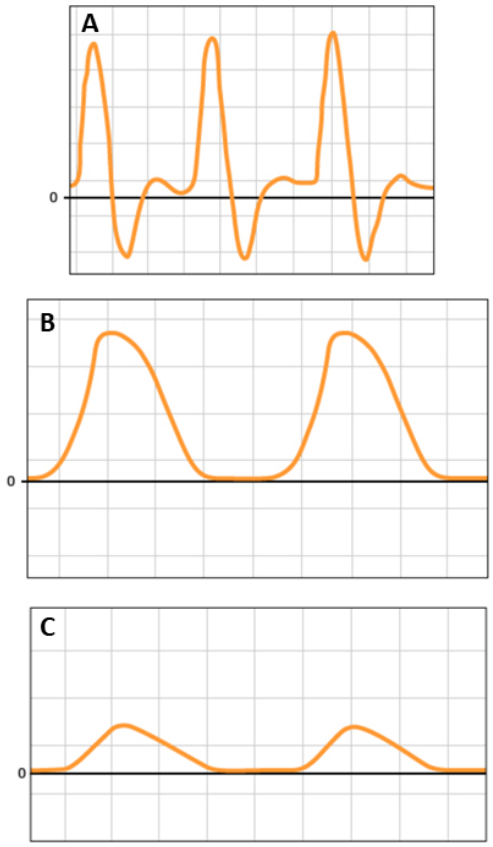


Figure 1-8 Doppler waveforms.

A. The normal Doppler waveform has a rapid upstroke, sharp peak, rapid downstroke, flow reversal and resumption of forward flow. B. The biphasic signal has a rapid upstroke, sharp peak, and fairly rapid downstroke, with a short period of antegrade flow in diastole (there is no flow below baseline). C. The monophasic Doppler signal has a slow upstroke, rounded peak, slow downstroke, no flow reversal, and is non-pulsatile.

Ultrasound is very convenient, rapid, relatively cheap and it provides precise anatomic localisation and accurate grading of lesion severity. It can be done in real time, is non-invasive, it has no ionising radiation involved and no need for intravenous contrast. Its limitations in assessment of kidney transplant recipient candidates include technologist dependence, less accuracy in the aortoiliac segments secondary to obesity or bowel gas, and the interference of calcification with US assessment of the arterial vasculature.

1.3.4 Non-contrast CT

Characterisation of atherosclerotic changes in the iliac vessels is crucial in transplant planning. Arterial calcifications can be seen with pelvic x-ray, but CT may be needed to better describe the presence, location, size and conformation of calcifications across the aortoiliac tree. This is reflected in the recent KDIGO guidelines (Chadban et al., 2020), where non-contrast CT of the abdomen and pelvis to evaluate arterial calcification is

suggested for patients with clinically apparent PAD, abnormal non-invasive testing, or prior vascular procedures. Unenhanced CT provides adequate depiction of calcifications and can be safely used in patients with advanced CKD or those on dialysis with residual kidney function. It also provides additional information of extravascular structures if further surgical interventions are planned, i.e. to assess and plan nephrectomy in patients with large polycystic kidneys in order to make space for the transplanted kidney.

In a prospective evaluation of 114 helical CT scans of pre-transplant candidates with risk factors for iliac stenosis, a 29% rate of iliac artery calcification sufficient to preclude transplantation was reported (Andres et al., 2003). In another study assessing the degree of iliac artery calcifications using CT before kidney transplantation, the calcification morphology score of the arterial segment used for anastomosis was independently predictive of a higher rate of surgical complexity and delayed graft function (Davis et al., 2016). Based on these findings, routine pre-transplant CT for estimation of calcification could enable selection of the optimal artery for anastomosis in selected groups of patients (older, diabetics, with known PAD) and optimise outcomes.

The utility of non-contrast CT as a prognostic tool is shown in studies assessing the vasculature post-kidney transplantation. In a study of 120 incident KTRs without prior history of coronary revascularisation who had electron beam CT, 34% had aortic calcification, and this was predictive of CV events (DeLoach et al., 2009). In another study of 281 prevalent KTRs, coronary artery calcification (CAC) assessed with chest spiral CT was a strong independent predictor of CV events (Nguyen et al., 2010). Roe et al. used the Agatston method in 112 asymptomatic KTRs and showed that inflammatory markers (such as white cell count and CRP) were predictive of coronary artery calcification severity at time of transplant, and CAC score predicted CV events and mortality (Roe et al., 2010).

While unenhanced non-contrast CT of the abdomen and pelvis is an alternative to contrast-based imaging studies for pretransplant assessment, it has very low contrast discrimination, which is suboptimal for evaluation of vessel patency and extravascular structures. This can lead to failure to identify critical anatomical findings that could alter transplant planning.

1.3.5 Non-contrast magnetic resonance techniques

While non-contrast-enhanced MR angiographic methods, such as time of flight (TOF), phase-contrast, and ECG-gated quiescent-interval single-shot (QISS) MRA have been

available since the earliest days of MR imaging, prolonged acquisition times and image artefacts have generally limited their use in favor of gadolinium-enhanced MR angiographic techniques. However, non-enhanced MR angiographic techniques have made substantial progress over the last decade and are effectively used for visualisation of the coronary (Bi et al., 2006), renal (Coenegrachts et al., 2004), and lower extremity arteries (Stafford et al., 2008). Study protocols with more rapid sequencing and efficiency of cardiac gating have allowed greater spatial and temporal resolution to be obtained.

Time of flight MRA is a non-contrast MRI technique that creates vessel and background contrast by detecting flow in vessels. Fully magnetised (or unsaturated) blood flowing into a perpendicular imaging plane has relatively higher signal intensity than the stationary, progressively saturated background spins. Two-dimensional (2D) TOF has been established as an accurate method to diagnose peripheral arterial disease. In clinical practice, 2D TOF angiography is used for evaluation of tibial and pedal arteries and has been shown to be as accurate as conventional angiography for the diagnosis of stenosis and occlusion (McCauley et al., 1994; Owen et al., 1992). The main disadvantage of TOF-MRA is prolonged imaging acquisition times making it difficult for patients, in addition to significant artefacts related to saturation bands, turbulent flow, patient motion, or ghosting artefacts, which can limit diagnostic accuracy (Leiner, 2005).

Since the late 1990’s, phase-contrast MR angiography has been used for peripheral MR angiography (Reimer & Boos, 1999; Steffens et al., 1997). Phase-contrast MRA is a non-contrast technique that separates blood flow from the background stationary tissue by observing the phase difference between non-zero phase protons of blood and the zero phase protons of stationary background tissue (Nesbit & DeMarco, 1997). It has some advantages compared to TOF-MRA, such as reduced acquisition times and fewer saturation-related artefacts (Leiner, 2005). It has high sensitivity and specificity for identifying high-grade stenoses in patients with PAD. For example, coronal 2D phase-contrast MR angiographic methods for three-station evaluation of the lower extremities—aortic bifurcation to tibioperoneal trunk—have been used, which resulted in an overall acquisition time of 20–30 minutes (Reimer & Boos, 1999). In a study of 115 patients with 253 atherosclerotic lesions, the sensitivity of phase-contrast MR angiography with this protocol was 95%, specificity was 90%, positive predictive value was 90%, and negative predictive value was 96% (Steffens et al., 1997).

Quiescent-interval single-shot MRA is a non-contrast ECG gated balanced steady state free procession (b-SSFP) MRA that has been recently developed for the imaging of PAD (Mihai et al., 2011). QISS is a 2D technique that uses saturation pulses to suppress background and venous signal followed by the quiescent inflow period where magnetised blood enters into the imaging slice. Benefits of this method include shorter acquisition time and total imaging time compared to TOF-MRA sequences (Hodnett et al., 2017). In addition, QISS uses non-subtractive single-shot image acquisition, which reduces sensitivity to patient motion (Edelman et al., 2017; Hodnett et al., 2011). In a study of 21 patients with advanced peripheral arterial occlusive disease high resolution QISS showed high sensitivity (94.1%), specificity (97.8%), positive (95.1%), and negative predictive value (97.2%) for the detection of significant (≥50%) stenosis compared with CE-MRA.

In a comparative study of 53 kidney transplant candidates who underwent US, non-enhanced CT and non-enhanced MRA, MRA showed low sensitivity in detecting severe arteriosclerotic disease and the authors advocate against its use for pre-operative imaging before kidney transplantation (Blankholm et al., 2015).

1.3.6 CT Angiography (CTA)

With the development of multi-slice computed tomography scanners that increased the resolution of the arterial system, CTA allows for anatomic depiction in detail, better recipient selection and accurate planning for the vascular anastomosis and placement of the renal graft (Andres et al., 2003). Correct perfusion of the graft is one of the keys to a good transplantation outcome. During presurgical evaluation of potential kidney transplant recipients, it is necessary to rule out alterations in vascular calibre (stenosis or aneurysms) and identify calcifications of the aortoiliac territories. Multidetector CT angiography is an accurate technique for demonstration of both stenotic and aneurysmal disease, allowing definition of the site, grade, and extent of alterations in vascular calibre with substantial inter-observer agreement (Catalano et al., 2004; Martin et al., 2003; Willmann & Wildermuth, 2005). Although calcific atherosclerosis can be seen with non-contrast CT, contrast-enhanced CTA is best to evaluate for associated non-calcified plaque as a potential source of inflow disease. Another advantage of CTA is the contrast enhancement of incidental tumors, especially renal cell carcinomas, with an approximately 40-fold greater prevalence in the ESRD than in the general population (Denton et al., 2002; Hughson et al., 1996; Schwarz et al., 2007). However, it is limited by dense calcification,

arterial stents, and other implanted objects, such as hip and knee replacement, which interfere with the signal of the arterial system. In addition, it does not robustly evaluate venous anatomy. This latter limitation is of importance as frequently indwelling femoral vein catheters will have been employed and may have resulted in venous stenosis.

In a study of 179 potential kidney transplant recipients who had pre-operative CTA, 24 of 152 patients (15.8%) who underwent transplantation had the site of anastomosis influenced by CTA findings. From the 43 (24%) pre-dialysis patients included, there were no changes in pre-and post-CTA serum creatinine levels and none of the patients required dialysis as a result of the CTA (Smith et al., 2012).Until now, the widespread use of CTA in the workup of the potential kidney transplant recipient has been limited because of concerns of contrast-induced acute kidney injury (CI-AKI), especially in predialysis patients. The risks of CI-AKI have been questioned in recent publications (J. S. McDonald et al., 2013; Wilhelm-Leen et al., 2017), although this remains controversial. Notably, in a series of similar design retrospective studies, McDonald and colleagues examined the rate of AKI in the 24–72 hours after intravenous contrast-enhanced CT or non-contrast-enhanced CT imaging (J. S. McDonald et al., 2014; McDonald et al., 2015; R. J. McDonald et al., 2013; R. J. McDonald et al., 2014). Although diminished estimated glomerular filtration rate (eGFR) was associated with an increased risk of AKI and patients who developed AKI had higher rates of dialysis and mortality, the occurrence of these outcomes did not differ significantly between the contrast and non-contrast groups in these studies. Nevertheless, these studies should be interpreted with caution, as despite matching, in a retrospective study there may have been bias present in selection of the controls, which may erroneously underestimate or even obscure the real effects of contrast medium.

1.3.7 MR angiography (MRA)

Since its clinical introduction in the 1990's MRA has become an increasingly important tool in the evaluation of the peripheral and renal vasculature (Prince, 1996; Prince et al., 1997). Traditional contrast-enhanced MRA employs timed, first-pass imaging of a GBCA bolus, focused on the arterial or venous territory of interest. For the majority of GBCAs, the volume of distribution is the extracellular fluid space, which is quickly accessed after a relatively short time within the blood pool; hence, the time window for a vascular phase is very short. MRA may also be timed for venous phase imaging at the same setting as the arterial imaging (Du et al., 2006).

In a comparative study of MRA and digital subtraction angiography (DSA) for evaluation of PAD, MRA precisely detected the presence and degree of stenosis (mild, moderate, severe), occlusion of the arterial vasculature and the presence of aneurysmal disease (Gozzi et al., 2006). In another comparative study of MRA vs CTA in patients with PAD before endovascular intervention, both techniques accurately classified disease in the aortoiliac and femoro-popliteal segments but CTA performed better in stratifying disease in smaller arteries (infrapopliteal segments and runoff arteries) (Cina et al., 2016).

Despite its clinically utility in identification of PAD, MRI is limited by the concerns around development of NSF when linear chelate GBCAs are used, especially in patients with advanced CKD. Practitioners are advised against the use of all linear GBCAs in patients with acute kidney injury or CKD with an eGFR <30 mL/min/1.73m^2. On the other hand, although NSF seems not to be a risk with more stable gadolinium agents such as the cyclic chelates, residual concerns have constrained use and contrast-enhanced MRA is only rarely used for pre-transplant evaluation of potential KTRs.

1.4 Imaging studies for vascular mapping and surveillance

Creation of vascular access for haemodialysis is a complex process involving a multidisciplinary team approach aiming to weigh issues such as life goals and expectancy, timelines for dialysis start, risks and benefits of access creation, referral wait times, as well as the risk for access complications. Arteriovenous fistulas require an adequate cardiac output to deliver required blood flow, an adequate arterial conduit, adequate vein size and compliance, as well as unobstructed outflow veins. Arteriovenous fistula failure has become more common over the last three decades as the demographics of the dialysis population have considerably changed; more patients are older, have diabetes or vascular disease and other comorbidities. Hence pre-operative investigations to assess the vasculature have been employed aiming to optimise patient selection and fistula outcomes.

Following successful fistula creation and maturation, problems may occur before or after the patient is established on HD and may lead to AVF failure. To minimise these risks, AVFs should be routinely monitored to detect potentially treatable causes of failure. Monitoring of haemodialysis fistulas usually involves routine clinical assessment or more elaborate surveillance programs.

Clinical monitoring falls into the following three broad categories: A) Abnormalities of physical examination such as fistula limb oedema, alterations in the pulse, thrill, or bruit, abnormal pulse augmentation test or failure of the fistula to collapse when the arm is elevated, B) Problems noted during the dialysis session, such as difficulty with cannulation, aspiration of clots, inability to achieve the target dialysis blood flow, or prolonged bleeding from the needle puncture sites and C) An unexplained (>0.2 units) decrease in the delivered dialysis dose (Kt/V) on a constant dialysis prescription.

Fistula surveillance methods require specialised equipment, specially trained staff and additional cost. The two major types of access surveillance are: A) Intra-access blood flow monitoring, such as the ultrasound dilution technique (Krivitski, 1995) and B) Duplex ultrasound, which was primarily used for evaluation of arteriovenous grafts (AVG), but data suggest that it may be useful for patients with native AVFs.

1.4.1 Ultrasound (US)

The type and site of vascular access placement is predominantly based on patient and vessel characteristics. Duplex ultrasound is routinely used to allow proper selection of a target vessel with adequate luminal diameter. Peripheral veins can be scarred or damaged by previous intravenous catheters. Central venous catheters, pacemakers, or cardiac implanted electronic devices can cause stenosis or occlusion of the central, cephalic and basilic veins and compromise arteriovenous access creation. Pre-operative evaluation with US reduces AVF failures and can reduce surgeries that are unlikely to be successful. Although US is of particular benefit when physical examination is insufficient, it has little added value when physical examination is satisfactory (Ferring et al., 2008).

In a comparative study the rate of successfully constructed AVF increased significantly from 75% to 97% ($p=0.001$) when pre-operative US vascular mapping was added to physical examination (Ilhan et al., 2013). In another study of 70 patients who underwent US assessment of the upper extremity arterial and venous anatomy, US mapping resulted in a change in the planned surgical procedure in 31% of patients and a drop in unsuccessful surgical explorations from 11% to 0% (Robbin et al., 2000). Wong et al. (Wong et al., 1996) compared the accuracy of predicting AVF failure by pre-operatively evaluating the forearm cephalic vein: positive predictive value was better for US than for physical vein palpation (1 vs 0.5), indicating that AVF failure occurred for all veins that were abnormal

on the ultrasound scan (defined by a diameter <1.6 mm or a stenosis). Wells et al. (Wells et al., 2005) followed 145 patients and found that clinical examination was insufficient in 27%; ultrasound made a relevant contribution for half of those. Furthermore, Nursal et al. (Nursal et al., 2006) studied 70 selected patients who had adequate vessels on physical examination and randomised them to have AVF formation on the basis of physical or US examination alone. There was no significant difference in terms of immediate or simple primary patency at 1 year, however, clinical examination was sufficient in 73% of patients. This shows that clinical assessment correctly identifies those patients who benefit from further imaging.

Following successful AVF creation, there are various physiologic processes until the outflow vein matures sufficiently to support HD, which if disrupted can lead to fistula failure. To promptly identify and correct problems that arise within the maturation process, many advocate monitoring of the growing fistula using different tools. Despite limited data and conflicting evidence in effectiveness, Duplex US has become the standard of practice for fistula surveillance with an increasing number of HD centres implementing fistula surveillance programs (Tonelli et al., 2001). In a systematic review of 4 randomised trials evaluating flow-based monitoring in native AVF (Tonelli et al., 2008), although blood flow screening with Duplex US prevented AVF thrombosis, it did not reduce the risk of access loss or extent of use (Tonelli et al., 2008). On the other hand, a single-centre randomised trial of 79 patients with fistula stenosis (Tessitore et al., 2006) reported a significantly lower fistula failure rate in patients undergoing flow monitoring with pre-emptive angioplasty or surgical revision than in patients without surveillance.

Duplex US is readily available, relatively cheap and non-invasive. Its major limitation is the relative inability to assess central vein patency, which is crucial in access planning, especially in patients at risk of CVS. Central vein stenosis occurs in over 40% of patients with previous percutaneous line insertions for dialysis (Taal et al., 2004). Another limitation is that the quantification of the amount of calcification in the artery by US can be difficult and interpretation somewhat subjective (Hakaim et al., 1998). This is particularly true for diabetics with arterial medial calcification lesions, which tend to preserve internal luminal diameter but limit the artery's ability to dilate or increase flow rates when a drop in outflow resistance occurs after AVF creation. Finally, it is time-consuming and requires operator’s skill and experience.

1.4.2 Digital subtraction angiography (DSA)

Central vein stenosis occurs in over 40% of patients with previous percutaneous line insertions for dialysis (Taal et al., 2004) and DSA is the gold standard for patients at risk of CVS. DSA can detect all haemodynamically significant stenoses (including inflow and outflow) and should be performed in addition to Duplex US before endovascular intervention in cases in which Duplex US has been used as the initial imaging modality of a dysfunctioning access (Doelman et al., 2005). Hyland et al. (Hyland et al., 2008) have shown that venography may identify clinically occult veins, which could be used for AVF formation and anatomic variants that could affect choice of access site. Patel et al. (Patel et al., 2003) found that while the combined use of Duplex US and venography increased the number of native AVFs created, paradoxically pre-operative imaging was associated with a decreased AVF maturation rate, most likely related to aggressive vein use.

DSA has the advantages of high spatial and temporal resolution and the ability to intervene but is invasive with the risk of vascular injury and stroke, does not provide a three–dimensional representation of what can be complex anatomy, and requires the use of iodinated contrast and ionising radiation. In addition, for optimum results DSA requires bilateral venous cannulation with good calibre cannulas to allow rapid injection of contrast to opacify the central veins, and this can be challenging in CKD patients.

1.4.3 MR angiography (MRA)

MR angiography is an expensive and less readily available technique, which may though supplement US, especially in patients with peripheral arterial disease and previous CVC insertions who are at increased risk for CVS.

Contrast-enhanced MRA provides excellent visualisation of both central and upper extremity vessels (Laissy et al., 2003; Paksoy et al., 2004). Contrast-enhanced MRA accurately detected upper limb arterial and venous stenosis and occlusions prior to AVF creation, not detected by Duplex US, that were associated with early failure and non-maturation in 33% of patients (Planken et al., 2008). In pre-dialysis patients, MR venography has been shown to have acceptable sensitivity and specificity when compared with conventional venography with good inter-observer correlation regarding imaging quality and strategy planning (Menegazzo et al., 1998).

In the era of NSF and its association with GBCAs, non-CE-MRA compared to CE-MRA was a feasible alternative in patients with ESRD requiring imaging of the upper extremity and central vasculature prior to dialysis access creation (Bode et al., 2012). Using computer modelling following pre-operative non-CE-MRA, Merkx et al. (Merkx et al., 2013) predicted arm inflows post-AVF creation. Non-CE-MRA was able to provide geometrical details of arterial stenoses, which could assist the vascular surgeon in creation of an AVF.

1.5 Associations between cardiac function and vascular access

The heart is a critical part of the dialysis access circuit, providing the driving force for blood flow necessary to meet the demands of the dialysis access. If cardiac function is poor, this adversely affects blood flow to the developing AVF, leading to non-maturation and fistula failure. This close relationship should be given consideration in dialysis access planning.

On the other hand, creation of an AVF may have deleterious effects on cardiac structure and function. In the first report of successful AVF creations for hemodialysis in 1966 by Brescia and Cimino (Brescia et al., 1966), the association of AVF and increased cardiac output was recognised and it was described as the major disadvantage of the new technique. They considered it clinically insignificant, and this was probably true in their cohort of young patients receiving dialysis, none of whom had diabetes mellitus or vascular disease. Over time, there have been significant changes in the demographics of the hemodialysis population, with trends toward increasing age and comorbidity, including vascular disease and impaired baseline cardiac function. Nowadays left ventricular hypertrophy (LVH) is almost universal in new dialysis patients. Nonetheless, vascular access-related cardiac decompensation remains a rare complication, even in patients with underlying cardiac dysfunction.

1.5.1 Cardiac function before vascular access creation

For an AVF to mature sufficiently to maintain haemodialysis, a blood flow of ≥600 mL/min is required. An inability of the heart to increase the cardiac output following AVF creation may lead to hypotension, reduced fistula flow and subsequent failure of

maturation. Despite these associations, the role of a low cardiac output state before AVF creation has not been investigated sufficiently.

At commencement of dialysis, up to 70% of patients with ESRD may have abnormal cardiac structure or function (Collins, 2003). According to the 2016 United States Renal Data System (USRDS) annual data report, 70% of patients older than 66 years with CKD had some form of CVD and 28% of them had heart failure (United States Renal Data System, 2016). In a study of 513 patients who received an AVF, the presence of CVD was associated with a reduction in primary (hazard ratio [HR] 1.84, 95% confidence interval [CI] 1.26-2.67) and secondary AVF survival AVF (HR 2.21, 95% CI 1.38-3.55)(Ravani et al., 2004). In a retrospective analysis of 444 incident first-time AVF, coronary artery disease was associated with AVF loss (HR 2.1, 95% CI 1.5-3.0) on multivariate analysis (Lok et al., 2005).

1.5.2 Congestive heart failure following vascular access creation

Creation of an AVF for haemodialysis leads to a localised area of high flow shunting of blood from the arterial to venous circulation. This exposes the low pressure, high capacitance venous system to the high pressure, low capacitance arterial system. The haemodynamic effects after AVF creation include an acute decrease in systemic vascular resistance while simultaneously increasing venous return to the heart, thus increasing cardiac output (Reddy et al., 2016; Reddy et al., 2017). As the fistula increases in size, the functional changes gradually lead to maladaptive structural changes in the heart. The increased blood volume result in increased right atrial, pulmonary artery, and left ventricular end-diastolic volumes, which initially do not lead to symptoms of congestive (or high-output) cardiac failure. Over time, the myocardium decompensates, the left ventricle dilates, and the ejection fraction declines, eventually leading to LVH or heart failure. Supplemental to these mechanisms, myocardial ischemia, which is caused by an imbalance between subendocardial oxygen supply and increased oxygen demand as a result of increased cardiac output is also implicated in the development of deleterious cardiac effects (Savage et al., 2002). These changes add a significant burden to the pre-existing LVH, dilatation, and dysfunction caused by the underlying uraemic cardiomyopathy as CKD progresses. Patients more susceptible to these effects are the ones with pre-existing heart disease and high flow fistulas. Symptoms and signs of heart failure may develop weeks or years after AVF creation.

Left ventricular hypertrophy is primarily an adaptive remodelling process as a response to increased cardiac workload aiming to minimise ventricular wall stress. The development, severity, and persistence of LVH are strongly associated with cardiovascular events and mortality risk in CKD, especially in patients in the highest tertiles of change in left ventricular mass treated with conventional haemodialysis (Zoccali et al., 2004). Despite its detrimental effects when present, the impact of LVH regression on mortality remains uncertain. London et al. (London et al., 2001) have demonstrated that a 10% decrease in left ventricular mass translated into a 28% decrease in risk of cardiovascular mortality over a 5-year period. Contrary to these results, Foley et al. (Foley et al., 2000) found that improvements in left ventricular mass over a 1-year period after the initiation of dialysis were associated with a subsequent reduced likelihood of cardiac failure but not with mortality risk. This is explained by the fact that the normal geometry of the left ventricle is not restored, and the reduction in mass is a result of the reduction in left ventricular end-diastolic volume rather than a decrease in wall thickness (Unger et al., 2004).

The effects of AVF creation on functional and structural cardiac parameters have been previously studied. Using cardiac MRI in 24 patients with stage 5 CKD undergoing fistula creation, Dundon et al (Dundon et al., 2014) showed a mean increase of 25% in cardiac output, 12.7% in left ventricular mass, and 21% in left ventricular end-systolic volumes 6 months after AVF creation. In another study of 16 patients with CKD who underwent AVF creation, significant elevations in cardiac output (15%) and left ventricular end-diastolic diameter (4%) were noted immediately after the AVF operation (Dixon et al., 2002). In a prospective study of 562 CKD patients, from whom 95 (17%) developed at least one episode of pre-dialysis congestive heart failure (CHF), the presence of a functioning AV access was amongst the risk factors associated with acute heart failure (OR=9.54, 95% CI: 4.84-18.81, $p < 0.001$) (Martínez-Gallardo et al., 2012). In a retrospective study of 137 CKD patients who underwent echocardiography before and a median of 2.6 years following AV access creation, 43% of patients developed incident heart failure. From these, 75% had heart failure with preserved ejection fraction (HFpEF) (Reddy et al., 2017). However, these results should be interpreted with caution, as there was no comparison group who did not undergo AV access placement.

Patients with a fistula blood flow >2 L/min or an upper arm AVF are traditionally at increased risk for the development of heart failure (Basile et al., 2008; Martínez-Gallardo et al., 2012; Schier et al., 2013; Wijnen et al., 2005). In a prospective study of 96 CKD

patients with AVFs, 10 developed high-output cardiac failure after the fistula was placed; 7 of them had an upper arm AVF ($p < 0.04$) (Basile et al., 2008). Significantly higher blood flow rates were seen in the upper arm vs the forearm fistulas (1.58 vs 0.948 L/min). In an observational study of 562 CKD patients (Martínez-Gallardo et al., 2012), the incidence of CHF was much higher in patients who had a brachiocephalic compared to those with a radiocephalic AVF (40 vs 8%).

The effects of AV access closure in cardiac parameters have been studied in the renal transplant population (Unger et al., 2002; van Duijnhoven et al., 2001), where fistula ligation results in significant reductions in both left ventricular end-diastolic diameter and mass. In a randomised controlled trial of 54 kidney transplant recipients equally randomly assigned to AVF ligation or no intervention, a 15% reduction in left ventricular mass in the AVF ligation group associated with a decrease in cardiac output was observed. There was a 20% decrease in left ventricle and atrial sizes and a reduction in N-terminal pro-B-type natriuretic peptide levels (Rao et al., 2019). In a retrospective study of 797 kidney transplant recipients previously undergoing haemodialysis via a fistula or graft, 113 (25.7%) patients required AV access closure, mostly because of symptoms of CHF. Shunt closure resulted in significant symptomatic improvement. The mean blood flow in the intervention group was 2,197 mL/min compared with 851 mL/min among patients who did not undergo AV access closure (Schier et al., 2013).

1.6 Ferumoxytol-enhanced magnetic resonance angiography (FeMRA)

1.6.1 Ferumoxytol

Ferumoxytol (Feraheme; AMAG Pharmaceuticals, Waltham, MA, USA) is an ultrasmall superparamagnetic iron oxide (USPIO) particle encapsulated by a semisynthetic carbohydrate (Balakrishnan et al., 2009) that prevents redistribution outside the vascular space. Ferumoxytol was originally designed as an intravascular contrast agent for MRI (Weissleder et al., 1990). However, a strategic decision to license the drug as a therapeutic iron supplement eclipsed its use as MRI contrast agent. During the last decade the identification of the association of NSF with linear chelate GBCAs in patients with advanced CKD has led to renewed interest in ferumoxytol as a contrast agent (Bashir et al., 2015; Chalouhi et al., 2013; Hasan et al., 2012; Walker et al., 2015). In addition, recent

data supporting potential gadolinium retention in patients with normal kidney function have generated additional controversies surrounding the use of GBCAs in MRI (United States Food and Drug Administration, September 8, 2017).

Ferumoxytol has high relaxivity at 1.5 T and 3.0 (Knobloch et al., 2018) with advantages as a contrast agent for MRA. It is not filtered by the glomerulus but is removed from the circulation via macrophage phagocytosis with the remaining iron oxide particles taken up by the reticuloendothelial system of the liver, spleen and bone marrow being incorporated into body iron stores for red blood cell synthesis. Due to its large molecular weight of approximately 750 kD (Balakrishnan et al., 2009), ferumoxytol resides in the blood pool and does not diffuse out into the extracellular fluid space. Given its long intravascular half-life (>14 hours) (Landry et al., 2005), it can potentially be used without the need for bolus timing with imaging in a ‘steady state’ when the arterial and venous vasculatures are equally enhanced. It also allows for a longer time window for data acquisition, higher spatial resolution during the equilibrium phase and repeat imaging, if necessary, with negligible loss of intravascular signal intensity (Bashir et al., 2015; Bremerich et al., 2007; Ersoy et al., 2004). Early and late phases of ferumoxytol biodistribution are shown in Figure 1-9.

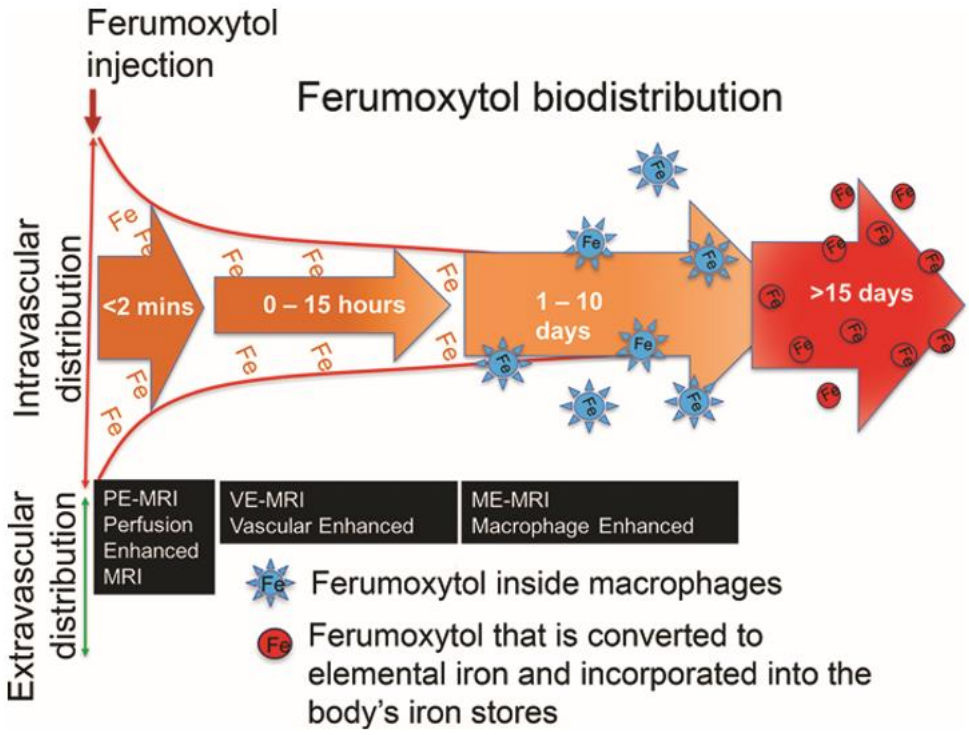


Figure 1-9 Ferumoxytol biodistribution and diagnostic applications in MRI.

Ferumoxytol preferentially enhances the intravascular space compared with other tissue compartments at less than 15 hours. Reproduced with permission from Radiology. 293(3):554-564 (2019). Copyright 2019 Radiological Society of North America.

On the downside, the agent can be present in the blood pool for weeks following administration and months in the reticuloendothelial system, potentially complicating the appearance of follow-up studies (Storey et al., 2012). Moreover, a susceptibility artefact mimicking vascular thrombosis has been described with higher concentrations of ferumoxytol (Fananapazir et al., 2014).

1.6.2 Clinical use

In June 2009, ferumoxytol was approved for parenteral treatment of iron deficiency anaemia in patients with CKD (Macdougall et al., 2014) and in February 2018, a broad label was granted across all conditions associated with iron lack in adults who were intolerant of, or had an inadequate response to oral iron (Adkinson et al., 2018). The labelled method of administration was a single vial consisting of 510 mg in 17 mL, administered as fast as 1 mL/s or as fast as 17 seconds. The dosage of ferumoxytol is expressed in terms of milligram of elemental iron, with each millilitre of ferumoxytol containing 30 mg of elemental iron. Given concerns about possible serious adverse events, albeit rare from post-marketing reports, in 2015 the label was modified to include a boxed

warning to highlight the potential for serious adverse events and ways to possibly mitigate them. In addition, the approved rate of infusion was changed from the 17 seconds bolus administration to at least a 15 minutes infusion for the 510 mg dose. This should be administered as an intravenous infusion in 50-200 mL 0.9% sodium chloride or 5% dextrose, followed by a second 510 mg dose 3 to 8 days later.

From published evidence, it became readily apparent that the dose of ferumoxytol was not related to the presence or absence of adverse events. Recently a total dose infusion of 1020 mg at a single administration over ~30 minutes has been proposed, which has the advantages of improved ease of administration, improvement in convenience for both physicians and patients at decreased cost without a decrement in efficacy or safety (Auerbach et al., 2013). In addition, by administering ferumoxytol in one visit, the chance for an infusion reaction or extravasation of the intravenous line is halved and multiple insurers in USA now approve this improved method of treating iron deficiency (Karki & Auerbach, 2019).

1.6.3 Off-label use

Despite its imaging properties, ferumoxytol is not yet licensed for clinical diagnostic imaging and it is only used off-label. Ferumoxytol has gained appeal as an MRI contrast agent in patients with eGFR of less than 30 mL/min/1.73m^2 where there is a pressing clinical question but no other viable angiographic option. There is an increasing number of reports in the literature demonstrating its safe use and utility in both adult and paediatric patients with CKD (Bashir et al., 2013; Bashir et al., 2014; Corwin et al., 2016; Fananapazir et al., 2017; Luhar et al., 2016; Mukundan et al., 2016; Nayak et al., 2015; Sigovan et al., 2012; Stoumpos et al., 2018) (Figure 1-10). It has been used for both arteriography and venography and provides excellent visualisation of central and peripheral vessels without the confounding effect of dense vascular calcification on luminal assessment often seen at CT.

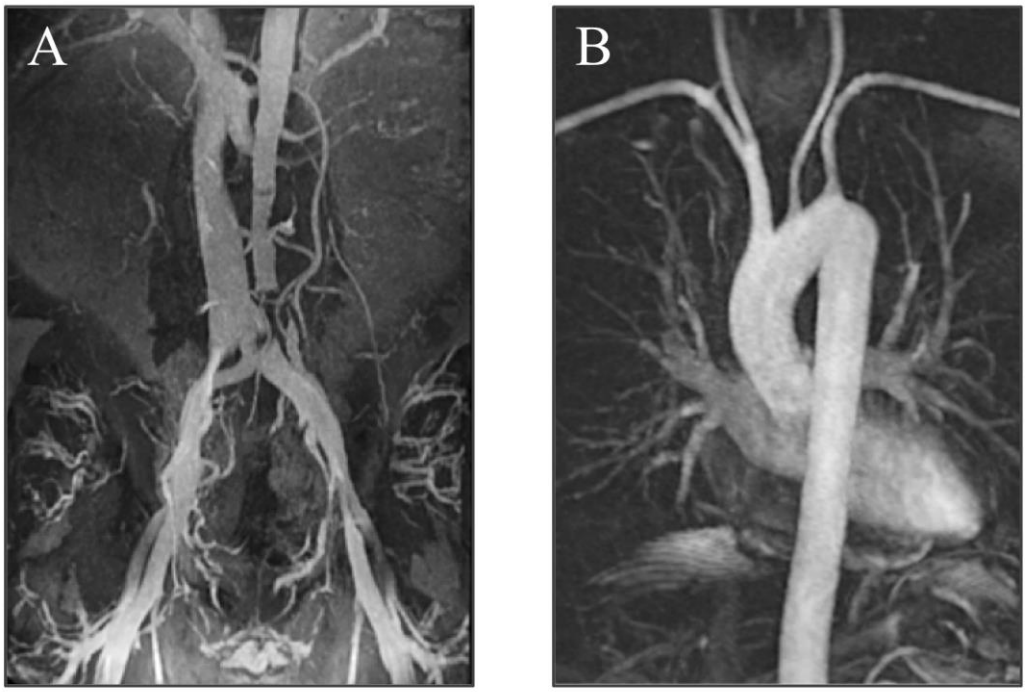


Figure 1-10 FeMRA of aortoiliacs.

A. Iliac vessels with ferumoxytol-enhanced MRA (FeMRA) in a kidney transplant recipient B. FeMRA of central vasculature. Reproduced with permission from Eur Radiol. 28(1):115-123. (2018). Copyright 2017 The Authors.

The typical dose used for imaging is 20-40% that for iron replacement, therefore the safety profile for imaging is more attractive than for iron replacement. In our studies a dose of 3 mg of ferumoxytol/kg of patient weight was used (up to a maximum of 300 mg) based on the results of a dose-finding study (Stoumpos, Hennessy, et al., 2019b). This is much less compared to the therapeutic dose of approximately 7.3 mg of ferumoxytol/kg for a 70-kg man (or a dose of 14.6 mg of ferumoxytol/kg over 3–8 days). In all cases ferumoxytol was diluted to a concentration no greater than 1 part ferumoxytol to 4 parts 0.9% sodium chloride. Patients were divided into 13 dose bands according to body weight using increments of 5 kg. The dose given within each weight group was rounded up to the dose required for the upper limit of the group. The average rounding is a 6% increase in dose (range 4-13%) compared to actual dose at the lowest weight of the band. For patients exceeding 100 kg, a total dose of 300 mg was administered irrespectively of weight. Details of the total dose and infusions volumes administered for each dose band are shown in Table 1-1.

Weight (kg)	**Ferumoxytol dose (mg)**	**Volume of ferumoxytol injection required to prepare infusion (ml)** (1ml of solution contains 30mg iron as ferumoxytol)	**Volume of 0.9% sodium chloride required to prepare infusion (ml)**	**Final prepared ferumoxytol infusion volume (ml)**	**Infusions 1-3:** Infusion volume (ml) per infusion	**Infusions 4-5:** Infusion volume (ml) per infusion
40-45	135	4.5	18.0	22.5	2.3	7.8
46-50	150	5.0	20.0	25.0	2.4	8.9
51-55	165	5.5	22.0	27.5	2.7	9.7
56-60	180	6.0	24.0	30.0	3.0	10.5
61-65	195	6.5	26.0	32.5	3.3	11.3
66-70	210	7.0	28.0	35.0	3.4	12.4
71-75	225	7.5	30.0	37.5	3.7	13.2
76-80	240	8.0	32.0	40.0	4.0	14.0
81-85	255	8.5	34.0	42.5	4.3	14.8
86-90	270	9.0	36.0	45.0	4.4	15.9
91-95	285	9.5	38.0	47.5	4.7	16.7
96-100	300	10.0	40.0	50.0	5.0	17.5
≥100	300	10.0	40.0	50.0	5.0	17.5

Table 1-1 Ferumoxytol infusion protocol.

Ferumoxytol-enhanced MRI has been used in small cohort studies in CKD for a plethora of applications. Sigovan et al. (Sigovan et al., 2012) found that FeMRA provided better image quality and reduced flow artefacts compared to non-contrast MRA in dialysis fistula evaluation, with a much shorter acquisition time (19 vs 270 seconds). FeMRA has been used in kidney transplant recipients with graft dysfunction, where steady-state imaging was better for evaluation of transplant vasculature compared to first-pass imaging (Corwin et al., 2016) and better for detection of graft artery abnormalities compared to US (Bashir et al., 2013). When compared with DSA, FeMRA was similarly sensitive and accurate in assessing the severity of transplant renal artery stenosis (Fananapazir et al.,

2017). In a comparative study of ferumoxytol-enhanced versus gadofosveset-enhanced MR venography for abdominopelvic and lower extremity venous assessment, there was no difference in signal intensity between the two techniques (Bashir et al., 2014). In two paediatric cohorts of 30 children with CKD who needed detailed vascular mapping for various indications (i.e. vascular access planning or complication, pre- or post-kidney transplant evaluation), FeMRA examinations were reported to be diagnostic and safe (Luhar et al., 2016; Nayak et al., 2015). Recently it has been used for transcatheter aortic valve replacement (Nguyen et al., 2018) and it is currently being tested for detection of coronary artery stenosis (NCT02954510). Apart from vascular imaging, ferumoxytol-based imaging has been successfully used for the delineation of primary pancreatic tumours (Hedgire et al., 2014) and as an ionising radiation-free staging method in children and young adults with malignant lymphomas and sarcomas (Klenk et al., 2014). In all studies FeMRA had good performance with comparable or superior image quality, reduced flow artifacts and reduced scanning time compared with conventional DSA and non-enhanced or gadolinium-based MR angiography.

1.6.4 Safety profile

Since its introduction in clinical practice in 2009, ferumoxytol has an established safety profile with no propensity to cause nephrogenic systemic fibrosis or any other long-term toxicity (Toth et al., 2017). The rates of adverse reactions in clinical trials and post-marketing safety data on therapeutic use of ferumoxytol are very low (Auerbach et al., 2013; Hetzel et al., 2014; Macdougall et al., 2014; Vadhan-Raj et al., 2014). Rates of adverse events are similar to those seen with ionic iodinated contrast agents (Toth et al., 2017) and the more commonly used intravenous iron formulations (Airy et al., 2015; Bircher & Auerbach, 2014). Most reported adverse events were mild, transient and typically associated with the infusion process, although mild arthralgia or myalgia and headaches occurred up to 48 hours post-infusion in one study (Auerbach et al., 2013), where 1,020 mg of ferumoxytol was administered over 15 minutes. Serious adverse events included hypersensitivity (Schiller et al., 2014; Vadhan-Raj et al., 2014) and hypotension (Schiller et al., 2014) with a pooled aggregate rate of anaphylaxis of 0.03% (3/10,425) based on published studies (Hetzel et al., 2014; Macdougall et al., 2014; Schiller et al., 2014; Vadhan-Raj et al., 2014). The main concern has been reported cases of 'anaphylactic-type’ reactions with rapid therapeutic bolus injections of undiluted compound leading to the US Food and Drug Administration (FDA) recommendations for

controlled infusion of dilute ferumoxytol (United States Food and Drug Administration, 2015).

In March 2015, the US FDA Adverse Event Reporting System reported 79 anaphylactic reactions, of which 18 were fatal. These deaths resulted in a black-boxed warning (http://www.fda.gov/Drugs/DrugSafety/ucm440138.htm) of rare, but serious hypersensitivity reactions including anaphylaxis. Twenty-four percent of these patients had multiple drug allergies, and nearly half of these anaphylactic reactions occurred within 5 minutes of administration. At that time approximately 1 million administrations of ferumoxytol had been given. This rate of adverse events is lower than the rates initially reported in Phase 2 and 3 clinical trials. New therapeutic prescribing recommendations included dilution, infusion over 15 minutes (in contrast to the originally advocated bolus injection over 17 seconds), and haemodynamic monitoring up to 30 minutes after infusion.

Ferumoxytol’s carbohydrate shell is substantially different from prior dextran compounds, which diminishes immunogenicity, retards phagocytosis and slows the release of elemental iron from the core. Nevertheless, as is the case with all formulations of intravenous iron, a varying amount of labile free iron is released upon administration (Jahn et al., 2011). Labile free iron release can cause a constellation of symptoms termed a Fishbane reaction (acute myalgias, arthralgias, headache, chest pressure, and/or back pain, without clinical findings of wheezing, stridor, periorbital oedema, or persistent hypotension) associated with intravenous iron infusions (Auerbach & Macdougall, 2017). The published frequency of these symptoms ranges from 1 to 3% (Bircher & Auerbach, 2014) and they are self-limited, resolve without therapy and may be due to complement activation related pseudoallergy (Macdougall & Vernon, 2017). However, they are often mistaken for severe hypersensitivity with resultant treatment with vasopressors and/or antihistamines, converting the minor infusion reaction to a hemodynamically significant serious adverse event, ostensibly attributable to the intravenous iron. Rather than true allergy it is most likely a chemotoxic phenomenon related to high concentrations of the iron compound when infused rapidly interacting with mast cells in the vascular wall (Bircher & Auerbach, 2014). True, severe hypersensitivity reactions due to mast cell activation are extremely rare and occur in fewer than 1:200,000 administrations (Chertow et al., 2006).

To address concerns about serious adverse events, especially true hypersensitivity, which is very rare, AMAG Pharmaceuticals, ferumoxytol's manufacturer initiated a program of

studies to assess safety and efficacy. The largest of these was a 2000 patient double blind, randomised comparison of the FDA approved administration of 1020 mg of ferumoxytol (two vials) to 1500 mg of ferric carboxymaltose (two vials), also FDA approved administration (Adkinson et al., 2018). Both formulations were administered over two visits 1 week apart and at five weeks no difference in safety or efficacy was observed.

A recent report on off-label diagnostic use of ferumoxytol from 11 institutional partners worldwide (including our centre), demonstrates no serious adverse events and 83 minor acute adverse reactions (<2% of all injections), including hypertension, nausea, flushing, backache, pruritus, headache, and vomiting following 4,240 ferumoxytol injections (Nguyen et al., 2019a). Common indications included vascular, liver, and tumour imaging and evaluation of congenital heart disease (Figures 1-11 and 1-12).

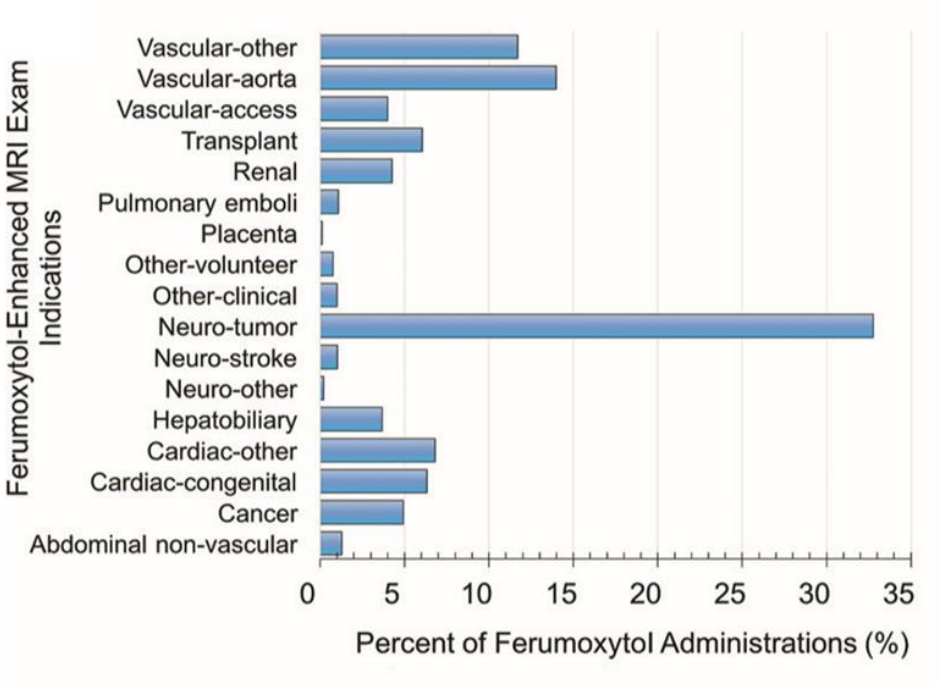


Figure 1-11 Ferumoxytol applications.

Graph of first-pass and steady-state FeMRA for a wide spectrum of indications (n = 4,240). Reproduced with permission from Radiology. 293(3):554-564 (2019). Copyright 2019 Radiological Society of North America.

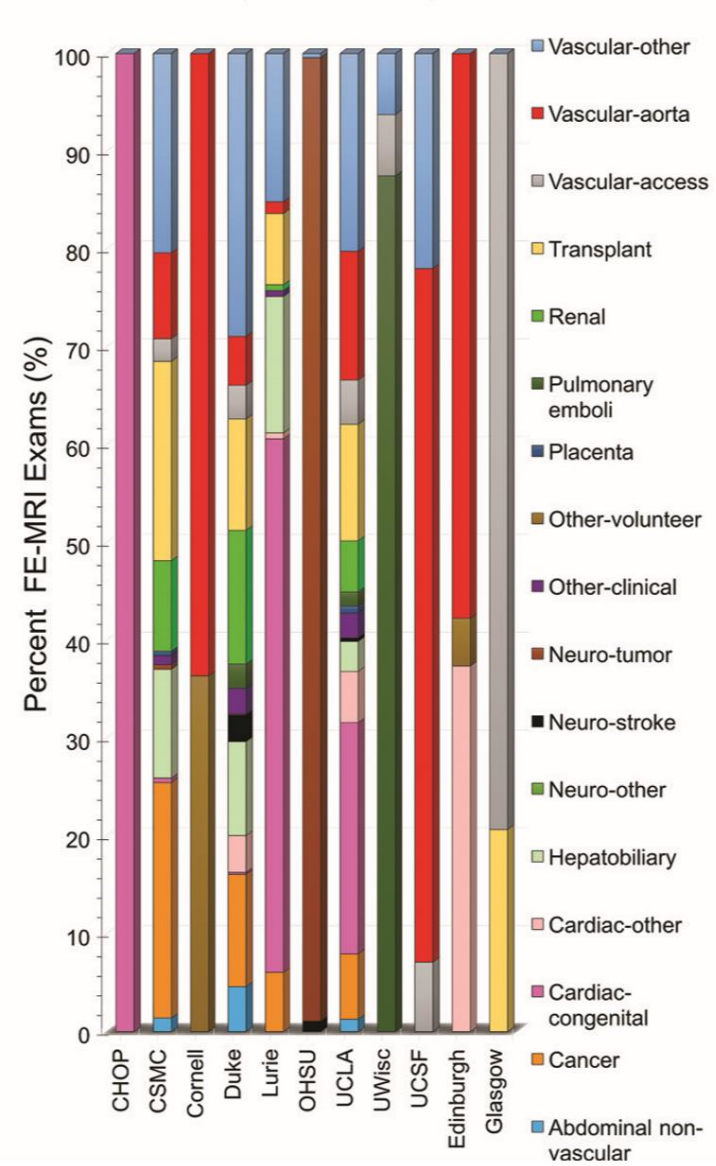


Figure 1-12 Spectrum of clinical and research applications varied by institution.

Three centres (Duke, UCLA, and CSMC) had the widest spectrum of clinical indications. CSMC = Cedars-Sinai Medical Center; CHOP = Children's Hospital of Philadelphia; OHSU = Oregon Health State University; UCLA = University of California, Los Angeles; UCSF = University of California, San Francisco; UWisc = University of Wisconsin. Reproduced with permission from Radiology. 293(3):554-564 (2019). Copyright 2019 Radiological Society of North America.

1.6.5 Limitations in ferumoxytol use

The potential disadvantages of ferumoxytol merit mention. First, administration of ferumoxytol may transiently affect the diagnostic ability of MRI and alteration of MRI studies may persist for up to 3 months following infusion (Storey et al., 2012). This is the case when the higher therapeutic doses are used for iron supplementation. Anticipated MRI

studies should be conducted prior to the administration of ferumoxytol. If MRI is required within 3 months after ferumoxytol administration, use of T1- or proton density-weighted MR pulse sequences to minimise the ferumoxytol effects should be performed; MRI using T2*-weighted pulse sequences for iron estimation purposes should not be performed earlier than 4 weeks after the administration of ferumoxytol. Ferumoxytol may affect the appearances only of certain organs (e.g. liver or bones) and this is not different of what happens when intravenous iron (any preparation) is administered for therapeutic purposes. Ferumoxytol does not interfere with any other imaging modalities available for diagnosis. Once aware of expected changes, radiologists can learn to interpret the images in context and without confusion.

Second, in the steady state, ferumoxytol enhances arteries and veins equally and independently of bolus timing. While this attribute can simplify vascular imaging of the chest, abdomen, and pelvis (where arteries and veins are readily distinguishable based on anatomy), this is not the case in the brain and extremities, and alternative approaches will be required for efficient separation of arteries and veins.

Third, excessive therapy with parenteral iron can lead to excess storage of iron with the possibility of iatrogenic haemosiderosis.

Fourth, cost is an important consideration with any diagnostic agent, and the commercial landscape surrounding the diagnostic use of ferumoxytol is complicated. Although approved in the United States and Europe to treat iron deficiency anaemia, ferumoxytol is only commercially available in the United States at this time and is marketed as a single-dose 17 mL vial (510 mg of iron). Ferumoxytol is priced as a therapeutic agent, and its typical price point (approximately $700 per 17 mL vial) is not realistic for an MRI contrast agent (other than for very limited applications). A further complication is the fact that the typical dose used for diagnostic imaging is less than a full vial, and any unused product must be discarded.

1.7 Hypotheses and Aims

Cardiovascular disease is prevalent, associated with traditional and non-traditional cardiovascular risk factors and it is the most common cause of death in CKD patients. Currently used imaging techniques have limitations in assessing vasculopathy in CKD.

Ferumoxytol is a novel, non-nephrotoxic, superparamagnetic contrast agent for MRI, which provides an alternative for vascular imaging.

We are applying ferumoxytol-enhanced MR angiography (FeMRA) in two district groups of CKD patients requiring vascular imaging for a) evaluation of the iliac vasculature prior to kidney transplantation, b) vascular mapping before arteriovenous fistula creation. In both cohorts FeMRA was compared to the currently used imaging technique (standard of care). In the second group of patients we have also performed cardiac magnetic resonance imaging (CMR) before and after AVF creation to evaluate the effects of AVF creation on cardiac structure and function. The study objectives are:

a. to evaluate the image quality and diagnostic utility of FeMRA compared to standard imaging techniques in advanced CKD, and

b. to establish the most appropriate imaging modality for cardiovascular assessment in patients with advanced CKD.

Our study hypotheses are:

I. Cohort 1: FeMRA vs CT angiography for the assessment of potential kidney transplant recipients

FeMRA is superior to CT angiography for characterisation of aortoiliac anatomy before implantation of a kidney graft because:

a) FeMRA can robustly evaluate arterial lumen and calcification. For assessment of calcification a non-CE-MRI sequence was used.

b) FeMRA can robustly evaluate venous anatomy due its properties (blood pool agent with prolonged half-life) without the need for time-consuming venography protocols, or increased contrast and radiation doses.

c) FeMRA can identify venous abnormalities that may affect transplant planning and the site of kidney graft implantation.

II. Cohort 2: FeMRA vs Duplex US for vascular mapping before haemodialysis arteriovenous fistula creation

FeMRA is superior to Duplex US for vascular mapping before arteriovenous fistula creation because:

a) FeMRA can robustly evaluate central arterial and venous vasculature.

b) FeMRA can assess arm vasculature more accurately as images can be reformatted and vascular sections can be visualised in multiple levels.

c) FeMRA can identify central vessels pathology that may affect vascular access planning and the side of AVF creation.

d) FeMRA can better predict AVF outcome.

III. Cohort 3: Effects of haemodialysis arteriovenous fistula creation on cardiac structure and function

a) Creation of an AVF contributes to maladaptive cardiovascular remodelling.

b) Left ventricular (LV) mass and other cardiac parameters (LV end-diastolic volumes, LV end-systolic volumes, LV ejection fraction, cardiac output, and LV global longitudinal strain) change significantly following AVF surgery.

c) Changes in structural and functional parameters are associated with changes in cardiac biomarkers [N-Terminal-pro B-type Natriuretic Peptide (NT-proBNP) and high-sensitivity Troponin I].

d) These changes are directly associated with the AVF blood flow and are more prominent in high flow fistulas.

e) Changes in cardiac parameters occur early (within weeks) after AVF surgery.

Chapter 2. METHODS

2.1 Study design

We performed a series of prospective single-centre studies to investigate the clinical utility of ferumoxytol-enhanced MRA in phenotyping the vasculature of patients with CKD. These studies were registered in ClinicalTrails.gov (NCT02997046 - https://clinicaltrials.gov/ct2/show/NCT02997046?term=ferumoxytol&draw=11&rank=64) and approved by the institutional review board [Research Ethics Committee (REC) reference: 16/NS/0099]. The full study protocol is available at http://dx.doi.org/10.36399/gla.pubs.215112. All patients provided written informed consent for the FeMRA studies and inclusion into our research protocols. The risks and benefits were explained by an attending physician who was present throughout all MRI studies.

2.1.1 Study population

For all studies patients with advanced kidney disease older than 18 years with eGFR of < 15 mL/min/1.73m^2 were recruited from the renal clinics.

For the preliminary feasibility and dose finding studies, the evaluation of the use of ferumoxytol as a new potential clinical service was approved by the Clinical Governance Committee of the Diagnostics Directorate of NHS Greater Glasgow & Clyde. The regional Research Ethics Committee ethics officer was consulted and confirmed that formal ethics committee approval was not required. Nevertheless, as this was an off-label use of the agent, informed consent was obtained from all subjects. Investigations were performed between 1 December 2015 and 1 August 2016.

In the feasibility study CKD patients requiring vascular imaging prior to wait-listing for kidney transplantation were included. Criteria for vascular imaging included intermittent claudication, known PAD with previous angioplasty or revascularisation procedure or leg amputation, extensive disease in other vascular beds, and the presence of risk factors for PAD (diabetes, smoking, hypertension, obesity). In some instances, patients had FeMRA in addition to prior conventional CTA if the clinician felt that additional investigation was required to characterise the vessels before placement of a kidney graft. These were usually patients who had blooming artefacts from dense calcifications on initial CTA. Dialysis

patients were included if there was evidence of extensive vascular calcification or they had residual renal function with a risk of accelerated decline in function after CTA.

The dose-finding study was performed to optimise our protocol before the main comparative studies. In the dose-finding study CKD patients were referred for FeMRA if the clinician felt that an angiogram was required for one the following indications: characterisation of the aortoiliac vasculature prior to wait-listing for kidney transplantation, investigation of renal artery stenosis or to assess PAD. In all patients, standard contrast-enhanced imaging techniques were avoided due to potential risks of CI-AKI or NSF.

For the comparative studies, CKD patients requiring vascular imaging as part of kidney transplant assessment or mapping before creation of an autogenous upper arm AVF were recruited between 12th December 2016 and 30th August 2018. We compared FeMRA with standard imaging techniques in assessment of vascular anatomy with an emphasis on imaging quality and diagnostic accuracy. The primary end-point of the comparative studies was the identification of clinically significant anatomic characteristics or lesions. Multiple cross sections of various vascular beds were obtained with currently used imaging techniques and compared with matched sections obtained with FeMRA in a blinded fashion. Patients were selected from those referred for vascular assessment prior to listing for a kidney transplant or prior to AVF creation for haemodialysis and were divided in 2 groups. The first group (group A) included patients who had CTA of abdominal and aortoiliac vasculature performed for pre-transplant assessment. The second group (group B) included patients who had US vascular mapping performed before AVF creation for HD. Patients in the second group also had CMR at baseline and 6 weeks after AVF creation. Cardiac magnetic resonance imaging was performed to assess changes in cardiovascular anatomical and functional parameters (LV mass and volumes, LV ejection fraction, cardiac output etc.) associated with physiological responses to fistula creation. As part of the study patients in the second group also had AVF blood flows measured with Duplex US at 6 weeks following fistula creation as a surrogate for clinical maturation.

2.1.2 Inclusion and exclusion criteria

All adult patients with advanced CKD attending the renal clinics were eligible for participation in the studies and were screened using outpatient clinics lists. Main inclusion

criteria included: a) anticipated ability to comply with study procedures and b) ability to provide informed consent. For some of the studies, extra inclusion criteria apply, which are described separately in each study's Methods section.

Exclusion criteria were a) life expectancy ≤6 months, b) frail, elderly patients with multiple or serious co-morbidities (doctor's discretion), c) pregnancy, lactation or women of childbearing potential not willing to use effective contraception for the duration of the study, d) standard contra-indications to MRI: the presence of certain metallic objects in the body (e.g. non-MRI compatible cardiac pacemaker, artificial joints, previous cranial surgery with ferromagnetic clips, metal fragments in eye, etc.) and severe claustrophobia, e) history of allergic reaction to any intravenous iron product, known hypersensitivity to excipients, asthma, eczema, atopy, patients with immune or inflammatory conditions (e.g. systemic lupus, rheumatoid arthritis), any conditions associated with iron overload (e.g. haemochromatosis, chronic liver disease, or blood disorders requiring frequent blood transfusions), and known history of multidrug allergy and f) any other reason considered by a study physician to make subject inappropriate for inclusion.

2.1.3 Study procedures

The MRI, CT and US scans were performed at a single site, at Queen Elizabeth University Hospital research scanners in Glasgow. Participants were provided with a patient information sheet (PIS) and given at least 24 hours to consider their response before consent is taken and a screening visit is performed to check their eligibility by all the criteria.

MRI studies were performed on a 3.0 T Prisma MRI scanner (Magnetom, Siemens Healthineers, Erlangan; Germany) with phased-array imaging coils using a standardised protocol. The imaging protocol was similar to that of standard MRA studies with GBCAs. The FeMRA was scheduled at a suitable date and time - usually within 2-4 weeks after signing the consent form. For patients on HD, scans were scheduled on non-dialysis days. For practical reasons, the scans (clinical and research) were booked on the same day. There was not a minimum elapsed time recommended between MRA and CTA as they are using different contrast agents that are not interfering with each other's imaging quality.

Standard imaging tests took place as part of the routine clinical care, which involves CTA for pre-transplant assessment when indicated and Duplex US vascular mapping for all

patients before AVF creation. All these tests are part of our standard care, and results are available for clinical use. However, FeMRA images were not available to clinicians or study investigators unless there was a finding that could threaten the participant's health (e.g. impending rupture of pseudoaneurysm).

The participants remained in the study in person up to the completion of the study investigations. This was one day for the patients in group A (for the day of their FeMRA scan) and 6-12 weeks for the patients in group B (up until their second CMR). No patients were withdrawn from the study after enrollment, and they remained in the study for the entire duration of the follow up, which was 2 years. Follow up involved regular review of the medical records for identification of any outcomes of interest. Their images remain available for review after the end of the study.

2.1.4 MRI protocol

2.1.4.1 Ferumoxytol-enhanced MRA

Patients underwent MRA with ferumoxytol administered in an appropriate setting under supervision of trained medical personnel and were observed for a minimum period of 30 minutes following termination of ferumoxytol infusion. Ferumoxytol dosage was based on body weight on the day of scanning. All patients were imaged in the supine position.

2.1.4.2 Cardiac MRI

Cardiac magnetic resonance imaging was performed before contrast administration in patients in group B at baseline and 6-12 weeks later depending on the time interval between the baseline scan and the arteriovenous fistula surgery. Cardiac MR was not part of the comparative studies between standard imaging techniques and FeMRA but served to assess the cardiac effects following creation of a non-physiologic shunt to facilitate haemodialysis.

2.1.5 Ferumoxytol administration

Ferumoxytol was infused intravenously through a 22-gauge intravenous catheter placed in the antecubital fossa of either arm. In all cases ferumoxytol was diluted to a concentration no greater than one part ferumoxytol to four parts 0.9% sodium chloride. Ferumoxytol

infusions were delivered by an MRI compatible infusion pump for precise control over infusion rates, which were set at 1 ml/second of diluted ferumoxytol (equal to 6 mg/second of elemental iron) followed by 20 ml of 0.9% sodium chloride at a rate of 1 ml/second. The dose of ferumoxytol administered was estimated by pilot studies (feasibility and dose-finding studies), which were performed in advance of the comparative studies.

Patients were instructed to immediately alert the operator should they have any discomfort at any time and were continuously monitored by pulse oximeter (measuring both heart rate and oxygen saturation) while in the MRI scanner and had blood pressure measured before and after infusions. Care was taken to ensure that the total cumulative dose was not administered in less than 20 min.

2.1.6 Study flow charts

The study flow, study visits and study procedures charts for the different cohorts are shown below:

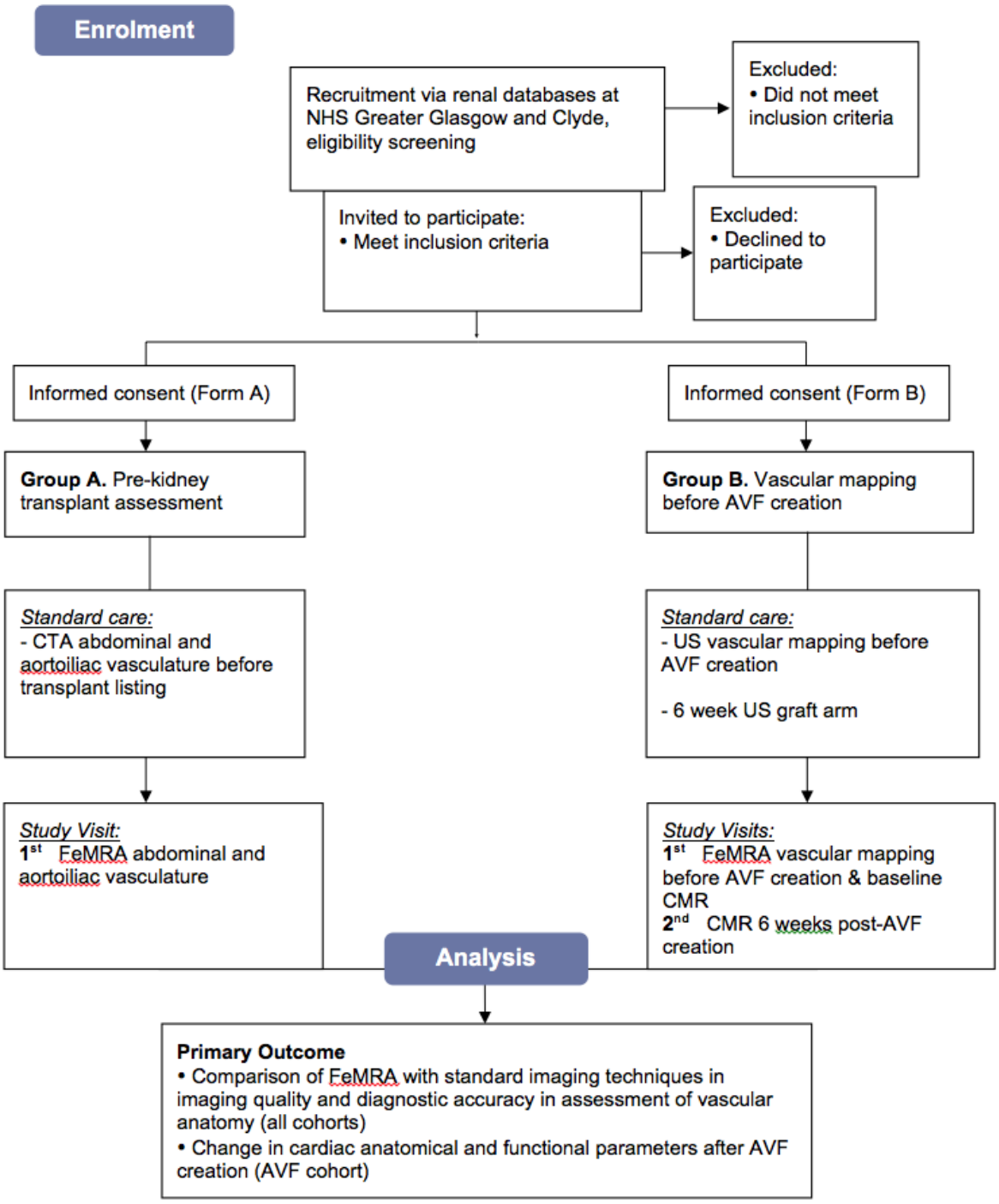


Figure 2-1 Study flow chart.

Recruitment process, study visits and outcomes of interest.

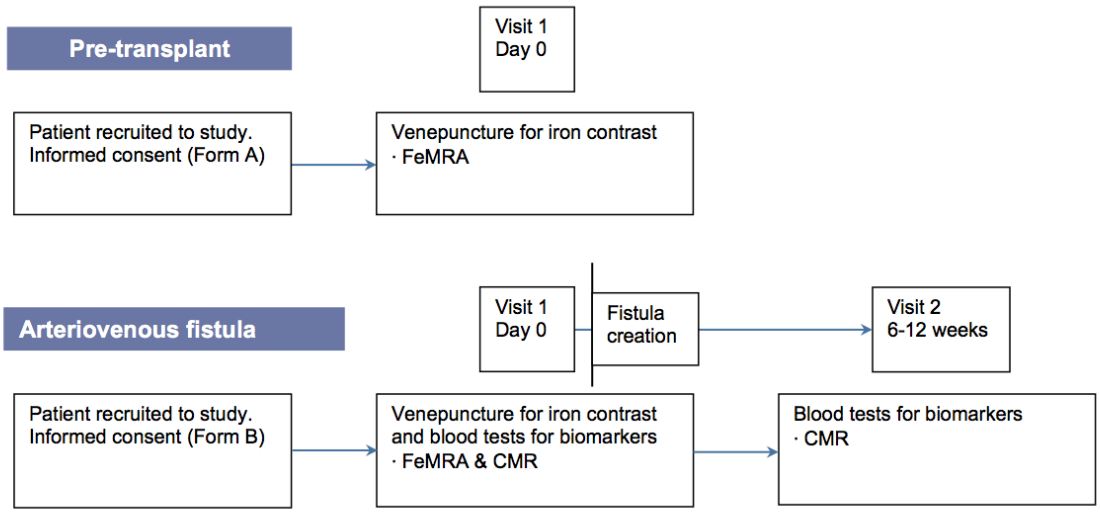


Figure 2-2 Study visits chart for the two cohorts.

GROUP A		
STUDY VISIT	**Screening visit**	**Visit 1**
	At clinic after notification	2-4 weeks after consent
Informed consent	**X**	
Doctor check inclusion/exclusion criteria	**X**	
Demographics	**X**	
Medical history	**X**	
Medications	**X**	**X**
Allergies	**X**	**X**
Body weight		**X**
Pregnancy test (for women who may be pregnant)		**X**
FeMRA[#]		**X**
CTA*		**X**
[#]Only if eligible after screening *Standard clinical care		

Table 2-1 Study procedures for the pre-transplant assessment cohort (group A).

GROUP B			
STUDY VISIT	**Screening visit**	**Visit 1**	**Visit 2**
	-1 to -4 weeks	-1 to -4 weeks	-3 to +3 days
Informed consent	**X**		
Doctor check inclusion/exclusion criteria	**X**		
Demographics	**X**		
Medical history	**X**		
Medications	**X**	**X**	**X**
Allergies	**X**	**X**	**X**
Body weight		**X**	**X**
Pregnancy test (for women who may be pregnant)		**X**	
FeMRA[#]		**X**	
CMR*		**X**	**X**
Duplex US^		**X**	**X**
Blood samples[$]		**X**	**X**

[#] *Only if eligible after screening

^1st scan as part of standard clinical care, 2nd scan to assess AVF maturation (research)

[$]To test biomarkers of cardiac function (NT-proBNP and high-sensitivity Troponin I)

Table 2-2 Study procedures for the vascular access mapping cohort (group B).

2.2 Feasibility study

2.2.1 Baseline data

Age, gender, aetiology of ESRD and co-morbid conditions [including estimation of the Charlson Comorbidity Index (CCI) scores] were recorded. Charlson Comorbidity Index quantifies an individual's burden of disease and corresponding 1-year mortality risk (Charlson et al., 1987) and has been shown to be an independent predictor of mortality in patients with CKD (Pugh et al., 2016). The rationale for using this index was to examine whether our study population is representative of our highly co-morbid HD population. We

also retrieved data on the last serum creatinine prior to FeMRA and calculated the eGFR using the six-variable Modification of Diet in Renal Disease (MDRD) formula (Levey et al., 1999).

CTA examinations were reviewed for patients who had had both imaging modalities performed as part of their assessment, and served as the reference standard for comparisons with FeMRA. Direct comparisons of predefined cross-sections of various vascular beds were performed to visually assess image quality. The CT and MR images were interpreted separately and the observer was blinded to patient identity, clinical findings and findings of the other imaging study.

2.2.2 Ferumoxytol dose and image acquisition

A total dose of 4 mg/kg of ferumoxytol (Feraheme; AMAG Pharmaceuticals, Inc., Cambridge, MA, USA) was delivered up to a maximum of 300 mg administered in four equally divided controlled infusions until the full standard dose was delivered.

Pre-contrast imaging was performed for morphological assessment. First-pass, breath-hold imaging with a dynamic contrast-enhanced technique was performed 15–20 seconds after delivery of the first infusion. These three-dimensional (3D), T1-weighted ultrafast spoiled gradient echo sequences were also obtained after each subsequent infusion and were considered first-pass (arterial phase) images. Further T1-weighted spoiled gradient echo sequences were used to obtain steady-state breath-hold (1 mm isotropic) and non-breath-hold higher spatial resolution (0.5 mm isotropic) abdominopelvic images after the first and each subsequent infusion until the full dose had been reached – each imaging initiated 3 minutes after contrast administration.

Average scan duration was approximately 45 min.

2.2.3 Data analysis

Both arterial and venous structures were assessed. The examined arteries included abdominal aorta, coeliac artery, superior and inferior mesenteric arteries, renal arteries, and common, external and internal iliac arteries. The examined veins included inferior vena cava, renal veins, common, external and internal iliac veins, and common, superficial and deep femoral veins in the upper thigh. Visual assessment of the subjective image quality

was performed independently by two radiologists (M.H and G.R.) with 5 years and >20 years of experience, respectively, in cardiovascular MR imaging.

Image quality was assessed following administration of the full cumulative dose and was rated on a scale of 1–4 (1: non-diagnostic; 2: poor definition such that only gross features such as overall patency are evaluable; 3: good definition such that pathology can be confidently visualised or excluded; 4: excellent definition such that detailed anatomy is clearly visualised with sharp borders for all vessels) with respect to the abdominal aorta, the inferior vena cava and the common, external and internal iliac arteries and veins. The same vessels were used for comparisons with CTA studies. Interobserver agreement was calculated using weighted kappa statistics (< 0.2: poor agreement; 0.2–0.4: fair agreement; 0.41–0.6: moderate agreement; 0.61–0.8: good agreement; 0.81–1.0: very good agreement). The IBM SPSS Statistics Package (version 22.0; SPSS, Inc., Armonk, NY, USA) was used for all analyses.

2.3 Dose-finding study

2.3.1 Baseline data

Age, gender and aetiology of ESRD were recorded. We retrieved data on last haemoglobin and serum creatinine prior to FeMRA and calculated the eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey, Stevens, Schmid, Zhang, Castro, Feldman, Kusek, Eggers, Van Lente, Greene, Coresh, & Collaboration), 2009). All patients were weighed on the day of the scan to calculate the doses of ferumoxytol given.

2.3.2 Ferumoxytol dose and image acquisition

A total dose of 4 mg/kg of ferumoxytol was delivered up to a maximum of 400 mg administered in 4–7 (median 4) divided controlled infusions (aliquots) until the maximum dose was delivered. The infusion time for each aliquot ranged up to 18 seconds depending on body weight and volume of the infusion. These aliquots were delivered with a minimum interval of 5 minutes between them to allow time for planning and different imaging components to be performed; thus, the total dose was delivered over a minimum of 20 minutes.

A full range of angiographic sequences was performed depending on the clinical indication; however, for the purposes of this study, the relevant one was a T1-weighted fast low-angle shot (FLASH) sequence of aortoiliac vasculature. This sequence was performed before giving contrast and 60 seconds after each aliquot of the diluted ferumoxytol was administered without changing the imaging field-of-view between sequences.

Average scan duration was 30 minutes.

2.3.3 Signal-to-noise and contrast-to-noise ratios

Signal-to-noise ratio (SNR) is a generic term, which in radiology is a measure that compares the level of a desired signal (i.e. reflecting actual anatomy) to the level of background noise (i.e. random quantum mottle). In MRI the signal-to-noise ratio is measured frequently by calculating the difference in signal intensity between the area of interest and the background (usually chosen from the air surrounding the object). In air, any signal present should be noise. The difference between the signal and the background noise is divided by the standard deviation of the signal from the background - an indication of the variability of the background noise. For data acquired through MRI, this quantification is typically used to allow comparison between imaging hardware, imaging protocols and acquisition sequences. In this context, SNR is conceptualised by comparing the signal of the MRI image to the background noise of the image (Parrish et al., 2000).

Contrast-to-noise ratio (CNR) is a measure used to determine image quality. It is defined as the difference in signal intensity (SI) between different tissues, divided by the background noise. The amount of lesion contrast relative to the amount of noise (mottle) is the key determinant of the visibility of a given lesion. Improving the CNR increases the ability to distinguish between two areas of clinical interest. This can be achieved by increasing lesion contrast or reducing the amount of noise or by a combination of these two methods.

Both metrics are equally important to dictate image quality especially when there is a significant bias in an image. For example if an image has high intensity but its features are washed out by the haze, it may have a high SNR, but will have a low CNR metric.

2.3.4 Data analysis

Images were analysed using OsiriX MD (Pixmeo). For quantitative analysis, signal intensities within the vessel lumen were measured using the regions of interest (ROI) placed in the abdominal aorta (AA), inferior vena cava (IVC), psoas muscle, intra-abdominal fat, liver and spleen that were cloned (in terms of position and size) across the acquisitions. An ROI was placed in air outside of the imaged body for noise calculation. The target ROI size was a minimum of 1 cm^2. If this size could not be achieved in small vessels, the largest practical ROI area for that vessel was assessed. Mean signal intensity (SI; arbitrary units, U) following each dose increment was recorded from all ROIs except those placed in air, from which the standard deviation (SD) was recorded. Contrast-to-noise and signal-to-noise ratios were calculated. Correlation analyses between CNR and SNR in the AA and IVC and ferumoxytol dose were performed. Assessment of the CNR and SNR was performed independently by two radiologists with 5 years and > 20 years of experience, respectively, in cardiovascular MR imaging. Following analysis of all images, discordances were adjudicated by discussion and consensus reached.

Descriptive statistics are expressed as means ± SD or numbers and percentages. Four quadratic regression models were used to plot the relationship between cumulative doses of ferumoxytol and CNR and SNR change within AA and IVC, respectively, and estimate the regression coefficients. The open-source statistics environment R (version 3.4.3; The R Foundation) was used for statistical analysis (R Development Core Team, 2017).

2.4 FeMRA vs CTA for assessment of kidney transplant candidates

2.4.1 Inclusion criteria

Patients with planned imaging of abdominopelvic vasculature as part of pre-transplant assessment were included in this study if they fulfilled the standard criteria mentioned in detail earlier in Methods.

2.4.2 Baseline data

Age, gender and aetiology of ESRD were recorded. Haemoglobin and serum creatinine prior to FeMRA were checked and eGFR calculated (Levey, Stevens, Schmid, Zhang, Castro, Feldman, Kusek, Eggers, Van Lente, Greene, Coresh, & Ckd, 2009).

2.4.3 CTA protocol

CTA of the aortoiliac segments was performed using a standard protocol with a 320-detector row CT scanner (Canon/Toshiba, Aquilion One Vision edition; USA). Images were obtained with 100kVp after injection of 100cc of high iodine concentration contrast (Omnipaque 350) followed by 50mL 0.9% sodium chloride flush injected at a rate of 4mL/second using an automatic power injector.

2.4.4 Ferumoxytol dose and image acquisition

Ferumoxytol was infused intravenously at a dose of 3mg/kg (up to a maximum of 300mg) based on preliminary data from feasibility (Stoumpos et al., 2018) and dose-finding (Stoumpos, Hennessy, et al., 2019a) studies.

For detection of arterial calcification, a specific MRI sequence [3D free-breathing (StarVIBE) FLASH] was performed before ferumoxytol administration. Gray-scale inversion of the maximum intensity projections (MIP) rendered the arterial calcifications as bright structures to facilitate comparisons with CTA. For analysis of the vessels, high-spatial-resolution 3D acquisitions were obtained after administration of the full dose of ferumoxytol. The imaging parameters for the StarVIBE and the post-contrast MRA acquisitions are available in Table 2-3.

	FeMRA	StarVIBE
Repetition time	2.88 msec	4.18 msec
Echo time	1.04 msec	2.46 msec
Flip angle	20 degrees	2.5 degrees
Slice thickness	1.0 mm	1.2 mm
Voxel dimensions	1.0 x 1.0 x 1.0 mm	1.2 x 1.2 x 1.2 mm
Field of view	400 x 325 mm	462 x 462 mm
Acquisition time	18 sec	4 min 30 sec
Signal averages	1	1
Bandwidth	300 Hz/pixel	720 Hz/pixel
Parallel imaging acceleration factor	3	N/A

Table 2-3 Pulse sequence parameters for the T1-weighted high-resolution 3D acquisitions.

Average scan duration was 15 minutes and patients were observed for a minimum of 30 minutes following termination of ferumoxytol infusion.

2.4.5 Data analysis

Steady-state MIP images of aortoiliac vasculature were analysed using the Horos image viewer (version 3.0; LGPL 3.0). CTA images were synchronized with FeMRA images using anatomical landmarks and prespecified arterial and venous vascular cross-sections (3 of each) were selected for comparative analysis. These circular cross-sections were placed in the infra-renal AA, right common iliac artery (RCIA), right external iliac artery (REIA), IVC, right common iliac vein (RCIV) and right external iliac vein (REIV) (Figure 2-3).

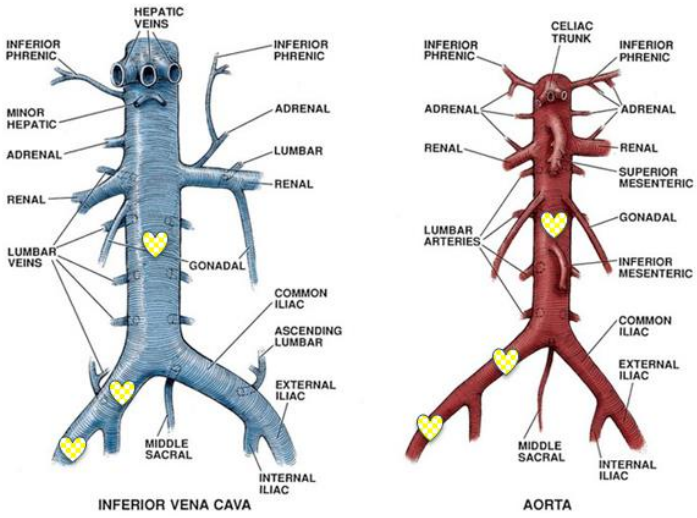


Figure 2-3 Anatomical sections used for analysis.

Schematic representation of arterial and venous sections selected for comparative analysis after synchronisation of CTA and StarVIBE/FeMRA

Regions of interest were drawn on each cross-section to estimate the a) arterial diameter, b) vein diameter, c) area of calcification (if present) and d) signal intensity. Vascular calcific morphology (eccentric or intimal vs concentric or medial) was also assessed (Figure 2-4). For estimation of arterial and vein diameter, a ROI was drawn across the perimeter of the vessel to include the wall and lumen. In non-circular vessels, the maximum estimated vessel diameter was used for analyses. For quantification of arterial calcification, a ROI was drawn on the outer limits of the calcified plaque and the area was measured in mm^2 using the bone window in CTA and a predefined window in StarVIBE. For quantitative signal analysis, signal intensities within the vessel lumen were measured using the ROI technique.

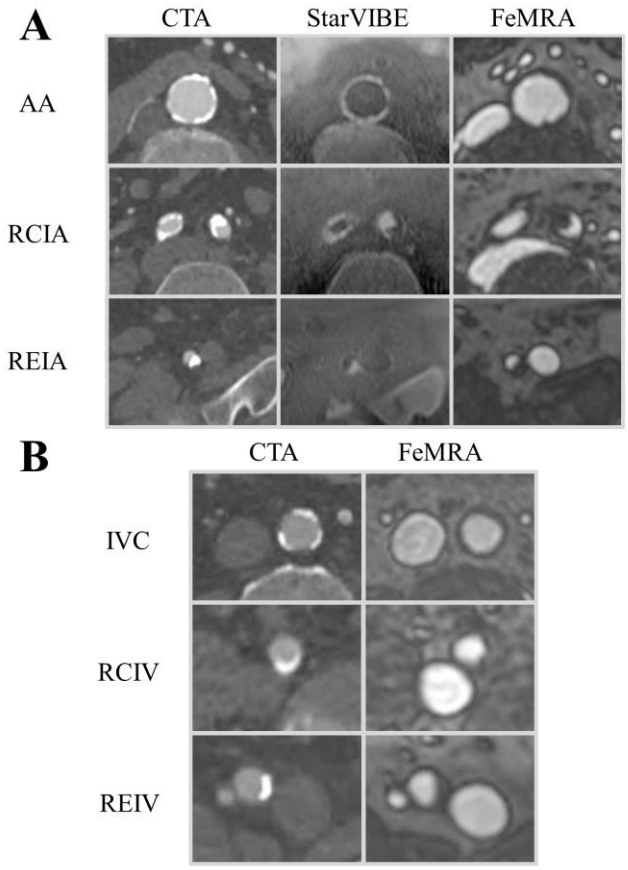


Figure 2-4 Method for the comparative analysis.

Arterial and venous vascular cross-sections used for analysis. Panel A. Arterial cross-sections at the level of infra-renal abdominal aorta (AA), right common iliac artery (RCIA) and right external iliac artery (REIA) used for comparisons between CTA and StarVIBE/FeMRA. Regions of interest (ROI) were drawn for estimation of arterial diameter, area of calcification and signal intensity. Note the consistency in the presence and conformity of calcifications between CTA and StarVIBE and the intraluminal filling defects in FeMRA, which correspond to calcified plaques. Panel B. Venous cross-sections at the level of inferior vena cava (IVC), right common iliac vein (RCIV) and right external iliac vein (REIV) used for comparisons between CTA and FeMRA. ROI were drawn for estimation of vein diameter and signal intensity.

Two independent readers assessed the FeMRA (new technique) and a third reader the CTA (standard technique). After establishment of the cross-sections analysis methodology, a training dataset of 10 clinical scans (not used in final analysis) performed as part of the previously reported feasibility study (Stoumpos et al., 2018) was used to calibrate the measurements between readers. To assess intra-reader agreement for the FeMRA, both readers repeated the analyses within a time interval of >30 days to avoid recall bias.

In addition, visual assessment of the FeMRA and CTA images was performed independently by two surgeons with 5 years and >20 years of experience as independent first operators, respectively, in kidney transplantation. Maximum intensity projection

images and cross sections of aortoiliac vessels were systematically evaluated to determine the arterial inflow, calcification and venous drainage. Based on the anatomical findings each surgeon commented on whether the preoperative plan for arterial and venous implantation was influenced by the findings, the necessity for further tests or revascularization procedures before proceeding to transplant listing, and if a definitive decision for transplant listing could be made relying on the scan.

The sample size was calculated using the identification of clinically significant venous lesions as the primary end-point. We made the assumption that FeMRA will identify vein abnormalities in 15% of patients, which will not be picked up by CT. Based on this assumption, then one would need to study 30 patients to show a significant difference between tests using chi-squared test, to achieve statistical power of 80% and probability of type 1 error of 5%. To include a rate of suboptimal scans that are difficult to interpret of 15%, the recruitment target was increased to 35 subjects.

Descriptive statistics are expressed as means ± SD or absolutes and percentages. Values of arterial calcification were log-transformed to normalize their distribution and were analysed as continuous variables. Interclass correlation coefficients (ICC) with 95% CI using two-way mixed effects models were performed to test intra- and inter-reader consistency of agreement. ICC was interpreted as follows: < 0.40 poor, 0.40–0.59 fair, 0.60–0.74 good, ≥0.75 excellent (Cicchetti, 1994). Comparisons of vessel diameter, area of calcification and signal intensity were performed between FeMRA and CTA. For all variables, mean differences (and 95% CI) were estimated and Bland-Altman plots(Bland & Altman, 1986) of inter-reader variability were created.

The Stata Statistics Package (Stata/SE, version 15.0; StataCorp LLC, USA) was used for all analyses. A *p*-value of < 0.05 was considered significant.

2.5 FeMRA vs Duplex US for vascular mapping before vascular access creation

2.5.1 Inclusion criteria

Additional inclusion criteria to the ones mentioned earlier in Methods were: a) planned surgical creation of an autogenous upper-extremity fistula and b) current treatment with

maintenance HD or anticipated treatment with maintenance HD within 6 months after planned AVF creation surgery.

2.5.2 Baseline data

Age, gender, aetiology of ESRD and previous AV access procedures or central venous catheterisations were recorded. Haemoglobin and serum creatinine prior to FeMRA were checked and eGFR calculated (Levey, Stevens, Schmid, Zhang, Castro, Feldman, Kusek, Eggers, Van Lente, Greene, Coresh, & Ckd, 2009).

2.5.3 Mapping technique

Veins were evaluated for diameter, patency, compressibility (Duplex US only), thrombus, course, side branches, depth from the skin surface, and linear length for future cannulation. The sites and length of any venous stenosis and the sites and sizes of vein branches were recorded. Venous mapping was performed with and without a venous pressure tourniquet in place. Arterial evaluation included measurement of the luminal diameter, patency, presence of inflow or outflow disease, calcifications (Duplex US only), and anatomic variants. Central arteries and veins were only assessed with FeMRA for the presence of stenosis or occlusion.

For comparative analysis arterial and venous vascular cross-sections (4 of each) were selected at specified locations. These circular cross-sections were placed in the radial artery (RA) at wrist, mid-forearm and elbow, brachial artery (BA) at elbow, cephalic vein (CV) at wrist, mid-forearm and elbow, and basilic vein (BV) at elbow (Figure 2-5). Internal diameter measurements of the arteries and veins, as well as depth of the anterior wall of the vein to the skin surface, were performed with FeMRA and Duplex US. In non-circular vessels, the maximum estimated vessel diameter was used for analyses. For estimation of vein diameter, the measurement obtained with the tourniquet was used as this is thought to more closely approximate to the size of the arterialised vein after fistula formation (Lockhart et al., 2006).

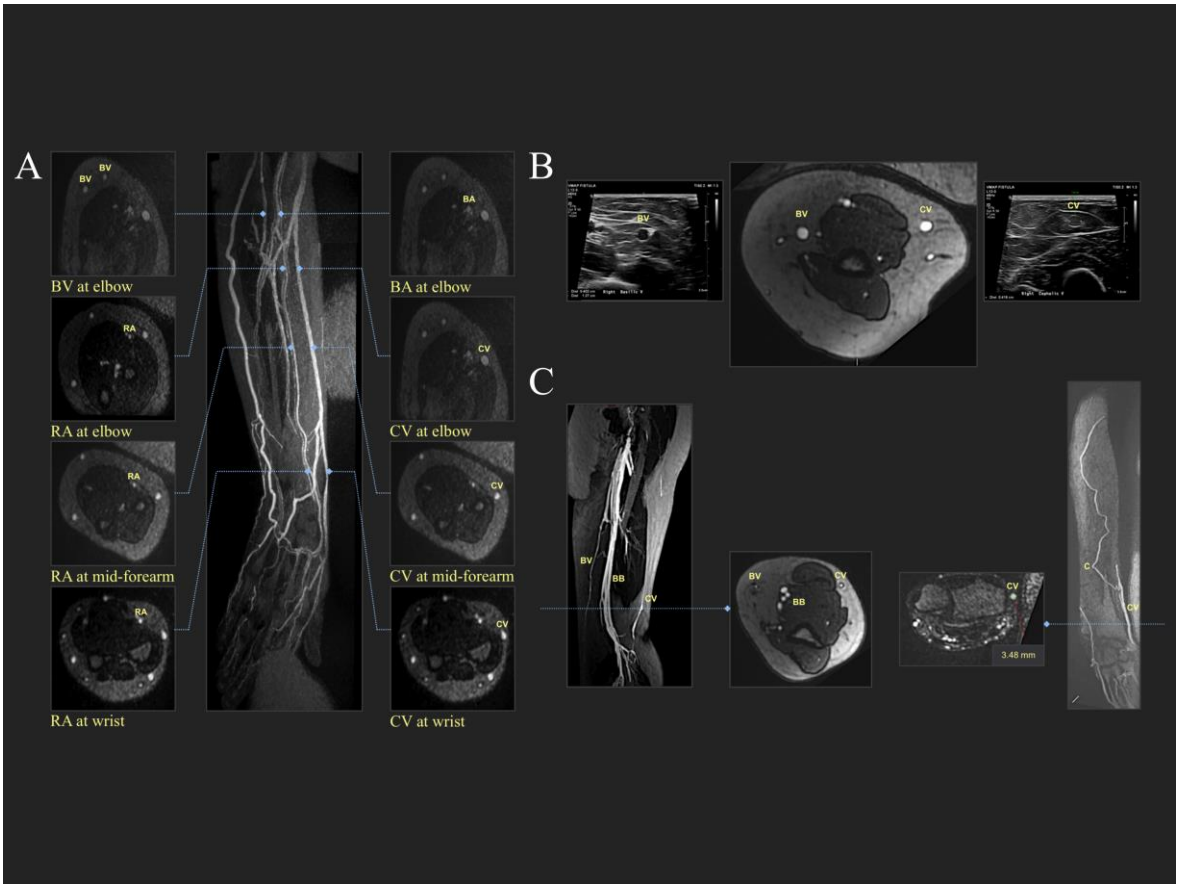


Figure 2-5 Method for the comparative analysis.

Comparative analysis using arterial and venous vascular cross-sections. Panel A. FeMRA high-resolution steady-state (HRSS) coronal and transverse sections of the arm at the level of wrist, mid-forearm and elbow. Regions of interest were drawn for estimation of arterial and vein diameter and vein depth from skin surface. Panel B. Transverse images at the elbow used for comparisons between FeMRA and Duplex US. Panel C. The additional information obtained from MIP coronal FeMRA images is crucial in access planning. HRSS coronal and transverse views of very small calibre basilic and cephalic veins throughout the entire length of the arm. Note that the brachial artery and concomitant brachial vein bundle (BB) lies in an intramuscular position (left). HRSS transverse view of good calibre cephalic vein (CV), which was incomplete in its length along the forearm draining into a very tortuous and small calibre collateral vein (C) on coronal view (right).

2.5.4 Ultrasound mapping

Duplex US mapping of bilateral upper extremities was performed in real-time using a Philips iU22 color duplex scanner (Philips Healthcare, Bothell, WA, USA) with a 5–17 MHz broadband linear-array transducer (Phillips L17-5). The patients were seated in front of the operator with the forearm resting on a stand.

Diameters of the radial artery, brachial artery, cephalic vein, and basilic vein at the arm and forearm level were measured according to a set protocol. Blood flow measurements were performed with the angle between the Duplex beam and blood vessel axis between 45^0–60^0, and the Duplex gate was set to cover the entire luminal cross-section. Transverse

views were used for assessment of vessel diameter and longitudinal views for blood flow and calcifications. Images of the relevant gray scale, color, and spectral Doppler waveforms were recorded and archived. Average Duplex US duration was 25 minutes for mapping of both arms.

2.5.5 FeMRA mapping

To reduce scanning time only one arm was assessed, unless there was uncertainty on the side of AVF creation, in which case both arms were scanned. The patients were positioned supine in the magnet with the arms lying alongside the body. The arm of interest was placed as close to the magnet center as possible, and the other arm was placed close to the side of the magnet bore. For imaging of the central vasculature, upper and the lower arm, we used different overlapping fields of view to minimise image distortion. For analysis of the vessels, high-spatial-resolution 3D FLASH acquisitions were obtained 2 minutes after administration of the full dose of ferumoxytol. The imaging parameters for the post-contrast MRA acquisitions are available Table 2-4.

Repetition time	2.88 msec
Echo time	1.04 msec
Flip angle	20 degrees
Slice thickness	Central vessels: 1.0 mm Upper arm: 0.7 mm Forearm: 0.6 mm
Voxel dimensions	Central vessels: 1.0 x 1.0 x 1.0 mm Upper arm: 0.7 x 0.7 x 0.7 mm Forearm: 0.6 x 0.6 x 0.6 mm
Field of view	Central vessels: 320 x 400 mm Upper arm: 300 x 480 mm Forearm: 180 x 400 mm
Acquisition time	18 sec
Signal averages	1
Bandwidth	300 Hz/pixel
Parallel imaging acceleration factor	3

Table 2-4 Table Pulse sequence parameters for the T1-weighted high-resolution 3D acquisitions

Ferumoxytol was infused intravenously at a dose of 3mg/kg (up to a maximum of 300mg) based on preliminary data from feasibility(Stoumpos et al., 2018) and dose-finding (Stoumpos, Hennessy, et al., 2019b) studies. To minimise susceptibility effects, ferumoxytol was diluted in sodium chloride 0.9% (1:4 dilution factor) and was delivered by an MRI-compatible infusion pump for precise control over at least 15 minutes. Average scan duration was 20 minutes (or 30 minutes for both arms) and patients were observed for a minimum of 30 minutes following termination of ferumoxytol infusion.

2.5.6 Algorithm to predict AVF outcome

As part of routine clinical practice, most patients in our center have pre-operative Duplex US vascular mapping before AVF creation. The surgeons creating the fistulas had this

information available, however were blinded to both the FeMRA and Duplex US mapping that were performed separately as part of the study.

Based on accepted anatomical criteria for AVF creation (Sidawy et al., 2008; Silva et al., 1998), an algorithm was formulated to predict AVF outcome relying on mapping findings (Figure 2-6). The parameters included in the algorithm were a) vessel diameter, b) patency, and the presence of c) arterial disease or d) central stenosis. A minimal arterial diameter of 2.0 mm and a venous diameter of 2.5 mm were predictive of a successful AVF outcome. Arterial or venous stenosis or occlusion and the presence of arterial disease were predictive of poor outcome. Stenosis was defined as reduction of the luminal diameter of ≥50% and occlusion as complete absence of any flow signal. Arterial disease was defined as extensive calcification or monophasic flow on Doppler US, and thready arteries with luminal interruptions on FeMRA. Subclavian artery and central vein stenoses were predictive of poor outcome in the unilateral arm. For brachio-cephalic fistulas, cephalic arch stenosis was also predictive of poor outcome.

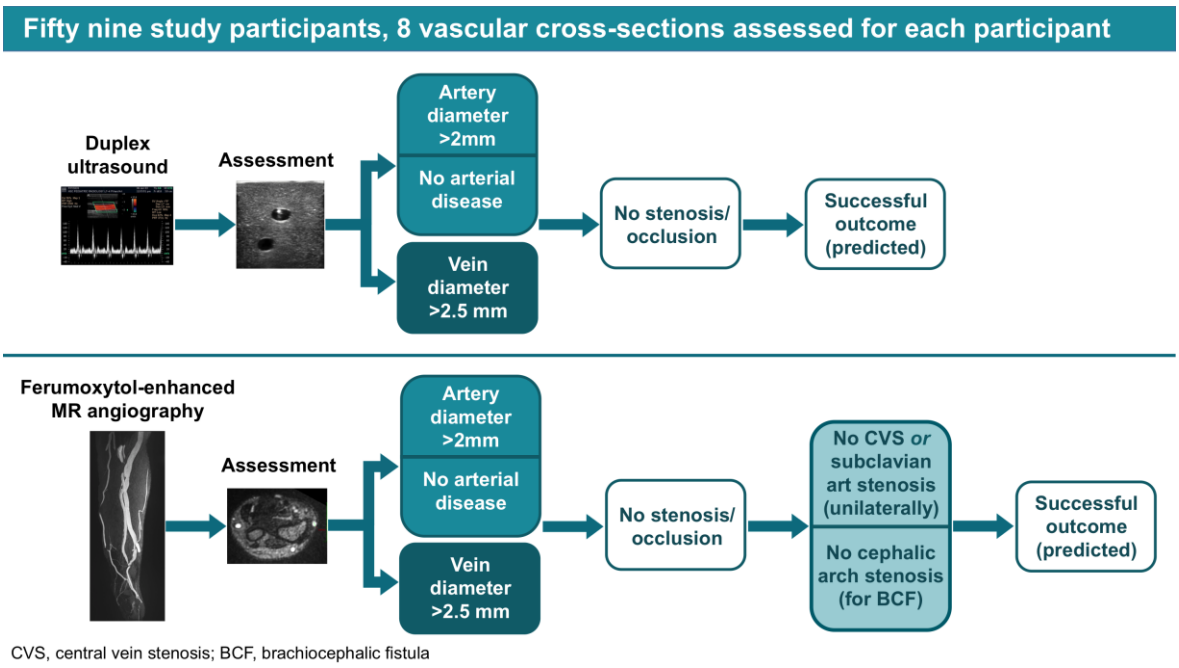


Figure 2-6 Predictive algorithm of fistula outcome.

Algorithm used to predict arteriovenous fistula outcome based on anatomical parameters evaluated with Duplex US and FeMRA mapping.

2.5.7 AVF outcome

We determined AVF clinical maturation using criteria for usability during dialysis. Successful use was defined as clinical use of the AVF with two needles for at least 75% of dialysis sessions over a minimum continuous period of 30 days. For patients not on dialysis at the end of follow-up, US criteria for AVF maturation at 6 weeks (600 mL/min blood flow, 6 mm diameter, and < 6 mm depth from the skin (Vascular Access 2006 Work Group, 2006)) were used as a surrogate of maturation.

2.5.8 Data analysis

Two independent readers assessed the FeMRA (new technique) and one reader the Duplex US (standard technique). To assess intra-reader agreement for the FeMRA, both readers repeated the analyses within a time interval of >30 days to avoid recall bias.

The sample size was calculated using the identification of clinically significant anatomic characteristics or lesions as the primary end-point and data from previous studies reporting 9-16% angiographically proven CVS in patients undergoing dialysis (Oguzkurt et al., 2004; Wang et al., 2015). We made the assumption that the difference in identification of peripheral vascular lesions is less than for the central pathologies, and we hypothesised that FeMRA will identify approximately 7% more lesions compared with US. Based on this assumption, then one would need to study 412 peripheral vascular sections in total (52 patients, 8 sections examined for each) to show a significant difference between tests using chi-squared test, to achieve statistical power of 80% and probability of type 1 error of 5%. To include a rate of suboptimal scans that are difficult to interpret of 15%, the recruitment target was increased to 59 subjects.

Descriptive statistics are expressed as means ± SD or absolutes and percentages. Interclass correlation coefficients with 95% CI using two-way mixed effects models were performed to test intra- and inter-reader consistency of agreement and Bland-Altman plots (Bland & Altman, 1986) of inter-reader variability were created. ICC was interpreted as follows: < 0.40 poor, 0.40–0.59 fair, 0.60–0.74 good, ≥0.75 excellent (Cicchetti, 1994). Three binomial logistic regression models were created with successful AVF outcome as the dependent variable and age, sex, and Duplex US mapping (model 1), or FeMRA central and peripheral mapping (model 2) or FeMRA peripheral mapping (model 3) as the

independent variables. Sensitivity, specificity, positive and negative predictive values were used as additional measures of the performance of each diagnostic test.

The Stata Statistics Package (Stata/SE, version 15.0; StataCorp LLC, USA) was used for all analyses. A *p*-value of < 0.05 was considered significant.

2.6 Changes in cardiac parameters following arteriovenous access creation

2.6.1 Baseline data

Baseline data were the same as described in the 'FeMRA vs Duplex US for vascular mapping before vascular access creation' study. Information on the history of diabetes mellitus, hypertension, ischemic heart disease, peripheral arterial disease was obtained from case records. In addition, study participants had biomarkers of cardiac function (NT-proBNP and high-sensitivity Troponin I) checked at baseline and follow-up visits.

2.6.2 Study procedures

All participants underwent two CMR; the first at baseline and the second 6-12 weeks later depending on the time interval between the first CMR and fistula surgery.

All scans were performed following a standardised protocol. Clinical history and blood tests were performed at the time first and second CMR. Analyses of CMR derived LV mass and chamber volumes were performed by a research fellow trained in CMR reporting. At follow-up, the investigator was blinded to results of the baseline scan. Brachial artery flows 6 weeks after AVF surgery were assessed independently using Duplex US. Serum NT-proBNP was measured by immunoassay (Elecsys® 204 proBNP, Roche Diagnostics).

2.6.2.1 Cardiac magnetic resonance imaging protocol

All CMR studies were performed on a 3.0 T Prisma MRI scanner (Magnetom, Siemens Healthineers, Erlangan; Germany). Images were obtained at end-expiration. Cardiac magnetic resonance imaging was part of a complex protocol including angiography of the great and arm vessels following CMR, hence only the left heart chambers were assessed to

shorten scanning time. Volumetric and functional analyses were performed using steady-state free procession (SSFP) sequences of the left atrium and ventricle (Maceira et al., 2010).

CMR images were retrospective electrocardiogram (ECG)-gated true fast imaging with steady-state free precession (TrueFISP). CMR sequences were performed during expiratory breath holding, to assess atrial area and ventricular structure and function (25 phases per cardiac cycle; repetition time 2.7 msec, echo time 1.4 msec, flip angle 60 degrees). Long-axis reference views were used for positioning 8–12 perpendicular LV short-axis slices from the level of the mitral valve to the LV apex. The short axis section thickness was 6 mm, with short-axis intersection intervals of 4 mm.

Analyses were performed by one trained CMR-reporting research fellow with utilisation of offline specialised software (CMR42, Circle Cardiovascular Imaging Inc., Calgary, Canada). We utilised a single reader to avoid inter-reader variability. The reader reviewed the baseline and follow-up scans at random order and was blinded to patients' demographic and clinical data.

Ventricular endocardial and epicardial contours were manually outlined at end-diastole and systole to permit calculation of ventricular volumes and myocardial mass by Simpson's method. Stroke volumes, ejection fractions and cardiac output were derived from these measurements and were also indexed to body surface area. The left atrial area was derived from the traces of left atrial at end-systole in both the horizontal long-axis and vertical long-axis plane taken at atrial end-diastole, immediately prior to mitral valvular opening. Ventricular short axis images were utilised for LV assessment, with epicardial and endocardial LV contours manually traced at diastole (start of the ECG R-wave) and at systole (determined by the timing of the smallest ventricular cavity size). As per standard CMR protocol, myocardial trabeculations and unattached papillary muscles were not ascribed to the left ventricular cavity. The basal LV slice was determined to be that slice where at least 50% of the cavity was surrounded by ventricular myocardium, and the apical slice was defined as the most apical slice still containing intra-cavity blood pool. A similar assessment of basal LV slice was then undertaken at systole; with the overall number of LV short axis images typically 1-2 slices less at end-systole, due to the well-recognized phenomenon of ventricular shortening associated with systolic contraction (Myerson et al., 2002). If the aortic valve appeared in the basal slice at diastole or systole, only the intra-

cavity volume up to the level of the aortic valve was included as a component of the ventricular volume, as per accepted protocol. The methodology of LV mass assessment is shown in Figure 2-7.

Cardiac output and cardiac index were derived from aortic flow. Using the coronal scout image, the imaging plane was placed perpendicular to the direction of flow several centimetres above the aortic valve at the level of bifurcation of the main pulmonary artery. The velocity encoding value was chosen just above the anticipated maximum velocity (1.5 m/sec in normal individuals and higher in aortic valve disease). Velocity measured at each voxel across the vessel was integrated over the cross-sectional area of the vessel and then integrated over the cardiac cycle (Pennell, 2010).

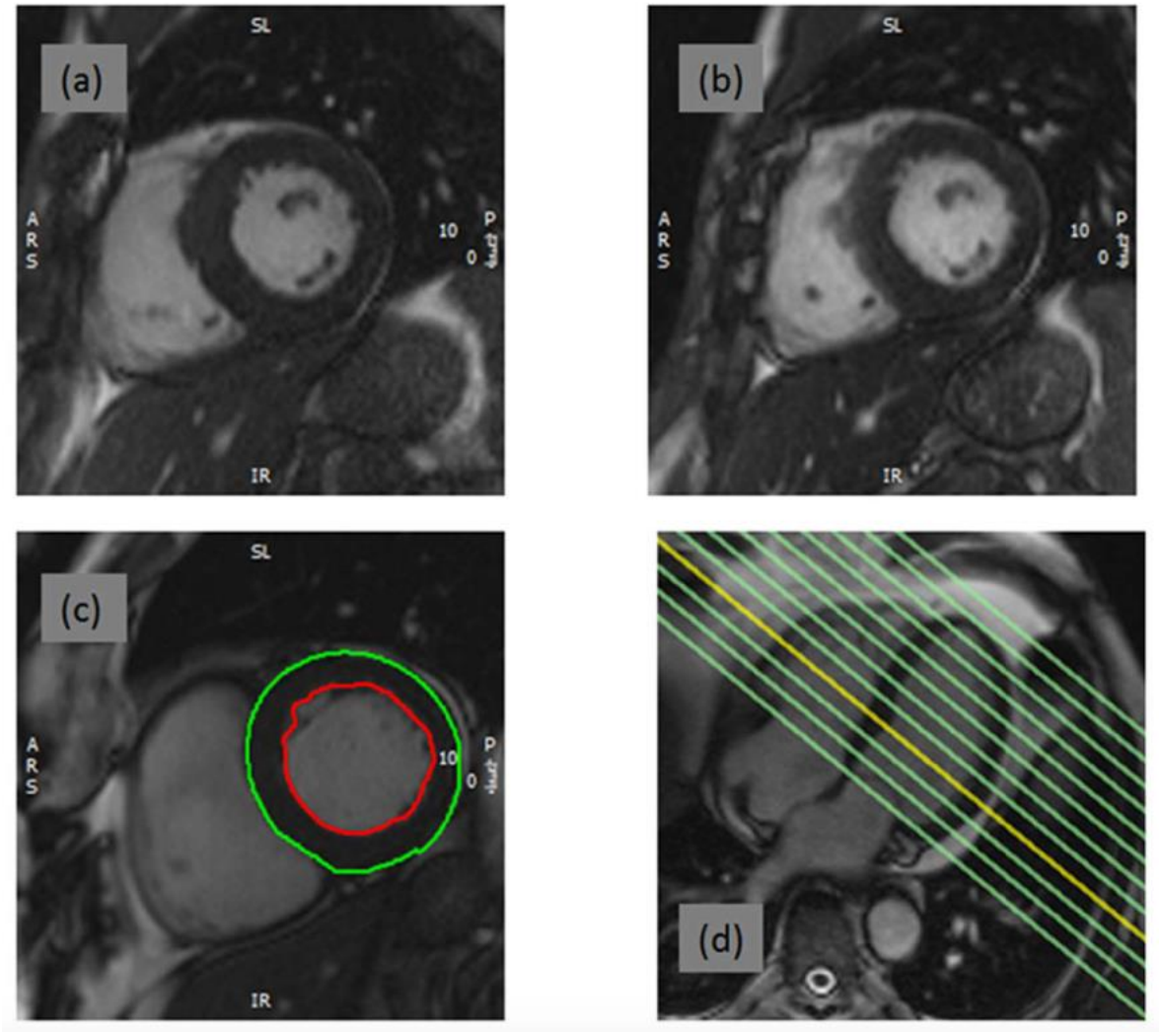


Figure 2-7 Cardiac magnetic resonance technique.

Images of left ventricle: Short axis image of the left ventricle taken at baseline (a), and following six weeks in the same patient following arteriovenous fistula creation (b). A tracing of the endocardial and epicardial border (c) and associated volumetric short axis stack representing methodology of left ventricular mass assessment (d).

2.6.2.2 Duplex US for brachial artery flow

The brachial artery flow rate and volume ipsilateral to the AVF was also quantified utilising Duplex US, which was performed the same day as the second CMR (6-12 weeks after the baseline scan).

Duplex US mapping of the fistula arm was performed in real-time using a Philips iU22 color duplex scanner (Philips Healthcare, Bothell, WA, USA) with a 5–17 MHz broadband linear-array transducer (Phillips L17-5). The patients were seated in front of the operator with the fistula arm resting on a stand.

Diameters of the feeding artery, anastomosis, outflow vein, brachial artery diameter, flow rate and volume (in mL/min) were measured according to a set protocol. Blood flow measurements were performed with the angle between the Duplex beam and blood vessel axis between 45^0–60^0, and the Duplex gate was set to cover the entire luminal cross-section. Transverse views were used for assessment of vessel diameter and longitudinal views for blood flow and calcifications. Arteriovenous fistulas were classified according to their volume in two groups; the high flow group (≥ 600 mL/min) and the low flow group (< 600 mL/min). The threshold of 600 mL/min was used as a surrogate of maturation based on the “rule of 6s” in fistula assessment at 6 weeks (Group, 2006). Thrombosed fistulas with no visible flow on Duplex US were excluded from analysis.

2.6.3 Study outcomes

The primary outcome was change in CMR derived LVM. Secondary outcome measures included changes in left ventricular end-systolic and end-diastolic volumes, left atrial volume, LV ejection fraction, cardiac output, cardiac index, brachial artery flow (ipsilateral to AVF), LV global longitudinal strain, septal thickness, NT-proBNP and high-sensitivity Troponin I.

2.6.4 Data analysis

The sample size was calculated based on data from a single-arm pilot study, where CMR was undertaken at baseline, and prior to and 6 months following AVF creation (Dundon et al., 2014). In that study, arteriovenous fistula creation was associated with an increase in

cardiac output, dilation of all cardiac chambers and significant increase in LV mass of 12.7% ($p < 0.01$). Based on the increment in LV mass as the primary end point, power calculations indicated that approximately 40 subjects would provide a 13% increase in the LV mass following AVF creation. This would deliver statistical power of 80%, at a two-sided alpha level of 0.05.

Descriptive statistics are expressed as mean and standard deviation or median and interquartile range for continuous measures as appropriate, and percentages are reported for categorical variables. Independent sample t-tests and Pearson χ^2 analysis were conducted to determine the differences in baseline characteristics. The change in LV mass and other cardiac parameters between the first and second scans were compared for the total population and between the two groups by use of the independent t-test. Two-sided tests were performed for all analyses, and the level of significance was set at $p < 0.05$. For the analysis of pre-AVF versus post-AVF differences, the Δ between initial and subsequent measurements was calculated for each person. The mean Δ was compared between the 2 groups with an unpaired t-test. Wilcoxon rank-sum and Wilcoxon signed rank tests were used for comparisons when the data were non-normally distributed. All statistical analyses were conducted with Stata/SE Statistical Software, version 15.0 (StataCorp, College Station, Tex).

Chapter 3. FEASIBILITY STUDY

3.1 Introduction

Kidney transplant candidates often require accurate assessment of their vascular anatomy before being wait-listed for transplantation. Conventional vascular imaging techniques are often problematic in kidney disease patients due to associated risks, invasiveness and imprecision. Ferumoxytol has potential as an MRI contrast agent in assessing the vasculature.

The aim of this a study was to test the feasibility and utility of ferumoxytol-enhanced MRA in assessing the arterial and venous vasculature in patients with advanced kidney disease due for transplant listing. This is a report of our preliminary experience in 20 patients with severely impaired renal function or on dialysis who underwent 'off-label' FeMRA for vascular evaluation prior to being wait-listed for kidney transplantation.

3.2 Methods

Patients with advanced kidney disease requiring aorto-iliac imaging as part of pre-operative kidney transplant candidacy assessment underwent FeMRA. All scans were performed for clinical indications where standard imaging techniques were deemed potentially harmful or inconclusive. Image quality was evaluated for both arterial and venous compartments.

3.3 Results

A total of 20 patients had FeMRA as part of their preoperative kidney transplant assessment. Eight (40%) were haemodialysis patients. The mean age was 61.2 [SD 11.5] years, 85% were men and 60% were diabetic. All patients had a high burden of co-morbidity and only one patient did not have diabetes, documented atherosclerotic vascular disease or heart failure. Nineteen (95%) patients had a high CCI (greater than 2) and, of those, 50% had a very high CCI (greater than 4) (Table 3-1). In four patients, arterial vascular anatomy had been examined with CTA prior to FeMRA.

Age, mean (SD)	61.2 (11.5)
Male sex, n (%)	17 (85.0)
Cause of ESRD	
Diabetes, n (%)	9 (45.0)
Renovascular, n (%)	4 (20.0)
Other[a], n (%)	4 (20.0)
Unknown aetiology, n (%)	3 (15.0)
Comorbidity	
Diabetes, n (%)	12 (60.0)
Vascular disease[b], n (%)	16 (80.0)
Heart failure, n (%)	3 (15.0)
None of the above, n (%)	1 (5.0)
Charlson comorbidity index (CCI) score	
CCI 1-2, n (%)	1 (5.0)
CCI 3-4, n (%)	9 (45.0)
CCI ≥5, n (%)	10 (50.0)
eGFR at time of scan[c], mL/min/1.73m^2; mean (SD)	14.0 (4.5)
Dialysis, n (%)	8 (40.0)
<15, n (%)	8 (40.0)
15-29, n (%)	4 (20.0)

[a] Glomerulonephritis (n=2), autosomal dominant polycystic kidney disease (n=1), congenital renal dysplasia (n=1)

[b] Coronary artery disease, cerebrovascular disease, peripheral vascular disease

[c] Excludes 8 patients on dialysis

SD, standard deviation; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; CT, computed tomography.

Table 3-1 Demographic and clinical characteristics of feasibility study.

All subjects completed first-pass and steady-state MRA acquisitions with ferumoxytol enhancement. There were no adverse events associated with ferumoxytol administration. The imaging parameters for the post-contrast breath-hold MRA acquisitions are listed in Table 3-2.

Repetition time (msec)	2.88
Echo time (msec)	1.04
Flip angle (degrees)	20
Slice thickness (mm)	1.0
Voxel dimensions (mm)	1.0 x 1.0 x 1.0
Field of view (mm)	400
Acquisition matrix	243 x 384
Timing of sequence[a] (sec)	60
Acquisition Time (sec)	18
Signal averages	1
Mean volume thickness	112
Bandwidth (Hz/pixel)	300
Parallel imaging acceleration factor	3
[a] after start of contrast infusion	

Table 3-2 Acquisition parameters.

Pulse sequence parameters for the T1-weighted 3D spoiled gradient echo sequences (post-contrast) of feasibility study.

Image quality on steady-state acquisitions was scored as grade 4 in 245 of 320 [76.6%; 90% confidence interval (CI) 72–79] and grade 3 in 75 of 320 (23.4%) vascular sections (at least diagnostic quality) when assessing the arterial and venous vasculature by both readers. There were no arterial anatomical characteristics or lesions of clinical significance that were identified on CTA and not on FeMRA, and vice versa. There was very good agreement on all individual assessments of image quality (kappa = 0.85 on assessment of the arteries; kappa = 0.76 on assessment of the veins; and kappa = 0.93 on assessment of the arteries on CTA vs. FeMRA).

Following each dose increment, signal intensity and image quality were improved in both arterial and venous compartments (Figure 3-1). First-pass acquisitions showed selective arterial enhancement (Figure 3-2B), with both arterial and venous enhancement on delayed

acquisitions (Figure 3-2A). Selective venous imaging was obtained by subtraction of arterial phase images from steady-state images (Figure 3-2C).

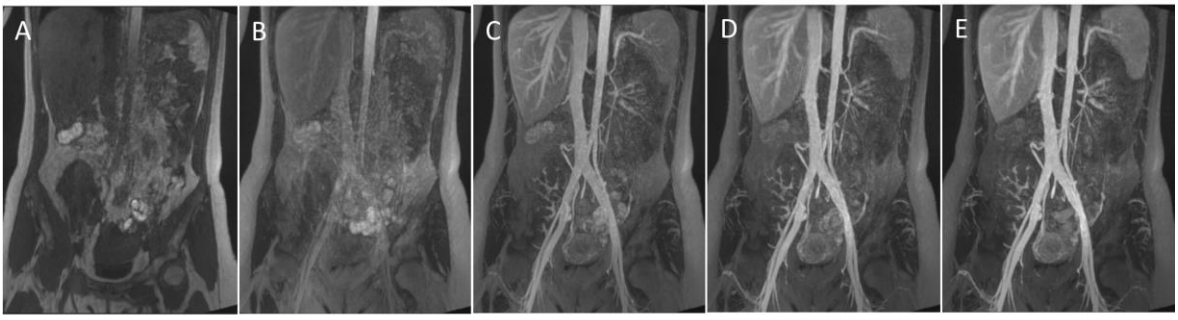


Figure 3-1 Arterial phase maximum intensity projection (MIP) images.

MIP images of abdominal and aorto-iliac vasculature after each increment of ferumoxytol. (A) Pre-contrast and after administration of (B) 1 mg/kg, (C) 2 mg/kg, (D) 3 mg/kg and (E) 4 mg/kg of ferumoxytol. Both arterial and venous compartments enhance due to contrast pooled intravascularly from previous infusions.

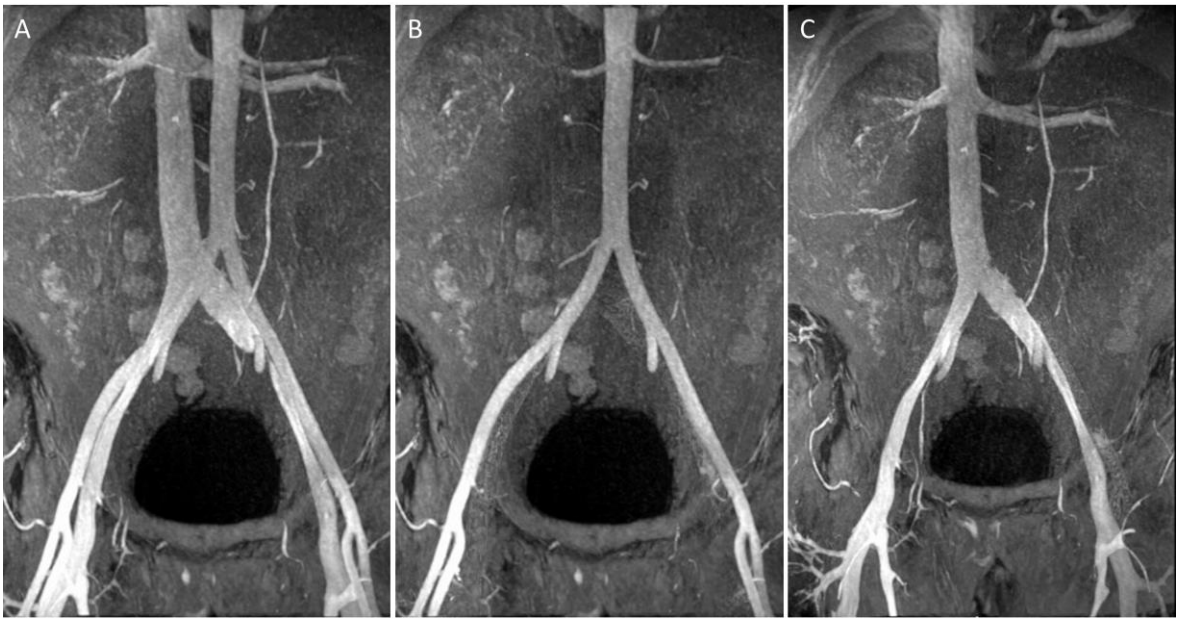


Figure 3-2 Abdominal ferumoxytol-enhanced magnetic resonance angiography (FeMRA).

Ferumoxytol-enhanced magnetic resonance angiography (FeMRA) of abdominal and aorto-iliac vasculature of patient referred for kidney transplant evaluation. (A) Steady-state acquisition showing enhancement of both arterial and venous vasculature. (B) First-pass imaging showing selective arterial enhancement (arteriography). (C) Steady-state acquisition showing selective venous enhancement after subtraction of the arterial compartment (venography).

A patient with extensive vascular disease was found to have bilateral renal artery and infrarenal abdominal aorta stenosis/occlusions and underwent aorto-bifemoral stent

grafting followed by stenting of the left main renal artery (Figure 3-3). Interesting anatomical variants were illustrated in a patient with a dual inferior vena cava (Figure 3-4) and one with a retro-aortic left renal vein (Figure 3-5). Two patients in this series were found to have incidental complex renal cysts of the native kidneys that had enhancing components with ferumoxytol (Figure 3-6); both of them were later confirmed to be renal cell carcinomas on histology.

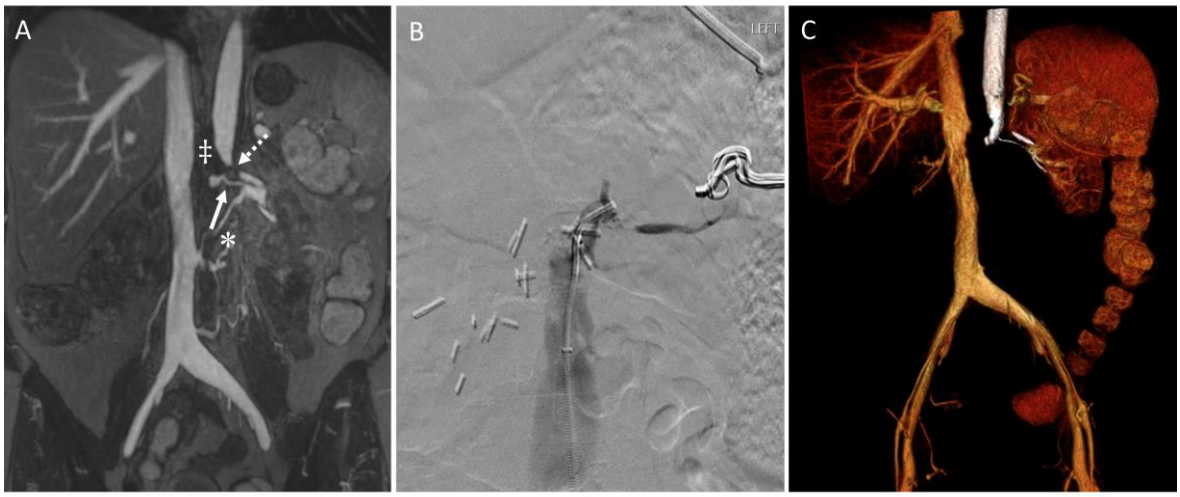


Figure 3-3 Renal artery ferumoxytol-enhanced magnetic resonance angiography (FeMRA).

(A) Ferumoxytol-enhanced magnetic resonance angiography (FeMRA) in an individual with a tightly stenosed left main renal artery (dashed arrow), a small patent accessory renal artery (solid arrow), and an occluded right renal artery (‡) and infrarenal abdominal aorta (*). (B) Digital subtraction angiography (DSA) after aorto-bifemoral stent grafting showing the tightly stenosed left main renal artery. (C) Three-dimensional reconstruction of aorta and inferior vena cava at the level of bifurcation of renal arteries.

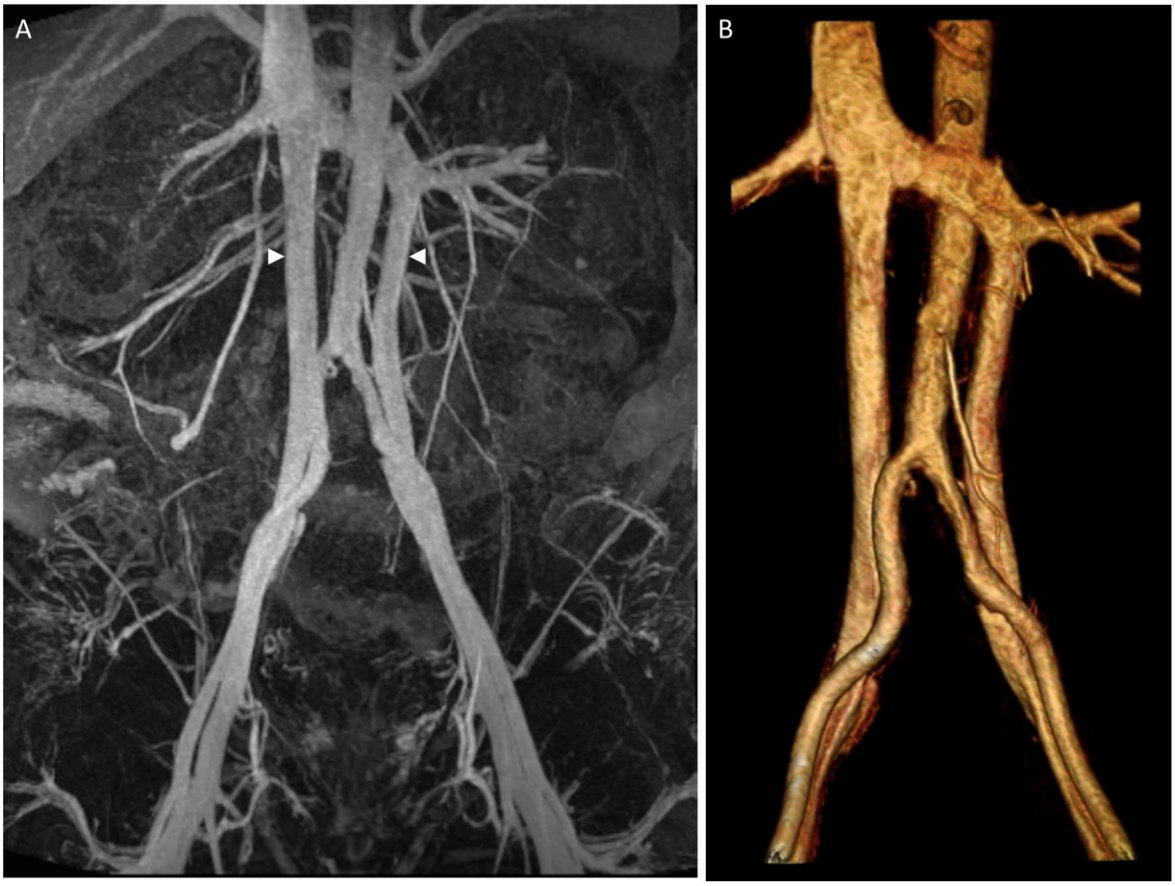


Figure 3-4 Ferumoxytol-enhanced magnetic resonance angiography (FeMRA) of IVC.

(A) Steady-state acquisitions with ferumoxytol-enhanced magnetic resonance angiography (FeMRA) in an individual with an anatomical variant of a dual inferior vena cava (arrowheads). (B) Three-dimensional reconstruction of abdominal vasculature at the level of the inferior vena cava duplication.

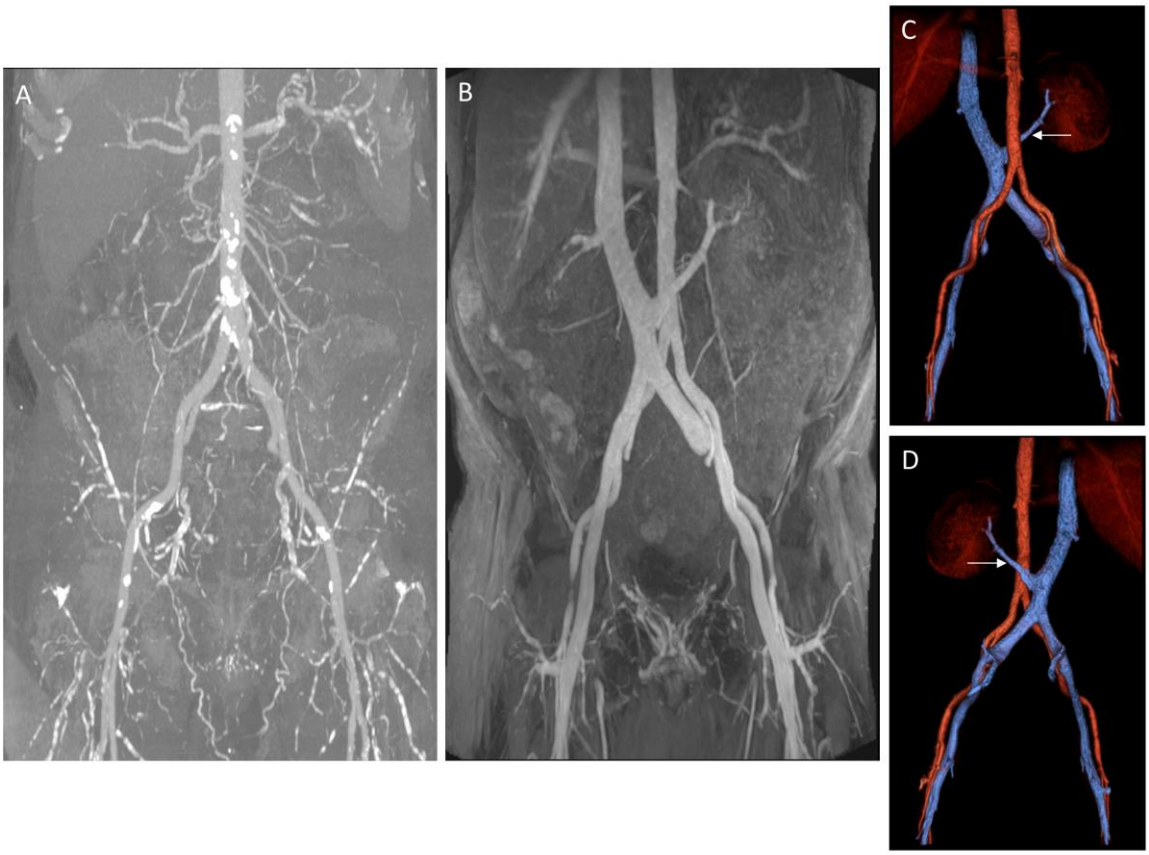


Figure 3-5 Kidney transplant assessment.

(A) Coronal CT angiogram through the upper abdomen showing foci of calcification at the aortic sector and iliac arteries. (B) Steady-state FeMRA of the same patient with synchronous illustration of aorto-iliac sector and inferior vena cava. (C) Anterior and (D) posterior views of three-dimensional reconstruction of abdominal and aorto-iliac vasculature showing an anatomical variant of a low-lying retroaortic left renal vein (arrow).

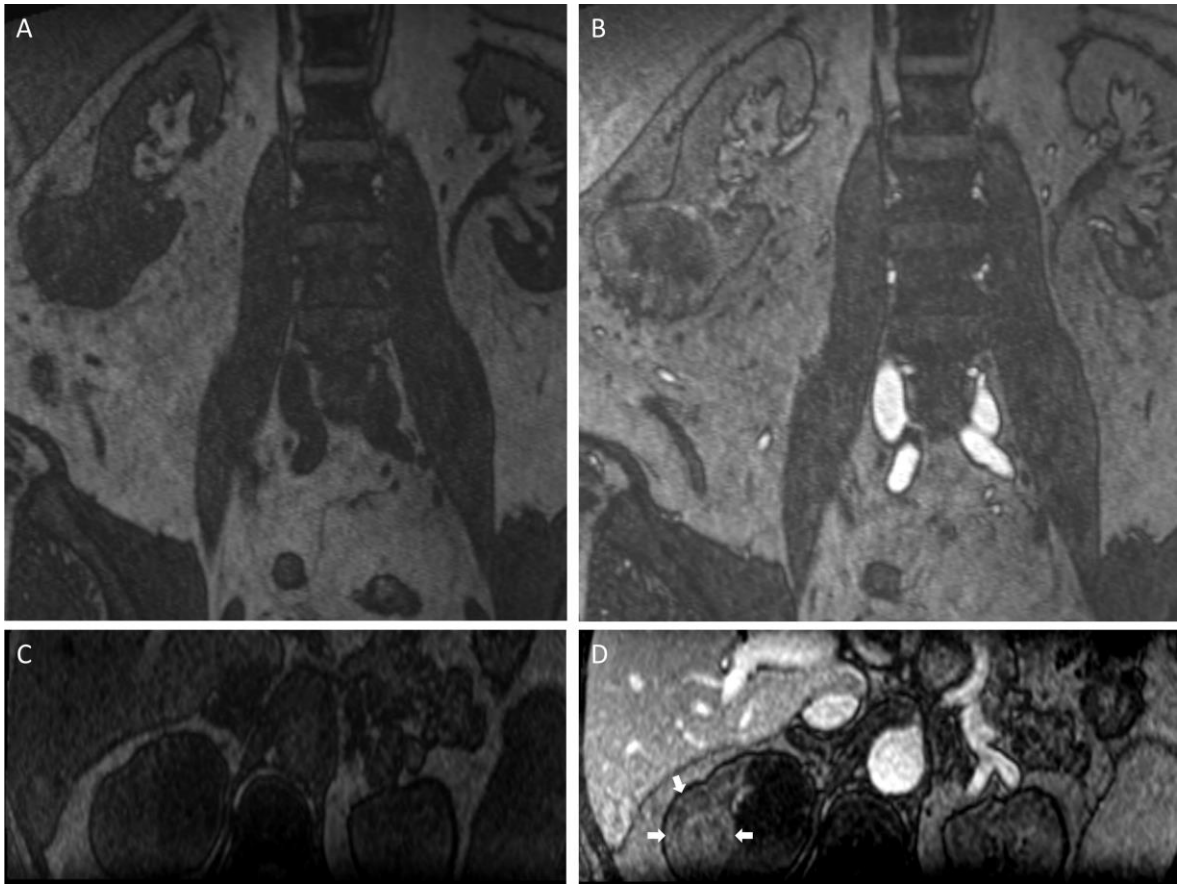


Figure 3-6 Incidental tumours.

Ferumoxytol-enhanced magnetic resonance angiography (FeMRA) showing incidental renal tumours in two patients. (A) Coronal pre- and (B) post-contrast T1-weighted first-pass acquisitions through the upper abdomen showing tumour with peripheral enhancement and central necrosis originating from the lower pole of the right kidney. (C) Transverse pre- and (D) post-contrast T1-weighted first-pass acquisitions through the upper abdomen from another patient showing a large partially enhancing right renal mass (arrows).

3.4 Discussion

We applied an MRA technique using intravenous iron as ferumoxytol to assess vessel characteristics, patency and course in a series of patients with severely impaired renal function or on dialysis whilst planning renal transplantation. Study participants underwent FeMRA as part of their clinical care instead of or in addition to standard imaging tests. We used a comprehensive protocol administering a total of 4 mg/kg of ferumoxytol diluted fourfold with normal saline and delivered in four equally divided infusions over a minimum of 20 minutes, and we achieved good signal intensity and image quality. The dose used was a fraction of the therapeutic dose (approximately a quarter of the full dose for a 70 kg adult), slowly infused (in 5-minute intervals between pulsed infusions) to minimise the risk of reaction, and we observed no adverse events. The information gained

from synchronous depiction of arterial and venous compartments using a single investigation is essential when planning kidney transplantation. In a subgroup of patients who had both FeMRA and CTA performed, FeMRA was not limited by calcification in assessing the arterial lumen and it was better for venous evaluation compared to CTA.

In our study, ferumoxytol-enhancing complex renal cysts were detected in two patients; both proved to be renal cell carcinomas.

The main limitations of this study are the single-centre design with a relatively small number of patients and lack of consistent reference standard. However, the purpose of this study was to address the technical feasibility of acquiring adequate abdominal and aorto-iliac vascular enhancement with a non-nephrotoxic, high relaxivity contrast agent in patients before wait-listing for kidney transplantation. Four patients had both CTA and FeMRA performed and although some comparisons were made, the study was not designed to estimate accuracy, sensitivity and specificity of the two different imaging techniques.

Despite being a case series, sequential enrolment minimised selection bias. In addition, differences in exposure to ferumoxytol were minimised by the use of a consistent protocol with standardised infusion rates and imaging parameters.

3.5 Conclusions

Using a consistent dosing regimen for contrast administration, we have shown that ferumoxytol-based vascular imaging has the potential to offer a clinically useful and reliable alternative in renal patients in whom standard imaging methods cannot be used.

Chapter 4. DOSE-FINDING STUDY

4.1 Introduction

Despite exponential use of ferumoxytol for imaging, dose-related efficacy studies are lacking with most centres using between 3 and 4 mg/kg based on limited clinical experience. Different doses having been reported in the literature, ranging from 120 mg of elemental iron as a bolus for angiographic assessment of arteriovenous fistulas (Sigovan et al., 2012) to 6 mg/kg for T2* renal perfusion mapping (Hedgire et al., 2014). Two studies were identified to formally evaluate the ferumoxytol dose when used as MRI contrast agent. In a small pilot study including 5 patients who had 3D MRA of the tibial artery trifurcation at 1.5 T, escalating doses of 0.4 mg/kg of ferumoxytol (for a total of 4 mg/kg) were administered. The mean SNR in the arteries increased with higher doses of ferumoxytol; however, a cut-off dose for optimal imaging was not determined (Prince et al., 2003). In the second study investigating ferumoxytol for MR lymphography in 15 patients undergoing prostatectomy with regional lymph node dissection, a dose of 7.5 mg/kg was found to be safe and effective in differentiating between malignant and benign lymph nodes 24 hours after ferumoxytol injection (Turkbey et al., 2015).

The aim of this study was to establish the optimal dose of ferumoxytol required for vascular imaging in patients with CKD. Optimal dose was selected on the basis of the minimum effective dose (MED) to achieve diagnostic imaging rather than maximum signal intensity criteria similarly to the ‘As Low As Reasonably Achievable (ALARA) principle’ employed to minimise radiation exposure.

4.2 Methods

Ferumoxytol-enhanced MRA was performed after dose increments up to a total of 4 mg/kg administered in 4–7 (median 4) divided controlled infusions (aliquots). T1-weighted fast low-angle shot (FLASH) sequences of aortoiliac vasculature were performed before giving contrast and 60 s after each aliquot of ferumoxytol was administered. Image quality was assessed by contrast-to-noise and signal-to-noise ratios in the abdominal aorta and inferior vena cava. Quadratic regression analyses were performed to estimate the effects of dose increments on CNR and SNR.

4.3 Results

A total of 25 patients had angiographic assessment with FeMRA. Two patients were excluded from analysis due to failure to acquire all repeated FLASH sequences because of claustrophobia necessitating abandonment of the scan. From the 23 remaining patients, 13 (57%) required imaging as part of pre-operative kidney transplant assessment, 7 (30%) had clinical manifestations of renovascular disease and 3 (13%) had PVD. Five (22%) patients were on haemodialysis and 18 (78%) had various degrees of renal failure (6 of them had a kidney transplant). The mean age was 59.8 (SD 12.8) years, 20 (87%) were men and almost half of them had diabetic nephropathy. An average of 325 mg (SD 65) of ferumoxytol was administered (Table 4-1).

Age (y), mean (SD)	59.8 (12.8)
Female sex, n (%)	3 (13.0)
Body weight (kg), mean (SD)	85.4 (22.9)
BMI categories, n (%)	
18.5-25	9 (39.1)
25.1-30	4 (17.4)
>30	10 (43.5)
Cause of ESRD	
Diabetes, n (%)	11 (47.9)
Renovascular, n (%)	3 (13.0)
Other[a], n (%)	6 (26.1)
Unknown, n (%)	3 (13.0)
Laboratory values at time of MR imaging	
Haemoglobin (g/L), mean (SD)	106.4 (21.2)
Creatinine (μmoL/L), mean (SD)[b]	359 (131)
eGFR (mL/min/1.73m^2), mean (SD)[b]	17.2 (7.5)
CKD stage, n (%)	
HD	5 (21.7)
5	10 (43.5)
4	8 (34.8)
Dose of ferumoxytol given (mg), mean (SD)	325 (65)

[a]Glomerulonephritis (n=4), Reflux nephropathy (n=1), Obstructive uropathy (n=1)
[b]excludes patients on dialysis
BMI, body mass index; ESRD, established renal failure; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; HD, haemodialysis

Table 4-1 Baseline characteristics of dose-finding study.

The imaging parameters for the post-contrast breath-hold MRA acquisitions are listed in Table 4-2. Minor changes to these values were made on an individual basis due to differences in patient body habitus and extracellular fluid status. All subjects completed MRA with ferumoxytol enhancement with no adverse events.

TR (repetition time)	2.88 ms
TE (echo time)	1.04 ms
Flip angle	20 degrees
Number of averages	1
Field of view	400 x 325 mm
Section thickness	1 mm
Voxel dimensions	1.0 x 1.0 x 1.0 mm
Data matrix	243 x 384
Timing of sequence[a]	60 s
Acquisition time	18 s
Mean volume thickness	112
Bandwidth	300 Hz/PX
Parallel imaging acceleration factor	3

[a] after start of contrast infusion

Table 4-2 Pulse sequence parameters for the T1-weighted FLASH sequences.

Cumulative doses of 0 (pre-contrast), 1, 2, 3 and 4 mg/kg of ferumoxytol yielded mean CNR of − 41 (± 36), 20 (± 26), 46 (± 29), 90 (± 66) and 86 (± 62) in AA and − 45 (± 37), 4 (± 31), 38 (± 26), 78 (± 46) and 95 (± 71) in IVC, respectively. Mean SNR values were 35 (±14), 92 (±63), 97 (±40), 155 (±96) and 153 (± 95) in AA and 30 (± 10), 77 (± 43), 89 (± 38), 138 (± 83) and 162 (± 109) in IVC, respectively.

Figures 4-1 and 4-2 demonstrate the distribution of the CNR and SNR, respectively, measured in AA and IVC against the cumulative dose of the administered ferumoxytol. Both graphs demonstrate a parabolic relationship between the administered dose and vascular signal with a line of best fit calculated by quadratic regression analysis.

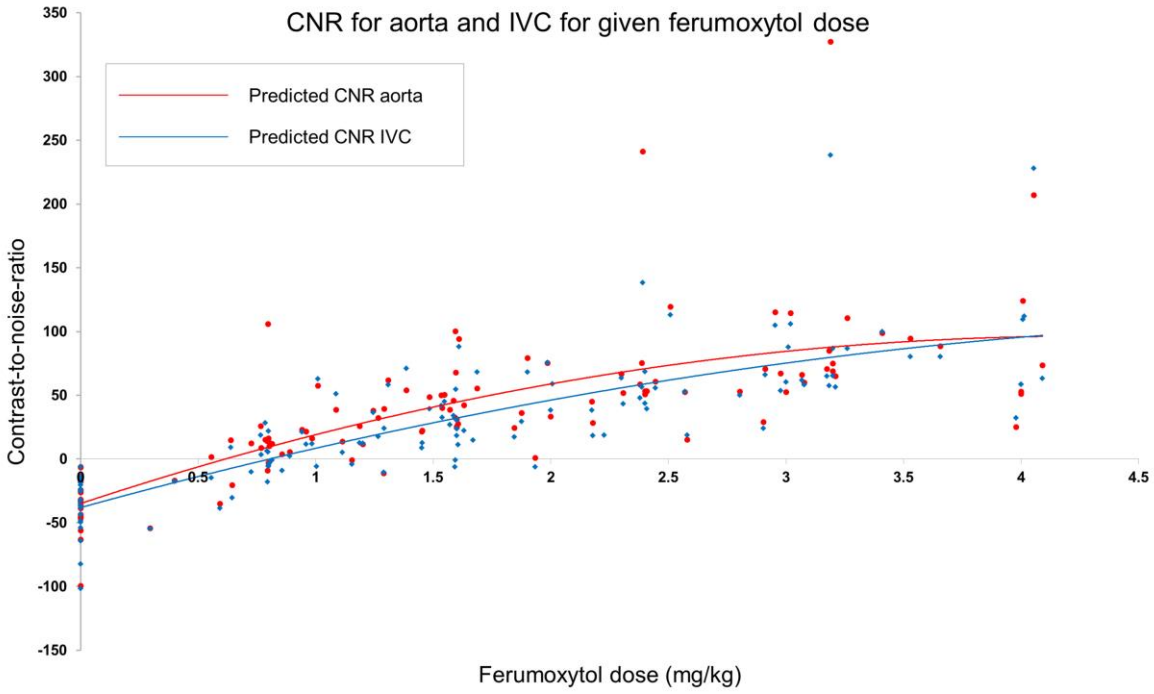


Figure 4-1 Distribution of CNR.

Distribution of CNR measured in abdominal aorta and IVC following incremental doses of ferumoxytol.

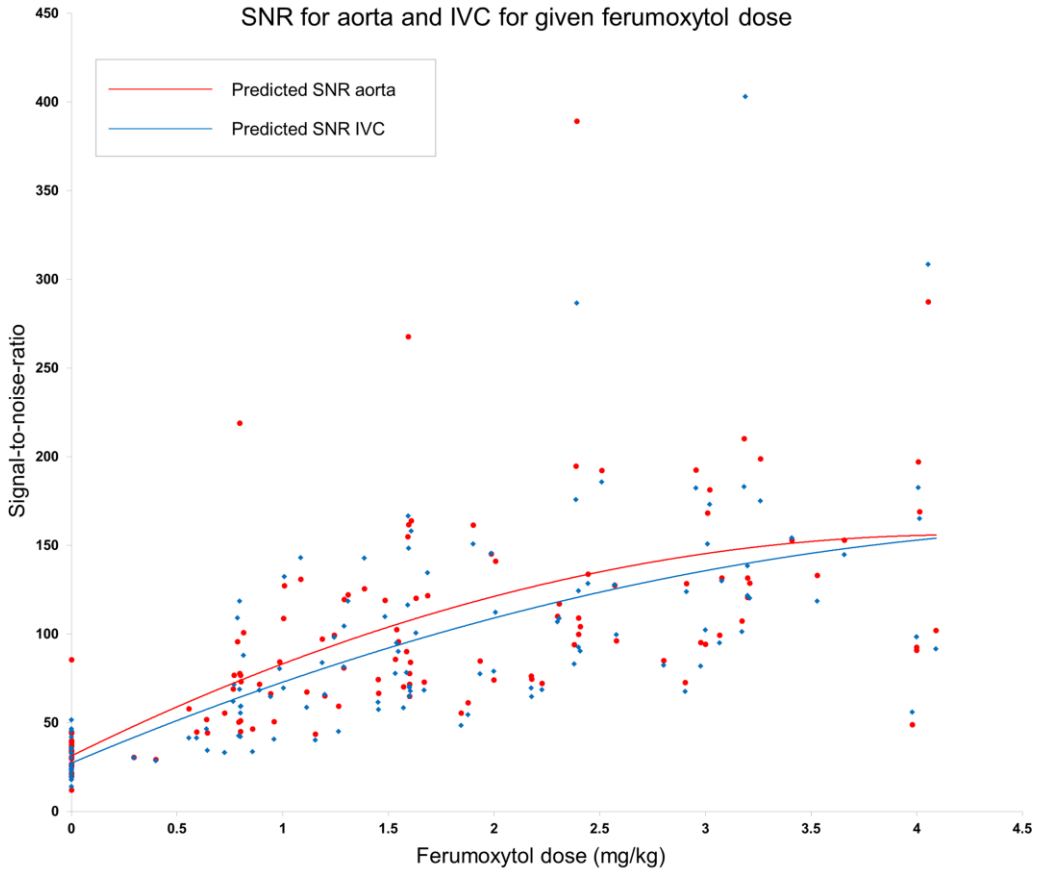


Figure 4-2 Distribution of SNR.

Distribution of SNR measured in abdominal aorta and IVC following incremental doses of ferumoxytol.

The calculated relationships for the AA are described below, where x represents the ferumoxytol dose and f(x) the returned signal:

$$\text{CNR: } f(x) = -6.6(x)^2 + 59.4(x) - 34.1$$

with an estimated regression co-efficient (R^2) = 0.56 and

$$\text{SNR: } f(x) = -7.0(x)^2 + 58.9(x) + 31.2$$

with an estimated R^2 = 0.35.

These equations predict peak aortic CNR and SNR at 4 mg/kg ferumoxytol with decrease in signal with higher doses (Tables 4-3 and 4-4). However, 85% of peak CNR in AA is predicted to be obtained after administration of 3 mg/kg of ferumoxytol and < 10% of SNR gain is predicted with administration of > 3mg/kg of ferumoxytol (Tables 4-3 and 4-4).

Ferumoxytol dose (mg/kg)	Predicted peak CNR in AA (%)	Predicted peak CNR in IVC (%)
0	-34	-38
1	19	8
2	58	46
3	85	75
4	98	95
5	98	106
6	85	109

Table 4-3 Predicted CNR.

Predicted CNR in abdominal aorta and IVC following ferumoxytol dose increments calculated by the regression equations.

Ferumoxytol dose (mg/kg)	Predicted peak SNR in AA (%)	Predicted peak SNR in IVC (%)
0	31	27
1	83	73
2	121	109
3	145	135
4	155	152
5	151	159
6	133	157

Table 4-4 Predicted SNR.

Predicted SNR in abdominal aorta and IVC following ferumoxytol dose increments calculated by the regression equations.

The calculated relationships for the IVC are described below, where y represents the ferumoxytol dose and f(y) the returned signal:

$$\text{CNR: } f(y) = -4.4(y)^2 + 50.9(y) - 38.1$$

with an estimated $R^2 = 0.65$ and

SNR: $f(y) = -4.8(y)^2 + 50.4(y) + 27.2$

with an estimated $R^2 = 0.44$.

These equations predict peak IVC CNR and SNR at 6 and 5 mg/kg ferumoxytol, respectively, with decrease in signal with higher doses. Still 75% of peak CNR in IVC is predicted to be obtained after administration of 3 mg/kg of ferumoxytol and < 15% of SNR gain is predicted with administration of > 3 mg/kg of ferumoxytol (Tables 4-3 and 4-4). Examples of the images obtained are shown in Figures 4-3, 4-4 and 4-5, where it is obvious that image quality was significantly improved in both arterial and venous compartments following ferumoxytol dose increments up to 3 mg/kg but no visual difference was apparent with higher doses.

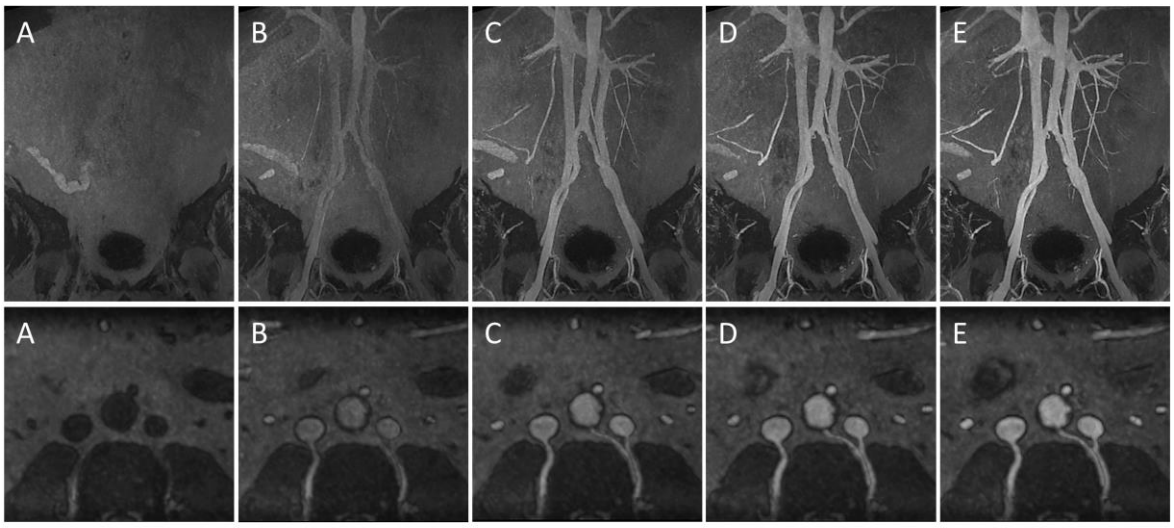


Figure 4-3 Serial coronal and axial images of abdominal vasculature.

Serial arterial phase maximum intensity projection (MIP) coronal and axial images of abdominal and aortoiliac vasculature after each increment of ferumoxytol. (a) Pre-contrast and after administration of (b) 1 mg/kg, (c) 2 mg/kg, (d) 3 mg/kg and (e) 4 mg/kg of ferumoxytol.

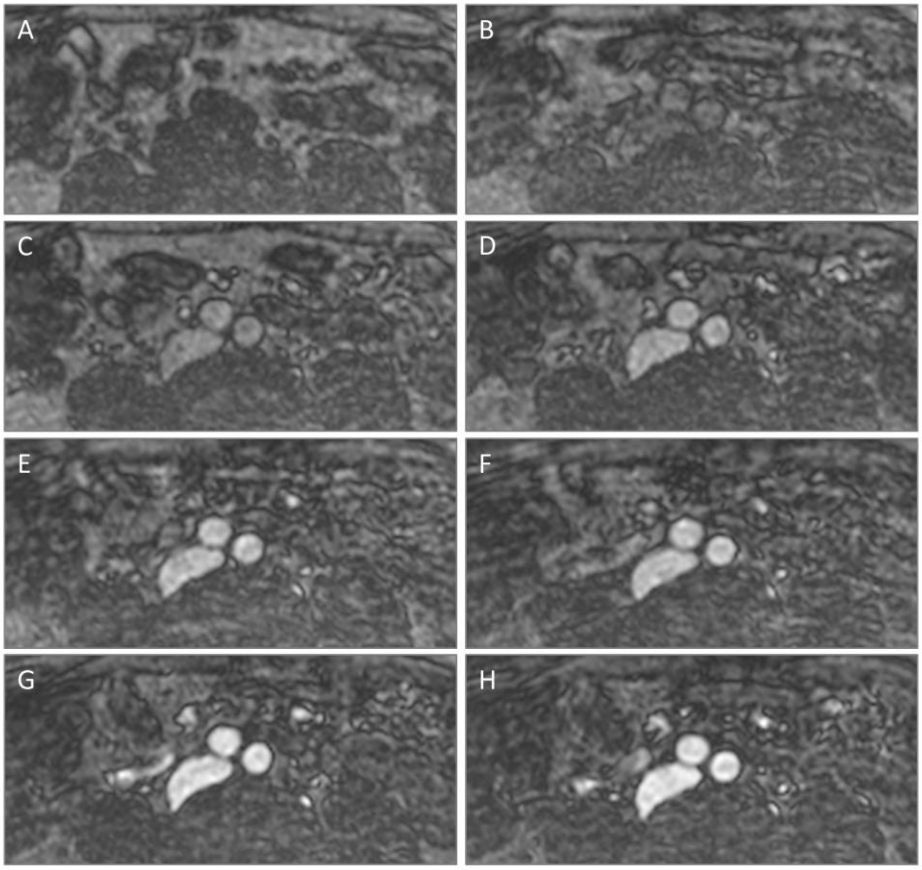


Figure 4-4 Cross-sections of aortic bifurcation.

Plane cross-sections of aortic bifurcation before ferumoxytol administration and after serial dose increments. (a) Pre-contrast, (b) 0.4mg/kg, (c) 0.8 mg/kg, (d) 1.2 mg/kg, (e) 1.6 mg/kg, (f) 2 mg/kg, (g) 3 mg/kg and (h) 4 mg/kg.

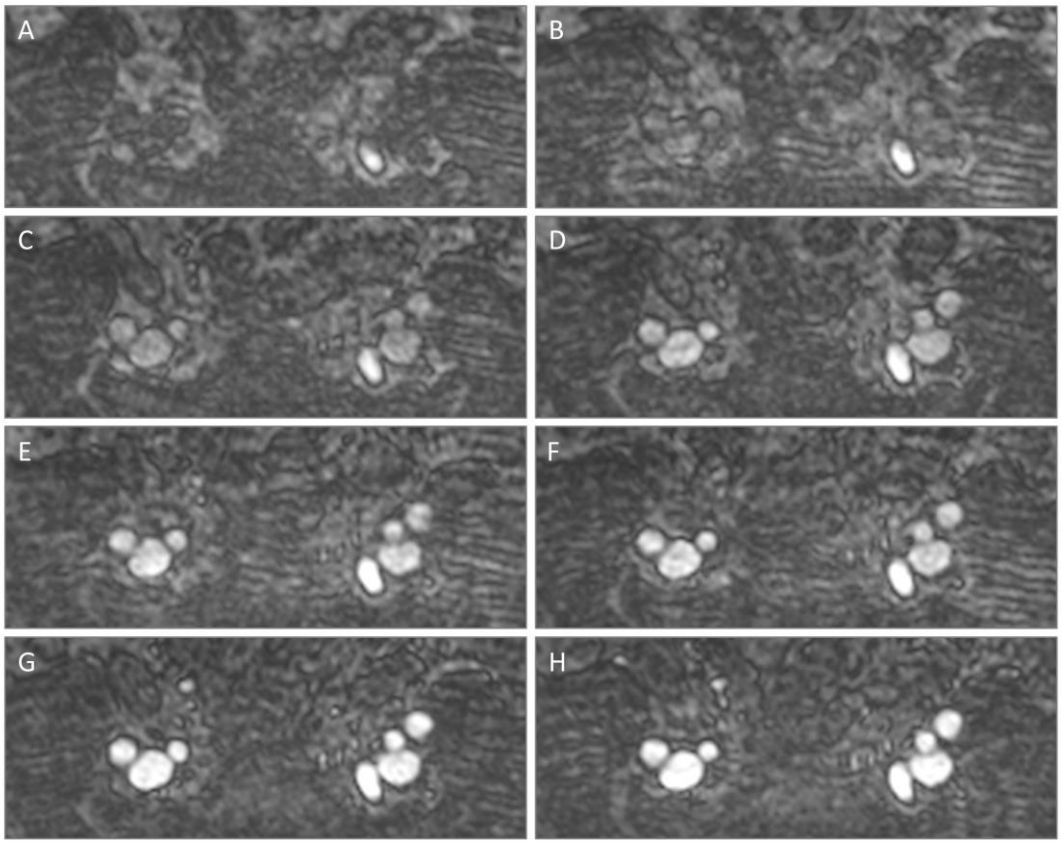


Figure 4-5 Cross-sections at the bifurcation of the common iliac arteries.

Plane cross-sections below the level of the bifurcation of the common iliac arteries before ferumoxytol administration and after serial dose increments. (a) Pre-contrast, (b) 0.4mg/kg, (c) 0.8 mg/kg, (d) 1.2 mg/kg, (e) 1.6 mg/kg, (f) 2 mg/kg, (g) 3 mg/kg and (h) 4 mg/kg.

With ferumoxytol, arteries and veins can be selectively depicted in a single exam. However, due to the prolonged residence of contrast in the intravascular space, there may be overlay of the arteries and veins, and this is more pronounced in steady-state thick MIP images of the peripheral vasculature (Figure 4-6).

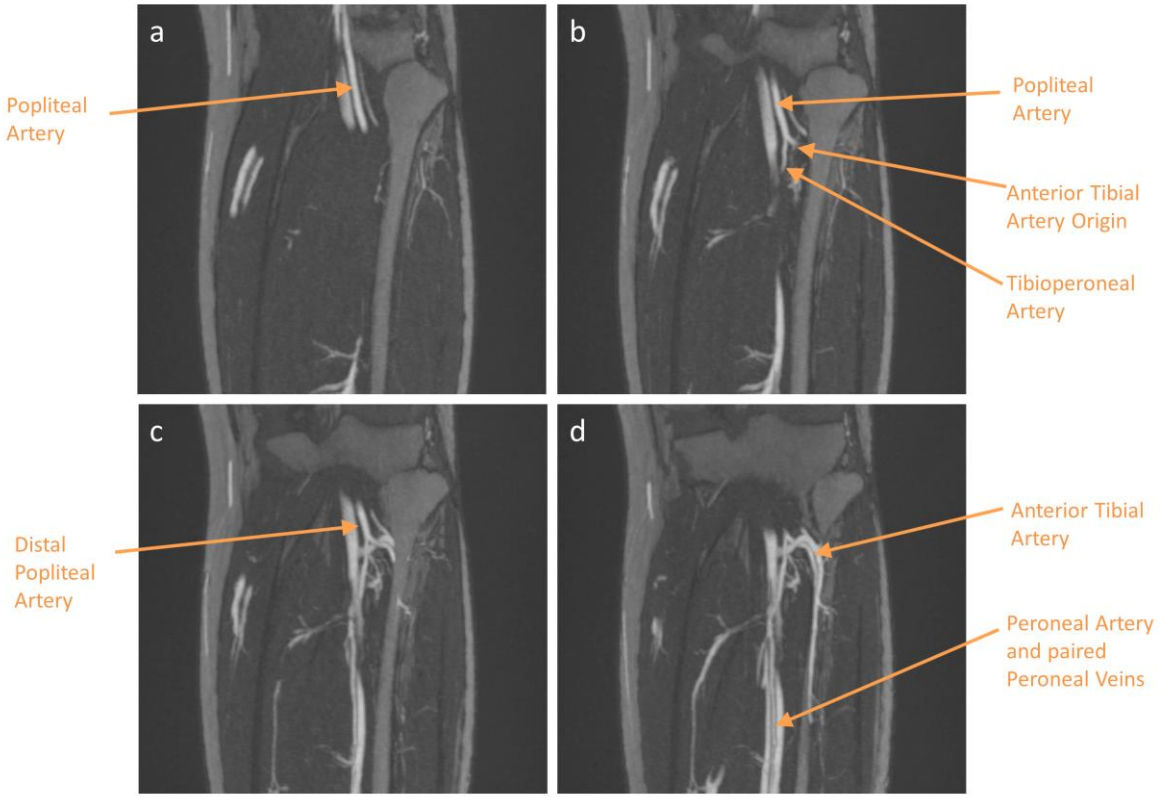


Figure 4-6 Steady-state coronal images of the left below knee vasculature.

Steady-state coronal thin slab (6mm) maximum intensity projection (MIP) images of the left below knee vasculature at level of tibial plateau and proximal fibula with ferumoxytol-enhanced MRA. Magnified images showing details of distal popliteal and proximal tibial artery branching.

4.4 Discussion

Ferumoxytol as a contrast agent results in profound shortening of the T1 relaxation time of blood, which increases the signal in blood vessels in T1-weighted sequences. However, high concentrations of the agent can cause artefacts (Fananapazir et al., 2014) because of signal loss through T2* shortening. We used incremental doses of ferumoxytol as an MRI contrast agent for assessing arterial and venous vasculature in patients with CKD to establish the optimal (minimum effective) dose and observed a parabolic relationship between the administered dose and vascular signal. After exceeding a threshold, a negative correlation between the injected dose and the signal intensity was confirmed which is explained by T2* shortening effects at higher doses of ferumoxytol.

Our findings demonstrate dose-dependent improvement in signal with ferumoxytol doses up to 3 mg/kg with no significant benefit (or even loss in signal) with higher doses of contrast. We defined the optimal dose as the minimum effective dose to maximise

diagnostic yield while minimising potential for reactions. Although it could be argued that ferumoxytol doses exceeding 3 mg/kg were predicted to achieve better CNR and SNR in the abdominal aorta and inferior vena cava, the gain in signal was minimal, especially considering that a 33% increase in dose above 3 mg/kg is required to yield just 10% increase in signal. Our images were judged as diagnostic when assessed by two readers. It has been argued that peak SNR correlates poorly with the subjective quality rating because it is essentially a pixel-based fidelity measurement method that does not match to the human perception (Yao et al., 2005). Hence, the 'more is better' approach is not always applicable for SNR. We advocate that 3 mg/kg is an acceptable dose with advantages in terms of protocol simplification, dose saving and minimisation of side effects without compromising diagnostic accuracy.

As ferumoxytol's pharmacokinetics are independent of renal function, the proposed dose of 3 mg/kg can be applied universally for MRI irrespectively of renal function. This creates the basis for adoption of this dose in current clinical practice with the caveat that further work is required to translate our protocol to 1.5 T. Reassuringly no adverse events occurred with this dose and there was no change in the recorded vital signs during or after administration of ferumoxytol.

This study has notable strengths. We used a consistent protocol with standardised infusion rates and imaging parameters; hence, differences in exposure to ferumoxytol were minimised. Instead of allocating patients into fixed-dose groups, all patients received multiple dose increments allowing for intra- and interpatient dose comparisons. To balance between risk and benefit, the optimal ferumoxytol dose was selected on the basis of maximising signal while maintaining a low-risk threshold rather on the basis of achieving the peak predicted signal.

Our study has several limitations. This is a single-centre study with a relatively small number of patients. However, we used a sequential design to eliminate variations in demographic and clinical factors and detect changes in signal after studying a small set of patients. Translation of the current protocol to 1.5 T needs to be studied but this should be feasible with alterations to echo time etc. to ensure reliable vascular enhancement. Lastly, we have examined dose based upon body weight; however, theoretically, the dose should be based upon the patient's intravascular blood volume which does not linearly increase with body weight; hence, a relatively lower dose may be appropriate for larger patients.

4.5 Conclusions

Using a consistent dosing regimen for contrast administration, we have shown that 3 mg/kg of ferumoxytol is effective for MR angiography in CKD patients in whom there are concerns in regard to standard contrast-based vascular imaging methods. In the era of growing use of ferumoxytol for diagnostic MR applications, this study fills unmet clinical needs by offering an effective dosing regimen.

Chapter 5. FEMRA VS CTA FOR ASSESSMENT OF KIDNEY TRANSPLANT RECIPIENTS

5.1 Introduction

Kidney transplantation is the treatment of choice for suitable patients with ESRD with around 90 000 kidney transplants performed every year worldwide (World Health Organisation, 2016). Vascular disease is almost universal in potential kidney transplant recipients, the evaluation of which is important in planning transplantation. Approximately 25% of patients with CKD have evidence of PAD on non-invasive studies (Jones et al., 2016). Even though PAD does not preclude transplantation, revascularisation procedures may be required before listing. Characterisation of PAD in kidney transplant candidates relies on history, physical examination and imaging studies. Evaluation of the iliac vasculature prior to kidney transplantation is challenging due to concerns of nephrotoxicity with CTA and NSF with gadolinium-enhanced MRA. For patients with diabetes, a history of claudication, or poor peripheral pulses on examination, options to assess the vasculature include abdominal radiograph (Aitken et al., 2012), Doppler studies of iliac and lower extremity vessels (Bunnapradist & Danovitch, 2007), and non-contrast CT of the abdomen and pelvis to evaluate arterial calcification (Kahn, Ram, Eberhard, Groselj-Strele, Obermayer-Pietsch, & Muller, 2017). Aortoiliac angiography is reserved for patients with signs or symptoms of aortoiliac occlusive disease or non-invasive studies suggestive of large-vessel disease (Kasiske et al., 2001).

Imaging studies with vascular mapping, including CTA (Andres et al., 2003), provide precise preoperative anatomy of vascular and extravascular systems allowing the surgeon to determine if kidney transplantation is possible, whether presurgical procedures are necessary, and the best surgical technique for each candidate. Furthermore, patients may have had previous transplants, abdominal surgery, or other iliofemoral interventions such as CVC that may have compromised the vessels. Until now the widespread use of CTA in the workup of potential kidney transplant recipients has been limited because of the perceived increased risk of nephrotoxicity in patients with residual renal function. This has implications particularly in predialysis patients requiring angiography before transplant listing, which is often delayed until they are established on dialysis.

Meanwhile, there is rising interest in ferumoxytol as a contrast agent for MRI (Bashir et al., 2015; Finn et al., 2017; Toth et al., 2017). Ferumoxytol is a carbohydrate-coated iron oxide nanoparticle (Balakrishnan et al., 2009) approved for intravenous treatment of iron deficiency anaemia. However, ferumoxytol was originally designed as an intravascular

contrast agent for MRI (Weissleder et al., 1990), and therefore, has powerful imaging attributes not present in other intravenous iron products nor the extracellular GBCAs. Amongst its properties, its large molecular weight of approximately 750kD (Balakrishnan et al., 2009) allows steady state imaging, which means it can be given slowly or before the patient is transferred to the MRI suite. Because of its long intravascular half-life (Landry et al., 2005) it allows enhancement of both the arterial and venous vasculature and has been used as a vascular MR angiographic contrast agent (Hope et al., 2015; Li et al., 2005).

The aim of this study was to assess the clinical utility of the use of ferumoxytol-enhanced MRA for assessment of aortoiliac vasculature before listing for kidney transplantation. We compared FeMRA with CTA using vessel diameter, the presence of calcification, and signal parameters as surrogates of diagnostic quality.

5.2 Methods

In a prospective comparative cohort study, kidney transplant candidates underwent CTA and FeMRA on the same day. As part of the FeMRA protocol, arterial calcification was detected using a contrast-free technique. Three independent readers compared arterial and vein diameter, calcification, and signal at prespecified vascular sections between FeMRA and CTA. Interclass correlation coefficients, mean differences (with 95% CI) and Bland-Altman plots were used to examine intra- and inter-reader variability. In addition, two transplant surgeons evaluated the scans to preoperatively plan the anastomoses.

5.3 Results

A total of 36 patients were recruited (aged 54±11 years; 61% male; 47% with diabetic nephropathy) and had FeMRA and CTA of their aortoiliac vasculature on the same day. Overall 216 vascular cross-sections were analysed for each imaging technique (6 sections per patient). Baseline characteristics of our cohort are shown in Table 5-1.

Age (y), mean (SD)	54.1 (11.2)
Male sex, n (%)	22 (61.1)
Body weight (kg), mean (SD)	76.5 (21.4)
BMI categories, n (%)	
<18.5	3 (8.3)
18.5 - 24.9	12 (33.3)
25 - 29.9	7 (19.5)
>30	14 (38.9)
Cause of ESRD	
Diabetes, n (%)	17 (47.2)
Renovascular, n (%)	5 (13.9)
Glomerulonephritis, n (%)	4 (11.1)
Other[a], n (%)	8 (22.2)
Unknown, n (%)	2 (5.6)
Laboratory values at time of MR imaging	
Haemoglobin (g/L), mean (SD)	107 (17)
Creatinine (mg/dl), mean (SD)[b]	5.3 (1.6)
eGFR (mL/min/1.73m^2), mean (SD)[b]	10.8 (1.6)
CKD stage, n (%)	
Stage 5 - non-dialysis	8 (22.2)
Stage 5 - hemodialysis	22 (61.1)
Stage 5 - peritoneal dialysis	6 (16.7)
Dose of ferumoxytol given (mg), mean (SD)	229 (54)
[a]Congenital dysplasia (n=3), Polycystic kidney disease (n=2), Cyclosporine toxicity (n=2), Obstructive uropathy (n=1) [b]Excludes patients on dialysis	
BMI, body mass index; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease	

Table 5-1 Baseline characteristics of study participants.

5.3.1 Repeatability studies

Among all patients there was excellent inter-reader agreement in assessment of the FeMRA across all vascular sections. Interclass coefficients were 0.88 – 0.92 for the arterial diameter, 0.79 – 0.89 for the vein diameter, 0.88 – 0.91 for the area of calcification and 0.92 – 0.97 for the CNR (Table 5-2). Twelve patients (one third of the cohort) were selected at random for intra-reader agreement. Among the patients selected (aged 58±12 years; 67% male; 50% with diabetic nephropathy), interclass coefficients for intra-reader agreement were between 0.79 – 0.99 for all parameters, indicating excellent agreement (Table 5-2).

	ICC (95% CI) values comparing cross-sections measurements		
	Inter-reader	Intra-reader	
		Reader 1	Reader 2
Arterial diameter			
AA	0.89 (0.80 – 0.94)	0.94 (0.82 – 0.98)	0.93 (0.77 – 0.98)
RCIA	0.88 (0.78 – 0.94)	0.84 (0.54 – 0.95)	0.79 (0.41 – 0.93)
REIA	0.92 (0.85 – 0.96)	0.86 (0.59 – 0.96)	0.84 (0.54 – 0.95)
All arteries	0.92 (0.88 – 0.94)	0.98 (0.95 – 0.99)	0.88 (0.77 – 0.93)
Vein diameter			
IVC	0.85 (0.73 – 0.92)	0.81 (0.46 – 0.94)	0.84 (0.55 – 0.95)
RCIV	0.79 (0.61 – 0.89)	0.97 (0.90 – 0.99)	0.91 (0.72 – 0.97)
REIV	0.89 (0.80 – 0.94)	0.94 (0.81 – 0.98)	0.92 (0.76 – 0.98)
All veins	0.89 (0.85 – 0.93)	0.96 (0.92 – 0.98)	0.95 (0.91 – 0.97)
Area of calcification			
AA	0.91 (0.82 – 0.96)	0.93 (0.79 – 0.98)	0.95 (0.83 – 0.98)
RCIA	0.90 (0.80 – 0.95)	0.90 (0.70 – 0.97)	0.95 (0.82 – 0.98)
REIA	0.88 (0.77 – 0.94)	0.95 (0.85 – 0.99)	0.97 (0.88 – 0.99)
All arteries	0.91 (0.87 – 0.94)	0.96 (0.92 – 0.98)	0.97 (0.95 – 0.99)
Contrast-to-noise ratio			
AA	0.95 (0.90 – 0.97)	0.99 (0.96 – 1.00)	0.96 (0.85 – 0.99)
RCIA	0.94 (0.89 – 0.97)	0.91 (0.71 – 0.97)	0.97 (0.89 – 0.99)
REIA	0.92 (0.85 – 0.96)	0.97 (0.90 – 0.99)	0.81 (0.47 – 0.94)
All arteries	0.94 (0.91 – 0.96)	0.95 (0.91 – 0.97)	0.92 (0.84 – 0.96)
IVC	0.97 (0.94 – 0.98)	0.99 (0.98 – 1.00)	0.95 (0.85 – 0.99)
RCIV	0.93 (0.86 – 0.96)	0.99 (0.96 – 1.00)	0.94 (0.79 – 0.98)
REIV	0.96 (0.92 – 0.98)	0.99 (0.95 – 1.00)	0.88 (0.64 – 0.96)
All veins	0.95 (0.93 – 0.97)	0.99 (0.98 – 1.00)	0.94 (0.89 – 0.97)

Table 5-2 Interclass correlation coefficients to test consistency of agreement in FeMRA.

5.3.2 Comparative studies

5.3.2.1 Arterial diameter and calcification

Comparison of FeMRA with CTA showed no significant difference in arterial diameter and area of calcification mean differences between the 3 readers across all vascular sections (mean differences -0.36 to 0.89 mm and -0.05 to 0.06 mm^2, respectively) (Table 5-3). There were no fixed or proportional biases, and >95% of differences fell within acceptable limits of agreement (Figure 5-1A, C).

5.3.2.2 Vein diameter and signal intensity

Evaluation of the vein diameter was difficult with CTA due to poor enhancement and this was reflected in both the variability and agreement of the mean differences. There was significant systematic difference in vein diameter mean differences across all vascular sections (mean difference 1.53 to 2.44 mm) (Table 5-3). There was lack of agreement between FeMRA and CTA, with FeMRA estimating a larger diameter by an average of 1.53 mm, with constant differences across the whole range of vein sizes (Figure 5-1B). CNR values were significantly higher in FeMRA in the arterial (mean difference 3.16 to 7.44) but predominantly in the venous vasculature (mean difference 16.78 to 24.70) (Table 5-3).

	Mean (SD)			Mean difference (95% CI) FeMRA vs CTA	
	Reader 1	Reader 2	Reader 3	Reader 1 vs Reader 3	Reader 2 vs Reader 3
Arterial diameter (mm)					
AA	18.34 (3.31)	18.78 (3.61)	18.50 (3.69)	-0.16 (-1.81 to 1.49)	0.28 (-1.44 to 2.00)
RCIA	12.54 (2.80)	13.58 (2.83)	12.89 (2.74)	-0.36 (-1.66 to 0.95)	0.69 (-0.62 to 1.99)
REIA	10.38 (1.97)	10.31 (1.86)	9.63 (1.47)	0.75 (-0.07 to 1.56)	0.69 (-0.10 to 1.48)
All arteries	13.75 (4.34)	14.56 (4.27)	13.67 (4.60)	0.08 (-1.12 to 1.28)	0.89 (-0.30 to 2.08)
Vein diameter (mm)					
IVC	20.33 (3.59)	21.17 (3.56)	18.73 (3.34)	1.61 (-0.02 to 3.24)	2.44 (0.82 to 4.07)^
RCIV	15.56 (2.54)	16.33 (3.07)	14.04 (3.07)	1.53 (0.17 to 2.89)^	2.30 (0.83 to 3.76)^
REIV	14.27 (2.84)	14.27 (3.04)	12.68 (2.88)	1.59 (0.24 to 2.93)^	1.59 (0.19 to 2.98)^
All veins	16.74 (4.00)	17.27 (4.33)	15.16 (4.03)	1.59 (0.50 to 2.67)^	2.11 (0.98 to 3.24)^
Area of calcification (mm^2; log transformed)					
AA	1.00 (0.66)	0.98 (0.68)	0.94 (0.69)	0.06 (-0.26 to 0.39)	0.05 (-0.29 to 0.38)
RCIA	0.62 (0.55)	0.63 (0.59)	0.67 (0.61)	-0.05 (-0.33 to 0.24)	-0.05 (-0.34 to 0.25)
REIA	0.36 (0.46)	0.36 (0.50)	0.34 (0.48)	0.02 (-0.21 to 0.25)	0.01 (-0.23 to 0.25)
All arteries	0.66 (0.61)	0.65 (0.64)	0.65 (0.64)	0.01 (-0.16 to 0.19)	0.003 (-0.18 to 0.18)
Contrast-to-noise ratio					
AA	21.35 (8.77)	20.98 (9.21)	14.03 (7.59)	7.32 (3.46 to 11.18)^	6.96 (2.99 to 10.93)^
RCIA	20.67 (8.64)	20.33 (8.40)	13.23 (6.89)	7.44 (3.76 to 11.12)^	7.10 (3.48 to 10.71)^
REIA	17.60 (7.36)	16.59 (7.74)	13.43 (7.10)	4.17 (0.77 to 7.57)^	3.16 (0.33 to 6.65)^
All arteries	19.87 (8.37)	19.30 (8.61)	13.56 (7.14)	6.31 (4.22 to 8.39)^	5.74 (3.62 to 7.86)^
IVC	22.44 (8.02)	21.33 (7.72)	0.25 (1.20)	22.18 (19.44 to 24.92)^	21.08 (18.48 to 23.67)^
RCIV	25.13 (10.83)	23.29 (9.28)	0.43 (2.09)	24.70 (20.92 to 28.48)^	22.87 (19.61 to 26.12)^
REIV	18.33 (7.40)	17.19 (7.36)	0.41 (2.97)	17.92 (15.25 to 20.60)^	16.78 (14.12 to 19.45)^
All veins	21.93 (9.21)	20.58 (8.47)	0.36 (2.19)	21.57 (19.76 to 23.38)^	20.22 (18.54 to 21.89)^
^$p<0.05$					

Table 5-3 Mean values and differences between FeMRA and CTA.

Mean values (mean of 36 readings for each anatomical site) and differences between FeMRA (readers 1 and 2) and CTA (reader 3) for all parameters examined.

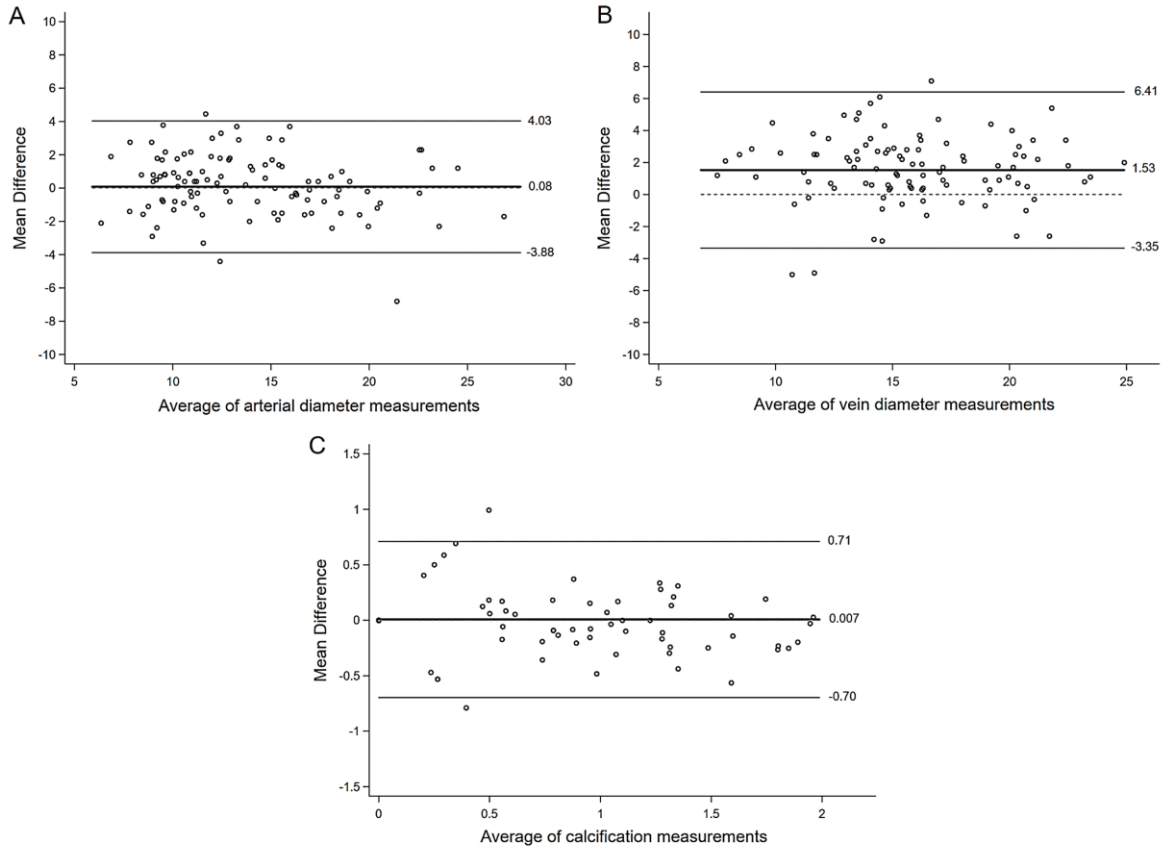


Figure 5-1 Bland-Altman plots of inter-reader variability (FeMRA vs CTA). The readings of one of the FeMRA readers (selected in random) were compared with the CTA readings.

A. Plot of arterial diameter measurements. The dark central line is the mean difference between the 2 analyses, which does not show any fixed or proportional biases. The light outer lines show the limits of agreement (mean of the differences ± 1.96 SD). B. Plot of vein diameter measurements. Note the presence of fixed biases with FeMRA overestimating the diameter by an average of 1.53mm. C. Plot of area of calcification measurements.

Figure 5-2 shows study examples of image quality and the ability of FeMRA combined with StarVIBE to depict arterial and venous sharp wall morphology, luminal features, and conformation of complex calcific atheroma, which correspond to CTA. The venous wall and lumen were clearly defined with FeMRA but poorly visualised with CTA (Figure 5-3A). There was complete concordance in the appearance of calcification between CTA and StarVIBE in all the arterial sections evaluated (Figure 5-3B).

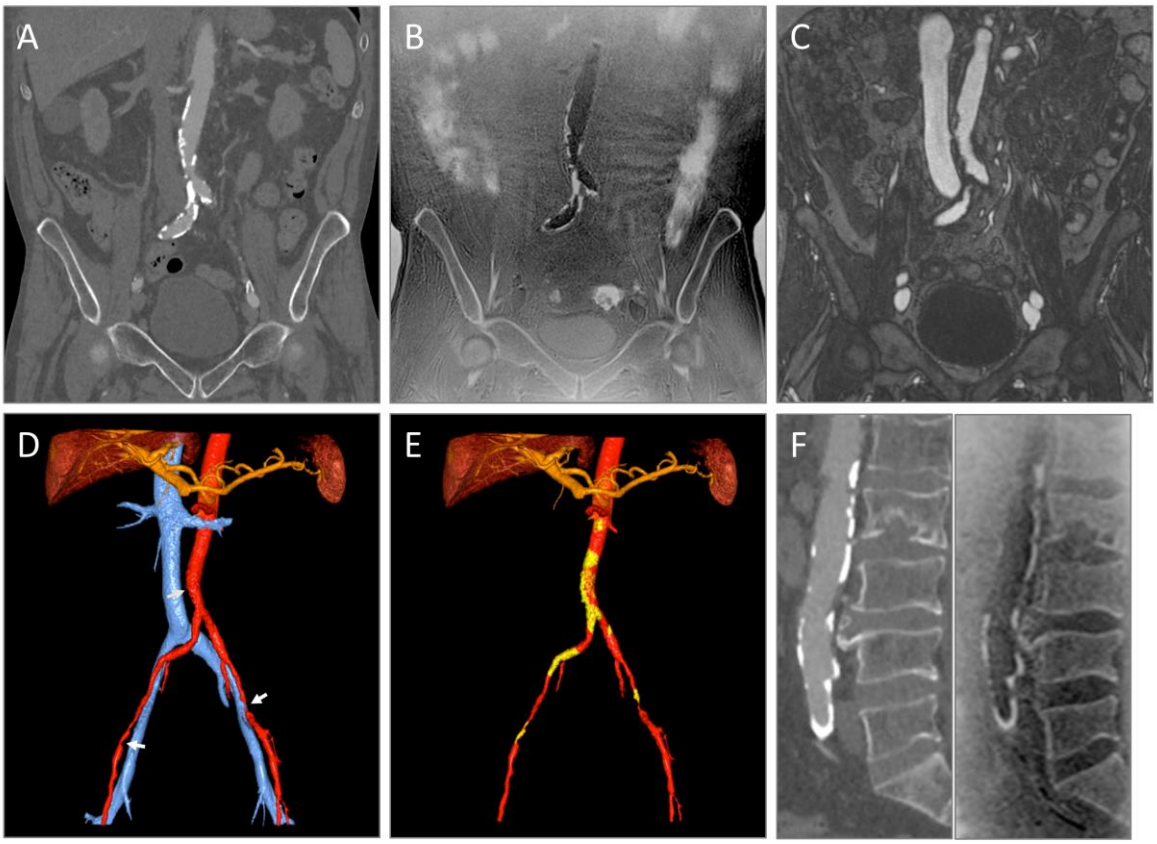


Figure 5-2 Coronal views of CTA, FeMRA and StarVIBE.

Coronal views showing excellent delineation of areas of calcification between A. CTA and B. StarVIBE, which correspond to intraluminal filling defects in abdominal aorta in C. FeMRA. Note the well-defined arterial and venous walls and luminal characteristics in FeMRA. D. Steady-state 3D volume-rendered FeMRA image of abdominal aorta and iliac vessels shows areas of atheromatous changes (arrows) near the bifurcation of infra-renal abdominal aorta and bilateral iliac arteries. E. Fused 3D volume-rendered FeMRA and StarVIBE provide additional information on calcific burden, location, and morphology. F. Sagittal views highlight the concordance in calcifications between CTA and StarVIBE.

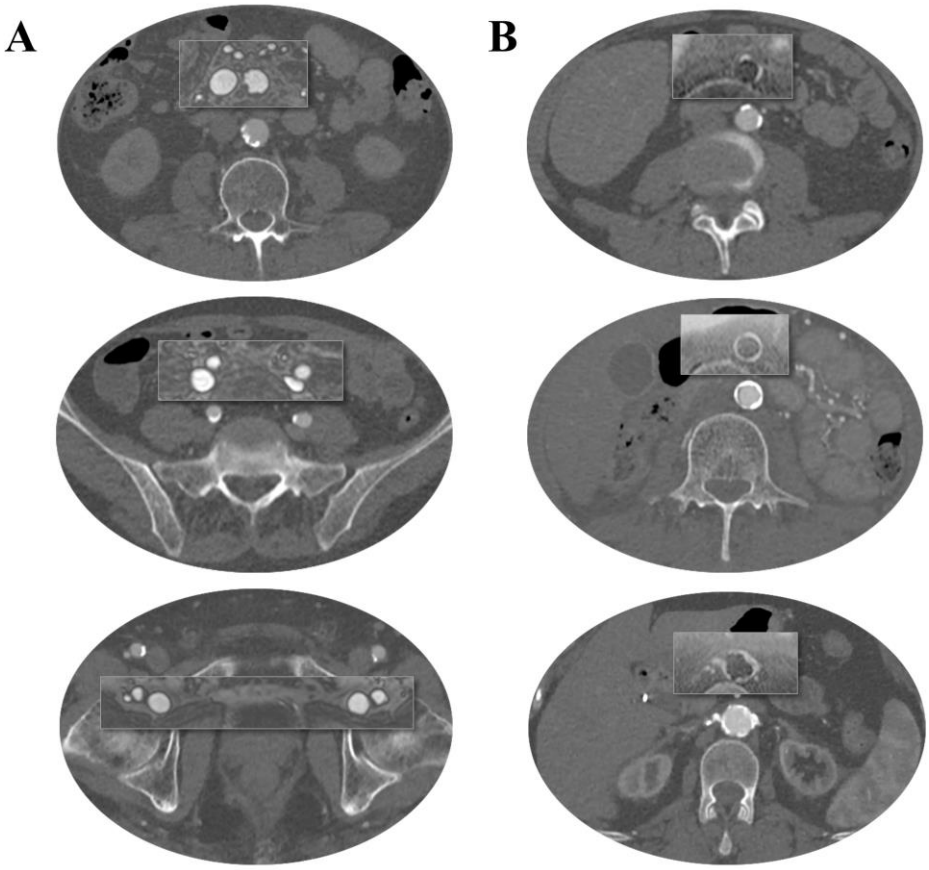


Figure 5-3 Transverse views of CTA, FeMRA and StarVIBE.

A. Transverse slices of CTA with superimposed FeMRA slices highlighting the excellent definition of the venous wall and lumen with FeMRA compared to poor venous enhancement with CTA at the levels of inferior vena cava (IVC), common iliac veins (CIV) and external iliac veins (EIV) from top to bottom. Note the simultaneous arterial and venous enhancement with FeMRA due to the prolonged intravascular half-life of ferumoxytol. Panel B. Transverse slices of CTA with superimposed StarVIBE slices demonstrating the concordance in calcific burden, location, and morphology in infra-abdominal aorta. Eccentric calcification usually involving the intima and related to atherosclerosis (top slice), concentric calcification usually involving the media causing arterial stiffening (middle slice), and mixed calcification (bottom slice).

5.3.3 Surgical assessment

Both FeMRA and CTA were deemed sufficient to assess the arteries (including calcification) whilst veins were poorly visualised on CTA. From the 36 patients included, 11 (30.6%) were considered at high risk for vascular anomalies based on their history (previous abdominal surgery, deep vein thrombosis (DVT), kidney transplantation or femoral CVC insertion) (Figure 5-4A). Arterial abnormalities (mainly extensive calcific stenosis of the iliac arteries) that would preclude kidney transplant in the ipsilateral iliac fossa were equally recognised with CTA and FeMRA and did not differ significantly between the 2 groups of patients (high risk vs not). Vein abnormalities that would impact

on the site of anastomosis were exclusively identified with FeMRA in 4 (11%) patients deemed at high risk for vascular anomalies (Figure 5-4A and B). Three of them had previous abdominal surgery for cancer (small bowel resection, bladder resection, bilateral nephrectomies and oophorectomies) and one had a previous femoral dialysis catheter insertion. In addition, 3 of them had previously documented DVT. The vein abnormalities found in these patients are shown in Figure 5-5. No vein abnormalities were apparent on CTA and in 15 (42%) patients the veins could not be appreciated as they were very poorly enhanced.

Arterial or venous occlusive disease necessitating further investigations or revascularisation procedures before consideration for transplant listing was identified in 13 (36%) patients with CTA vs 14 (39%) with FeMRA. Based on CTA, a definitive decision for transplant listing was made in 23 (64%) patients compared to 22 (61%) with FeMRA (Figure 5-4B).

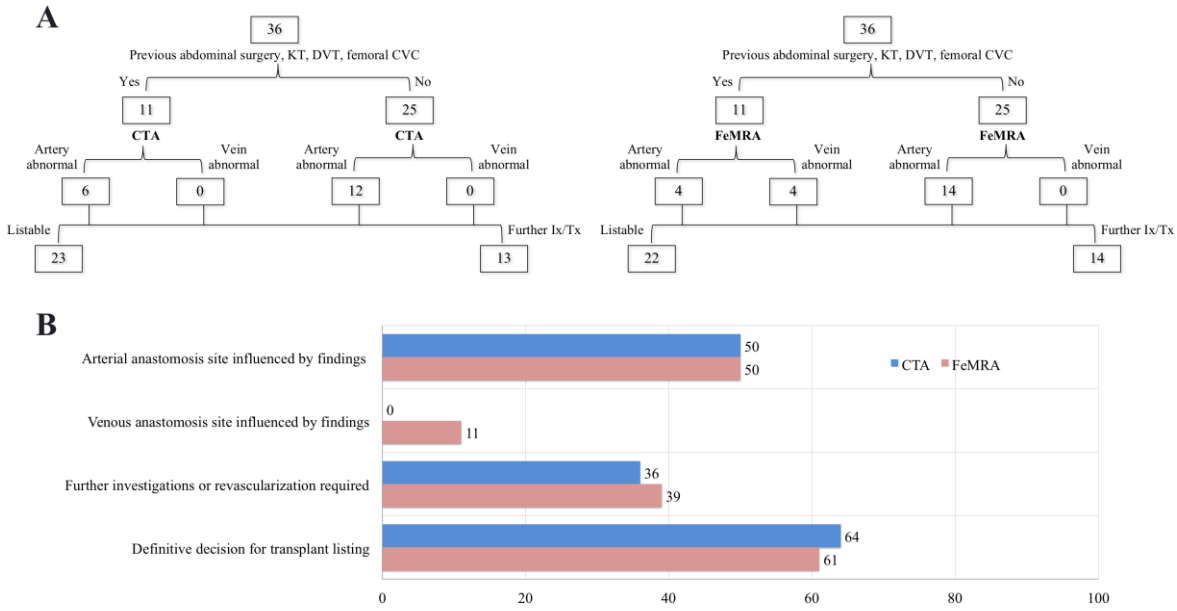


Figure 5-4 Surgical assessment of arterial inflow and venous outflow (CTA vs FeMRA).

A. Flow chart of anatomical abnormalities that impact on selection of the optimal anastomosis site. Patients are divided according to history of previous abdominal surgery or deep vein thrombosis (DVT), kidney transplantation (KT) and femoral central venous catheters (CVC) insertion. B. Graph displays distribution (percentages) of surgical decisions following assessment of CTA and FeMRA. Extravascular abnormal findings were not taken into account in decision-making. Ix, investigations; Tx, treatment.

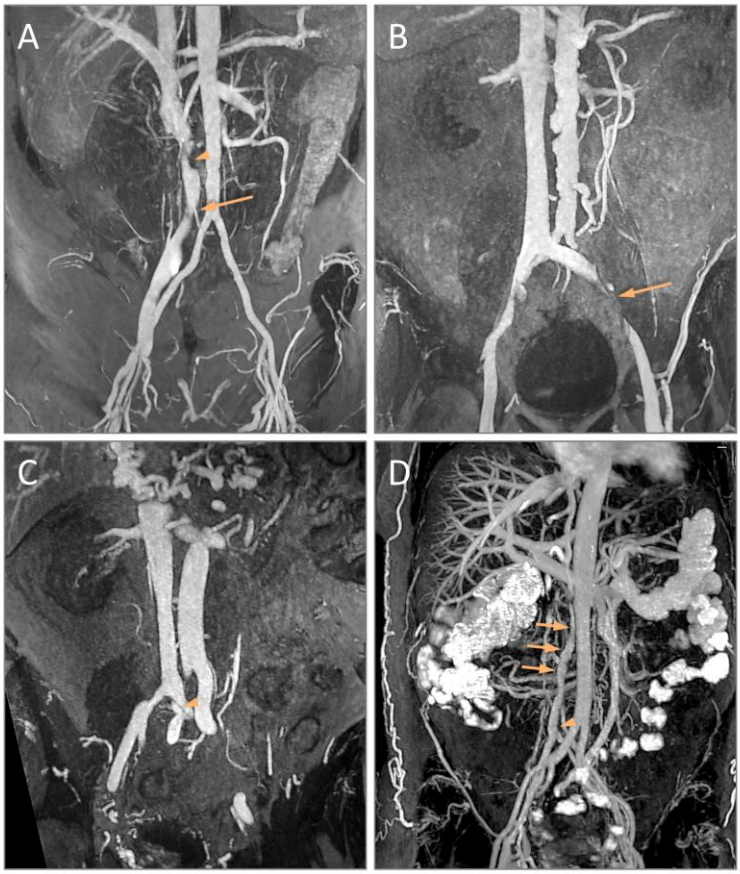


Figure 5-5 Coronal views showing anomalies of iliocaval vein segments identified with FeMRA.

A. Large intraluminal filling defect in infrarenal IVC corresponding to thrombus formation (arrowhead) and occluded left CIV before it joins the right CIV to form the IVC (arrow). B. Tightly stenosed left EIV (arrow) with patent left common femoral vein (distally) and left CIV (proximally). C. Linear intraluminal filling defect in left CIV representing a fibrin web (arrowhead). D. Occluded IVC with both CIV draining into the collateral azygos venous system (arrows) and clot retraction in left CIV (arrowhead).

5.4 Discussion

Ferumoxytol-enhanced MR angiography provides reliable depiction of arterial lumen and accurate detection of calcification in kidney transplant candidates, which is comparable to CTA. Of equal importance, the additional information obtained from delineation of the venous vasculature may determine surgical decisions on the site of anastomosis in a substantial proportion of patients. In addition, ferumoxytol's favorable pharmacokinetics allow imaging of predialysis patients without concerns for iodine or gadolinium toxicity, which impacts on timely decision-making about transplant listing. FeMRA can serve as an alternative or even replace currently used imaging methods in pretransplant assessment of CKD patients with known or suspected peripheral arterial disease.

We have demonstrated an MR imaging strategy that accurately detects aortoiliac calcifications that have a similar appearance to CT, but without the need for exposure to potentially hazardous ionising radiation. Arterial calcifications were distinguished with high conspicuity from fat, muscle, vessel lumen and non-calcified plaque. The location, conformation and quantification of the vascular calcifications corresponded with CT over a wide range of lesion and vessel sizes. Calcium blooming is an artifact noted with extensive and dense calcification that causes calcium to appear larger than it truly is. This is present in both CT and MRI and can be particularly problematic when immediately adjacent to an obscure vessel, as this may lead to overestimation of luminal stenosis. To overcome this problem we synchronised StarVIBE with FeMRA images and simultaneously projected the images on adjacent Picture Archiving and Communication System (PACS) portals. This allowed precise illustration of the unobstructed lumen in the absence of the superimposed calcium, which was separately assessed from StarVIBE.

Inherent to its properties that allow synchronous provision of arteriography and venography, FeMRA was superior to CTA in visualisation of the veins. Demonstration of a potential kidney transplant recipient's venous anatomy with venography is not routinely performed in clinical practice. Patients with venous thrombosis are often asymptomatic owing to extensive venous collateral flow, thereby masking signs of thrombosis. However, stenosis, thrombosis, and anomalies of the IVC and/or iliac veins can influence the venous anastomosis site. In an era of growing use of indwelling femoral dialysis catheters or prosthetic lower extremity access grafts for hemodialysis and the prolific rise in the number of patients referred for re-transplantation, complications in regard to the IVC and/or iliac veins are expected to be a more frequent occurrence, although data from studies are lacking. Undoubtedly most of these abnormalities would have been addressable at surgery in many cases, however this may have led in prolonged operative and ischaemia time if per se this would mean a change in the planned anastomosis site. This is highlighted in the recent KDIGO guideline on the evaluation of candidates for kidney transplantation (Chadban et al., 2020), where they recommend assessment of vascular anatomy and patency for these patients.

From a clinical standpoint, FeMRA ascertained anatomical variants and abnormalities which were vital in transplant planning. Although atherosclerotic calcification and arterial luminal stenosis are adequately elucidated with CTA, venous anatomy and patency are not routinely inspected with CTA. In a highly selected population that was referred for

angiography due to concerns about vascular disease, the effect of FeMR venography in surgical planning was remarkable: 11% of the patients demonstrated findings that assisted venous anastomosis decision. Strikingly, all these patients had prior abdominal or pelvic surgery and history or risk factors for venous thromboembolic disease. Arterial-phase CTA combined with CT venography can arguably be used instead but it requires higher doses of iodinated contrast material and increased radiation exposure, venous opacification can be suboptimal related to flow artifacts, and acquisition times vary considerably (Qanadli et al., 1999). Lastly, following current recommendations for ferumoxytol administration, no adverse events occurred in our cohort related to ferumoxytol infusions, and there were no systematic changes in heart rate, blood pressure or oxygen saturation following ferumoxytol administration.

Our study has limitations. First, while unenhanced MR angiography or non-contrast CT of the abdomen and pelvis are alternatives to contrast-based imaging studies for pretransplant assessment, the former is confined by long acquisition times and flow-related artifacts and the latter has very low contrast discrimination, which is suboptimal for evaluation of vessel patency and extravascular structures. Therefore, our work was focused on the comparison of FeMRA with CTA. Second, it is a single center experience reflecting local referring patterns and practices; nevertheless only patients with clinically apparent or at high risk for PAD are referred for imaging studies in our center broadly in keeping with European and UK practice (Maggiore et al., 2019; Pruthi et al., 2018). Third, the sample size in our study was relatively modest with respect to absolute patients' numbers, but a large number of vascular sections (>200) was analysed. Finally, whether or not the FeMRA findings truly altered the planned surgical operation is unclear, as the scans were performed for research purposes and were not necessarily available at the transplant surgeon at the time of surgery.

5.5 Conclusions

Ferumoxytol-enhanced MR angiography may complement CTA or other non-invasive imaging studies used for evaluation of the vasculature in CKD patients with PAD considered for kidney transplantation. Its applicability in predialysis patients fills unmet clinical needs and offers a safe and robust technique decisive to timely transplant listing. Lastly, the value of FeMRA in identifying under-recognised venous disease (in addition to arterial disease) is essential in preoperative planning especially in patients with prior

abdominal or pelvic surgery, transplant procedures, venous thromboembolic events, or venous dialysis catheters.

Chapter 6. FERUMOXYTOL MR ANGIOGRAPHY VS DUPLEX ULTRASOUND FOR VASCULAR MAPPING BEFORE ARTERIOVENOUS FISTULA SURGERY FOR HAEMODIALYSIS

6.1 Introduction

Primary AVF failure has always been a problem. When the radiocephalic AVF was first described by Cimino and Brescia in 1966 (Brescia et al., 1966), the primary AVF failure rate was approximately 11%. Subsequent studies reported primary failure rates ranging from 10 to 25% (Allon & Robbin, 2002). In later reports, the incidence has increased, ranging from 20 to 60% (Allon & Robbin, 2002; Robbin et al., 2002). This change is due to the change in demographics of the dialysis population in the recent era. The average dialysis patient age in the early period was 43 years, and almost all had chronic glomerulonephritis. Dialysis patients are now much older (>70 years), and 75% have five or more comorbidities; 90% have cardiovascular disease, and 50% have diabetes. It should not be surprising that creating and achieving a functional AVF is frequently a challenge in this population.

Preoperative sonographic mapping of arm vessels is an essential component of the creation of permanent HD access. It is used for both arterial and venous evaluation to optimise AVF placement and to avoid surgery that is unlikely to be successful (Allon et al., 2001; Robbin et al., 2000; Schmidli et al., 2018; Silva et al., 1998). Duplex US is limited, however, by an inherent operator-dependence, the inability to provide direct evidence of central stenosis (Patel et al., 1999) and the lack of image manipulation and reconstruction to inform the surgeon about vascular anatomical course, tortuosity etc.

Contrast-enhanced MRA can be used for visualisation of central and upper extremity vessels, however, its use in arteriovenous access planning was curtailed due to the risk of nephrogenic systemic fibrosis with the use of GBCAs in patients with CKD (Marckmann et al., 2006). Nonetheless, angiography of the central vessels may still be required in selected cases, where central stenosis is suspected. Traditional iodinated contrast-based angiography is an alternative imaging strategy but is limited by the theoretical risk of nephrotoxicity in patients with residual renal function.

In recent years, ferumoxytol has been increasingly used off-label for CE-MRA, particularly for patients with CKD (Hope et al., 2015; Li et al., 2005; Toth et al., 2017). Amongst its properties, its large molecular weight of approximately 750kD (Balakrishnan et al., 2009) delays contrast extravasation, which means it can be administered slowly or before the patient is transferred to the MRI suite. Given its long intravascular residence

time (half-life of approximately 15 hours) (Landry et al., 2005), it allows enhancement of both the arterial and venous vasculature without the need for bolus timing.

We aimed to assess the clinical utility of FeMRA for vascular mapping before autogenous AVF creation compared with Duplex US using anatomical parameters predictive of fistula outcome.

6.2 Methods

In a prospective comparative study, paired FeMRA and Duplex US were obtained the same day. Vessels were evaluated for diameter, stenosis or occlusion, arterial disease, and central stenosis by independent readers. Based on accepted standards for AVF creation, an algorithm was designed to predict AVF outcome relying on mapping findings. Logistic regression models were created with AVF success as the dependent variable and age, sex, and Duplex US or FeMRA mapping as the independent variables.

6.3 Results

In total, 59 patients (mean age 59 ± 13 years; 30 women; 27% with diabetic nephropathy) underwent a study specific FeMRA and Duplex US vascular mapping protocol during the period from December 2016 to August 2018. Overall 472 vascular cross-sections were analysed for each imaging technique (8 sections per patient). The overview of recruitment and AVF outcomes are outlined in Figure 6-1 and patients' characteristics in Table 6-1. The types of AVF created according to the anatomical site are shown in Table 6-2. Median follow-up after AVF creation was 21.6 (interquartile range 18 - 26.5) months.

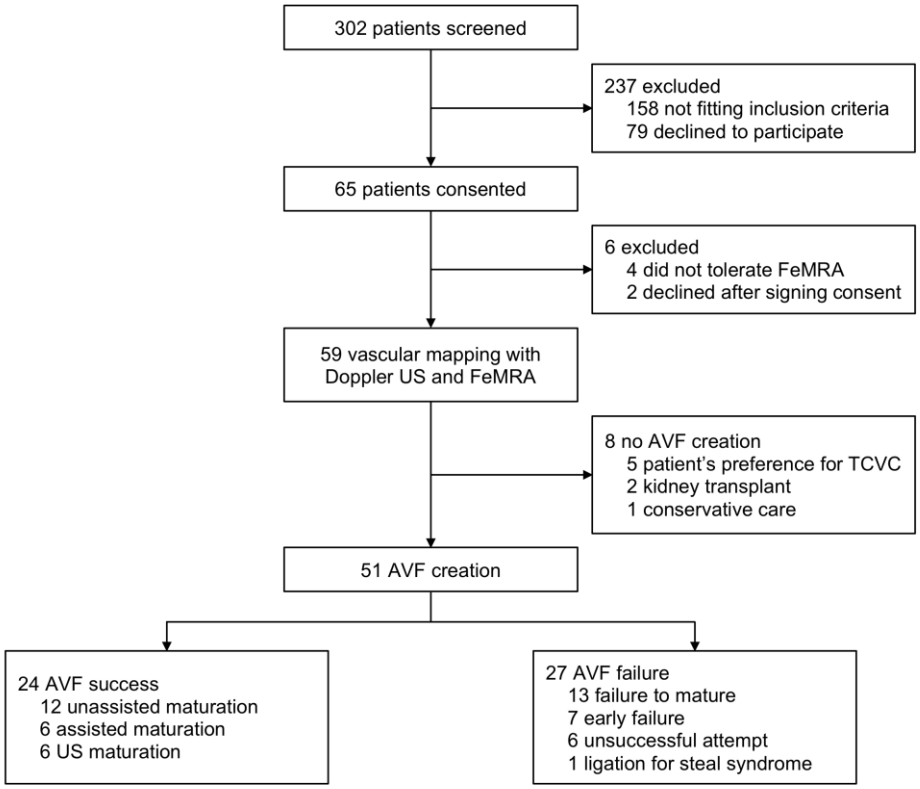


Figure 6-1 Overview of recruitment and AVF outcomes.

Age (y), mean (SD)	58.7 (12.9)
Male, n (%)	29 (49.2)
Race, n (%)	
White	49 (83.0)
Asian	9 (15.3)
Black African	1 (1.7)
Body weight (kg), mean (SD)	73.9 (17.1)
Body mass index categories, n (%)	
<18.5	5 (8.5)
18.5 - 24.9	16 (27.1)
25 – 30	18 (30.5)
>30	20 (33.9)
Cause of ESRD, n (%)	
Diabetes	16 (27.1)
Glomerulonephritis	13 (22.0)
Renovascular	7 (11.9)
Polycystic kidney disease	6 (10.2)
Unknown	7 (11.9)
Other[a]	10 (16.9)
Laboratory values at time of MRI	
Haemoglobin (g/L), mean (SD)	107 (17)
Creatinine (mg/dL), mean (SD)[b]	5.1 (1.6)
eGFR (mL/min/1.73m^2), mean (SD)[b]	11.8 (2.6)
CKD stage, n (%)	
Stage 4	5 (8.5)
Stage 5 - non-dialysis	33 (55.9)
Stage 5 – dialysis	21 (35.6)
Dose of ferumoxytol given (mg), mean (SD)	227 (48)
At least one previous AV access, n (%)	9 (15.3)
At least one previous CVC, n (%)	21 (35.6)
[a]Obstructive uropathy (n=3), Pyelonephritis (n=2), Tubulointerstitial nephritis (n=2), Cyclosporine toxicity (n=2), Congenital dysplasia (n=1) [b]Excludes patients on dialysis	
ESRD, end-stage renal disease; MRI, magnetic resonance imaging; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AV, arteriovenous; CVC, central venous catheterisation	

Table 6-1 Baseline characteristics of study participants.

Distal radiocephalic fistula, n (%)	15 (29.4)
Proximal radial artery fistula, n (%)*	13 (25.5)
Brachiocephalic fistula, n (%)	21 (41.2)
Brachiobasilic fistula, n (%)	2 (3.9)
*anastomosis between the proximal radial artery and the nearest suitable vein located in the antecubital fossa (median, perforating, or cephalic vein)	

Table 6-2 Types of arteriovenous fistulas created in the cohort.

6.3.1 Repeatability studies

The overall inter-reader agreement for FeMRA derived measurements of the arterial diameter (ICC: 0.90; 95% CI: 0.87, 0.93), venous diameter (ICC: 0.84; 95% CI: 0.78, 0.88), and vein depth from skin surface (ICC: 0.92; 95% CI: 0.89, 0.94) was excellent across all vascular sections (Table 6-3). In a subgroup of 20 patients (aged 58 ± 12 years; 11 women; 31% with diabetic nephropathy) selected at random for intra-reader agreement, interclass coefficients were between 0.88 – 0.97 for all parameters, indicating excellent agreement (Table 6-3). There were no fixed or proportional biases, and >95% of differences consistently fell within acceptable limits of agreement for all vessel sizes and vein depths from skin surface (Figure 6-2).

	ICC (95% CI) values comparing cross-sections measurements		
	Inter-reader	**Intra-reader**	
		Reader 1	**Reader 2**
Arterial diameter			
RA (wrist)	0.90 (0.84 – 0.94)	0.94 (0.82 – 0.98)	0.93 (0.77 – 0.98)
RA (mid-forearm)	0.90 (0.83 – 0.94)	0.84 (0.54 – 0.95)	0.89 (0.80 – 0.94)
RA (elbow)	0.89 (0.85 – 0.93)	0.86 (0.59 – 0.96)	0.84 (0.54 – 0.95)
BA (elbow)	0.94 (0.88 – 0.97)	0.91 (0.71 – 0.97)	0.95 (0.91 – 0.97)
All arteries	0.90 (0.87 – 0.93)	0.91 (0.87 – 0.94)	0.88 (0.77 – 0.93)
Vein diameter			
CV (wrist)	0.95 (0.92 – 0.97)	0.85 (0.73 – 0.92)	0.84 (0.55 – 0.95)
CV (mid-forearm)	0.96 (0.94 – 0.98)	0.97 (0.90 – 0.99)	0.91 (0.72 – 0.97)
CV (elbow)	0.98 (0.97 – 0.99)	0.94 (0.81 – 0.98)	0.92 (0.76 – 0.98)
BV (elbow)	0.96 (0.93 – 0.98)	0.92 (0.84 – 0.96)	0.85 (0.73 – 0.92)
All veins	0.84 (0.78 – 0.88)	0.92 (0.88 – 0.94)	0.89 (0.85 – 0.93)
Vein depth from skin surface			
CV (wrist)	0.91 (0.85 – 0.95)	0.93 (0.79 – 0.98)	0.95 (0.83 – 0.98)
CV (mid-forearm)	0.99 (0.98 – 0.99)	0.90 (0.70 – 0.97)	0.95 (0.82 – 0.98)
CV (elbow)	0.99 (0.98 – 1.00)	0.95 (0.85 – 0.99)	0.97 (0.88 – 0.99)
BV (elbow)	0.95 (0.91 – 0.98)	0.97 (0.90 – 0.99)	0.94 (0.89 – 0.97)
All veins	0.92 (0.89 – 0.94)	0.96 (0.92 – 0.98)	0.97 (0.95 – 0.99)
RA, radial artery; BA, brachial artery; CV, cephalic vein; BV, basilic vein			

Table 6-3 Interclass correlation coefficients to test consistency of agreement in FeMRA.

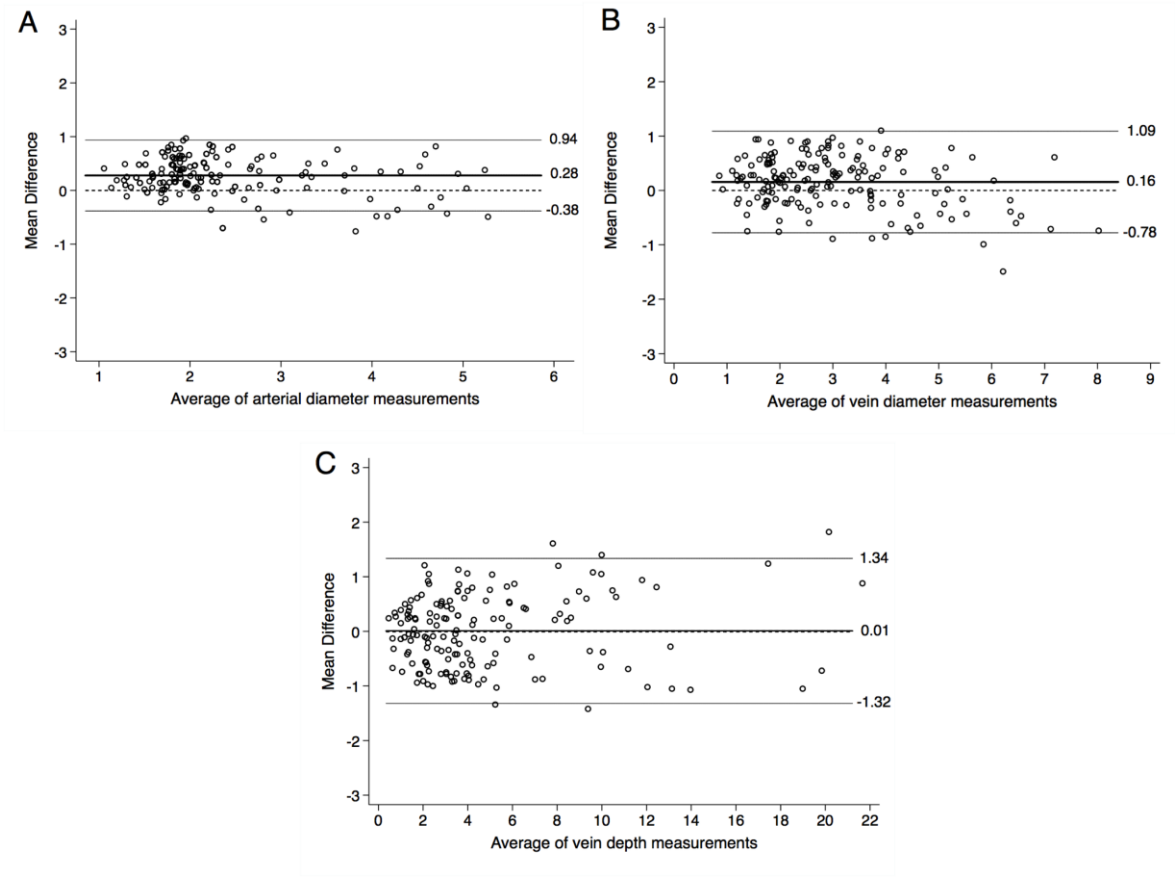


Figure 6-2 Bland-Altman plots of inter-reader variability for FeMRA. The measurements of the first and the second FeMRA readers were compared.

A. Plot of arterial diameter measurements. The dark central line is the mean difference between the 2 analyses and the light outer lines show the limits of agreement (mean of the differences ± 1.96 SD). B. Plot of vein diameter measurements. C. Plot of vein depth measurements. There are no significant fixed or proportional biases as the lines of equality are within the confidence interval of the mean differences for all measurements.

6.3.2 Predictors of AVF outcome

We used hypothetical models to predict fistula outcome (success vs. failure) in each anatomical site using the different imaging modalities and we subsequently compared our predictions with the actual outcomes. For the FeMRA we created 2 models, one including central and peripheral scan findings and a second one including information on the peripheral vessels only. The scope of the 2 different models used for the FeMRA was to identify whether any difference in prediction compared to US derives from the extra information obtained from the central vasculature or whether differences occur even when directly assessing the peripheral vessels. Three independent variables were tested in each of the binomial logistic regression models used for multivariate analysis: age, sex, and either Duplex US mapping (model 1), FeMRA central and peripheral mapping (model 2),

or FeMRA peripheral mapping (model 3). In univariable analysis for AVF outcome (success vs. failure) FeMRA central and peripheral mapping [odds ratio (OR) 5.14 (95% CI 1.52-17.38); p=0.008], and FeMRA peripheral mapping [OR 4.20 (95% CI 1.20-14.74); p=0.03] predicted a successful outcome. By multivariable analysis FeMRA central and peripheral mapping [OR 6.49 (95% CI 1.70-24.79); p=0.006], and FeMRA peripheral mapping [OR 4.58 (95% CI 1.25-16.83); p=0.02] were independent predictors of successful AVF outcome. There was no significant association between age, sex, or Duplex US mapping and outcome (Table 6-4).

	Univariable analysis		**Multivariable analysis (US prediction model 1)**		**Multivariable analysis (FeMRA prediction model 2)**		**Multivariable analysis (FeMRA prediction model 3)**	
	Odds ratio (95% CI)	**P-value**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**	**Odds ratio (95% CI)**	**P-value**
Age, per year	0.98 (0.93 – 1.02)	0.28	0.97 (0.93 – 1.02)	0.23	0.96 (0.91 – 1.01)	0.14	0.97 (0.92 – 1.02)	0.21
Sex	1.30 (0.42 – 4.01)	0.65	1.19 (0.37 – 3.85)	0.77	0.89 (0.25 – 3.18)	0.86	1.12 (0.33 – 3.79)	0.85
US mapping	2.29 (0.71 – 7.40)	0.17	2.49 (0.74 – 8.38)	0.14				
FeMRA mapping[a]	5.14 (1.52 – 17.38)	0.008			6.49 (1.70 – 24.79)	0.006		
FeMRA mapping[b]	4.20 (1.20 – 14.74)	0.03					4.58 (1.25 – 16.83)	0.02
[a]CVS included [b]CVS excluded								

Table 6-4 Univariable and multivariable analyses using hypothetical prediction models of arteriovenous fistula outcome.

Univariable and multivariable analyses of factors associated with arteriovenous fistula outcome (success vs. failure). Three different models were used in analysis; in model 1 Duplex US mapping findings were used to predict outcome, in model 2 FeMRA findings and in model 3 FeMRA findings of the peripheral vasculature (without using the findings from central vasculature) were used.

FeMRA and Duplex US equally identified peripheral vein sections unsuitable for fistula creation, but more arterial sections were classified as unsuitable for fistula attempt with

FeMRA (predominantly based on diameter criteria). Central vein stenosis was detected by FeMRA in 7 (12%) patients, of whom 5 had previous CVC insertions for dialysis. Cephalic arch stenosis was present in 6 (10%) and subclavian artery stenosis in 2 (3%) patients (Table 6-5 and Figure 6-3). Vessel course and tortuosity was better assessed with FeMRA but other anatomical characteristics (such as branches or vein depth from skin surface) were depicted with both imaging modalities (Table 6-5). The number of fistulas predicted to fail with FeMRA and Duplex US according to the anatomical site of the fistula is shown in Table 6-6.

	FeMRA	**Duplex US**
Unsuitable arterial sections		
Small diameter	72	48
Presence of arterial disease	11	11
Stenosis, occlusion	5	2
Absence	0	0
Unsuitable vein sections		
Small diameter	106	107
Stenosis, occlusion	30	5
Absence	1	7
Central stenosis		
Subclavian artery	2	-
Cephalic arch	6	-
Subclavian vein	4	-
Brachiocephalic vein	2	-
Superior venal cava	1	-
Other anatomical findings		
Tortuous cephalic/basilica veins	7	2
Vein depth >10mm	31	30
Cephalic vein ≥2 branches	15	16
Basilica vein ≥2 branches	10	12
High brachial artery bifurcation	4	3

Table 6-5 Anatomical lesions and variants identified with vascular mapping. FeMRA vs. Duplex US.

Predicted arteriovenous fistulas failures (N=59)				
	FeMRA		Duplex US	
	Suboptimal arterial sections	Suboptimal vein sections	Suboptimal arterial sections	Suboptimal vein sections
Distal radiocephalic fistula, n (%)	31 (53%)	38 (64%)	22 (37%)	45 (76%)
Proximal radial artery fistula, n (%)*	30 (51%)	30 (51%)	14 (24%)	21 (36%)
Brachiocephalic fistula, n (%)	2 (3%)	18 (31%)	0 (0%)	17 (29%)
Brachiobasilic fistula, n (%)	2 (3%)	16 (27%)	0 (0%)	6 (10%)
*anastomosis between the proximal radial artery and the nearest suitable vein located in the antecubital fossa (median, perforating, or cephalic vein)				

Table 6-6 Number of AVF predicted to fail at each anatomical site (FeMRA vs. Duplex US).

6.3.3 Sensitivity, specificity and predictive values

FeMRA and Duplex US had similar sensitivity but specificity, positive and negative predictive values were superior for FeMRA. To translate these findings FeMRA correctly classified less vascular sections as suitable for AVF creation, which could lead in less unnecessary procedures. On the other hand, Duplex US is prone to falsely characterise vascular sections as suitable for AVF creation increasing the risk of type I error and unsuccessful AVF surgeries.

	FeMRA	Duplex US
Sensitivity	71%	71%
Specificity	67%	52%
Positive predictive value	65%	57%
Negative predictive value	72%	67%

Table 6-7 Performance of each diagnostic test assessed with sensitivity, specificity, positive and negative predictive values.

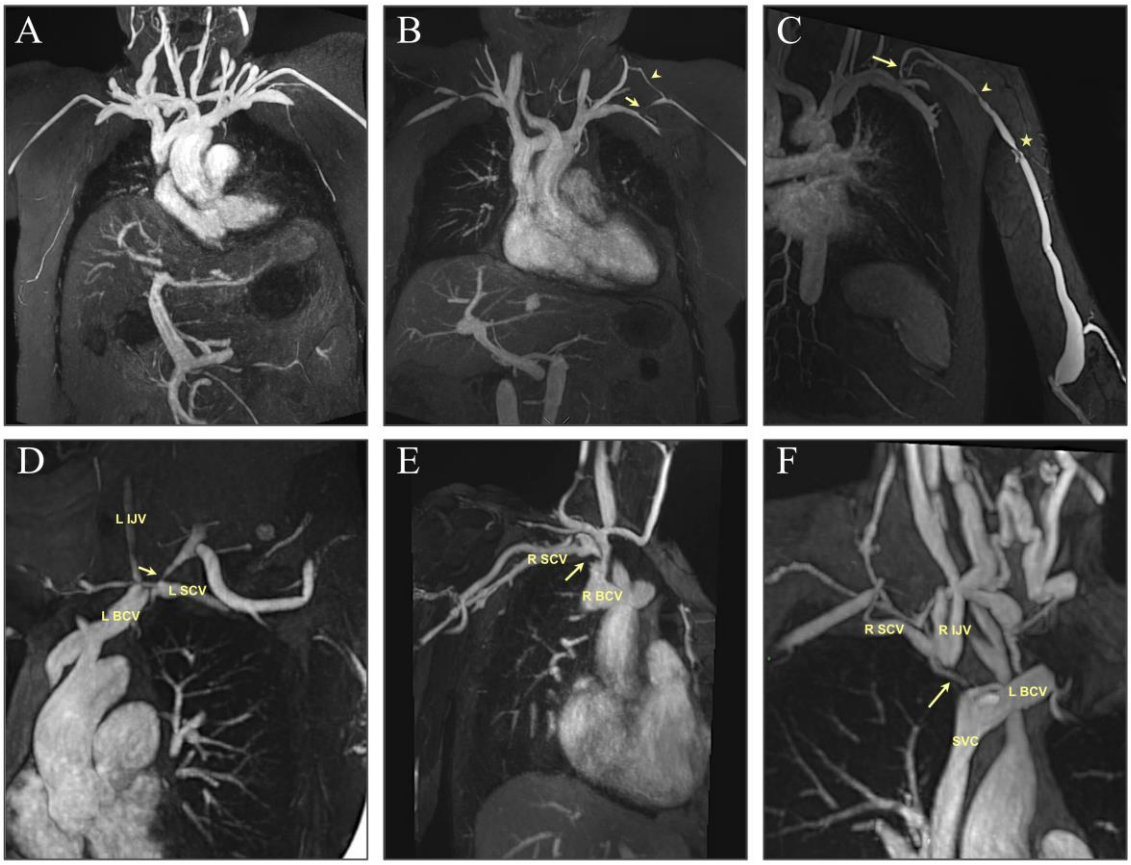


Figure 6-3 Steady-state coronal FeMRA images.

Steady-state thick slab maximum intensity projection (MIP) coronal FeMRA images showing central veins abnormalities. A. Well-defined cephalic arch bilaterally before it enters the axillary vein to form the subclavian vein. B. Left cephalic arch stenosis near the confluence with the subclavian vein (arrow) and collateral vein formation (arrowhead). C. Left cephalic arch stenosis with collateral vein formation (arrow), cephalic vein stenosis (arrowhead) and cephalic vein valve (star). D. Left cephalic arch stenosis at the confluence with the subclavian vein (arrow). E. Tight stenosis at the junction of the right subclavian and brachiocephalic veins. F. Occluded right brachiocephalic vein.

6.4 Discussion

Ferumoxytol-enhanced MR angiography provides high quality peripheral vascular mapping in CKD patients who are referred for arteriovenous fistula creation with the additional advantage of accurate depiction of the central vasculature. Compared with Duplex US, FeMRA of the peripheral vessels performed better in predicting successful fistula outcome as it identified small arteries unsuitable for fistula creation not recognised with US. In addition, ferumoxytol's favourable pharmacokinetics allow imaging of predialysis patients without concerns for iodine or gadolinium contrast toxicity. FeMRA can supplement Duplex US or serve as an alternative for vascular mapping in selected CKD patients with known or suspected central stenosis or peripheral arterial disease.

In this cohort where more than a third of patients had at least one previous CVC insertion for dialysis, 12% had central venous stenosis and another 10% cephalic arch stenosis. These rates are comparable with other studies, such as Oguzkurt *et al.*, who reported 16% angiographically-proven CVS in dialysis patients with temporary catheters (Oguzkurt et al., 2004) and Wang *et al.*, who reported 9% clinically noticeable CVS in dialysis patients (Wang et al., 2015). Central vein stenosis can occur due to trauma from catheter insertion, stagnation of blood at the catheter insertion site, and turbulent blood flow during hemodialysis (Cimochowski et al., 1990; Schwab et al., 1988). Although 71% of central venous stenosis was associated with previous catheters, it was conspicuously seen in a small number of patients without prior catheter use, and without the presence of non-dialysis factors that are closely associated with CVS development, such as transvenous pacemakers and previous admission to the intensive care unit.

Our results suggest that for the distinction of small diameter arteries (< vs. >2.0 mm), FeMRA had a significantly better discriminatory power than Duplex US, whereas for the distinction between small diameter veins (< vs. >2.5 mm), there was no significant difference in diagnostic performance. FeMRA was more conservative compared to Duplex US with more peripheral vascular sections deemed suboptimal for AVF creation. The reason for this discrepancy, especially with regards to the arterial sections, is not clear and in fact this was an unexpected finding. FeMRA has excellent spatial and temporal resolutions providing a more precise estimate of the vessel lumen, whereas US is operator-dependent and susceptible to the compression of the vessel by the transducer during the examination. This likely explains why the difference was only noted in the arteries (where a smaller diameter threshold was selected) and not in the veins. Patient positioning (seated vs. lying) or the lower temperature in the MRI suite could also have contributed in the discrepancy, however the effect of these factors (if any) is impossible to quantify.

From a clinical standpoint, FeMRA ascertained anatomical abnormalities, which were predictive of successful fistula outcome and could be vital in vascular access planning. Its effect could be magnified if we incorporated more parameters in our model, such as vessel course, tortuosity, and perception of anatomy from synchronous multiplanar depiction of arteries and veins or 3D reformations. In the wake of our findings, the adoption of FeMRA in clinical practice could significantly increase the number of successful first-time fistulas and thereby reduce the burden of repeated procedures. Nonetheless, Duplex

US remains the screening tool of choice in the initial workup of most patients before fistula creation due to its ease of use, lower cost and applicability to almost all patients. FeMRA could be reserved for patients with risk factors for venous complications, peripheral arterial disease, previous failed accesses or borderline vessels in US. This is highlighted in the recent European Society for Vascular Surgery (ESVS) (Schmidli et al., 2018) and Kidney Disease Outcomes Quality Initiative (KDOQI) (Lok, 2019) clinical practice guidelines for vascular access, where various imaging studies as needed are recommended to evaluate the suitability of peripheral vessels and central veins for occlusion.

Our study has limitations. First, we did not examine internal jugular and subclavian vein waveforms with Duplex US to indirectly predict the presence of CVS. However, this is time-consuming and technically difficult, with a number of pitfalls such as abnormal waveform with deep inspiration causing a functional narrowing, slow flow mimicking a thrombus, and turbulent flow from indwelling catheters or an ipsilateral hemodialysis fistula mimicking stenosis. Second, it is a single center experience reflecting local referring patterns and practices; nevertheless the arterial and vein diameter criteria used in our predictive models are universally acceptable (Sidawy et al., 2008). Third, the sample size in our study was relatively modest with respect to absolute patients' numbers, but a large number of vascular sections (approximately 500) was analysed. Finally, the lack of license for ferumoxytol use as a contrast agent for MRI and the increased cost and limited supply associated with it makes its immediate use in clinical practice unrealistic. Until it is more widely available, alternative imaging techniques for vascular imaging of the upper extremity can be used. Traditionally, DSA is used because of its dynamic nature and superior spatial resolution however, it is a costly and time-consuming invasive procedure and has potential complications. In recent years multi-detector CT angiography with standard post-processing techniques allows routine acquisition of submillimeter isotropic datasets and has become a non-invasive alternative to DSA.

6.5 Conclusions

In conclusion, our results demonstrate that ferumoxytol-enhanced MRA is a useful technique for vascular mapping before haemodialysis access creation that can minimise unnecessary surgical procedures. FeMRA is fast, operator-independent, reliable in the detection of central vein stenosis, and more accurate for visualisation of the arm vessels

and thus overcomes most of the limitations inherent in duplex sonography. However, it is not yet widely available and the extreme cost of ferumoxytol contrast and MR imaging hamper its use in clinical practice. A randomised study of FeMRA vs DUS mapping with appropriate stratification is needed to identify the patients that would benefit most from each technique.

Chapter 7. EFFECTS OF HAEMODIALYSIS ARTERIOVENOUS FISTULA CREATION ON CARDIAC STRUCTURE AND FUNCTION

7.1 Introduction

Arteriovenous fistula is the preferred type of access for maintenance haemodialysis; nonetheless it may contribute to maladaptive cardiovascular remodelling. The creation of an AVF leads to a localised area of high flow shunting of blood from the arterial to venous circulation, and exposes the low pressure, high capacitance venous system to the high pressure, low capacitance arterial system. Immediately following creation, AVF is associated with an increase in cardiac output and a decrease in subendocardial perfusion (Savage et al., 2002), predominantly as a consequence of reduced systemic vascular resistance, increased myocardial contractility, and an increase in stroke volume and heart rate (GUYTON & SAGAWA, 1961). Over the following weeks, circulating blood volume increases in conjunction with increases in atrial and brain natriuretic peptides (Iwashima et al., 2002; Ori et al., 1996). As the fistula increases in size and blood flow over months and longer, there are further increases in LV filling pressure and subsequent changes on atrial and ventricular chamber dimensions and function (Basile et al., 2008; Iwashima et al., 2002; Ori et al., 1996; Parfrey et al., 1996). Over time, because of the increase in blood volume, the right atrial pressure, pulmonary artery pressure, and LV end-diastolic pressure gradually increase until the myocardium decompensates, the LV dilates, the ejection fraction declines, and the patient has symptoms of heart failure.

Historically, AVF creation has been associated with worsening of LV hypertrophy and resultant diastolic dysfunction and left atrial dilatation (Iwashima et al., 2002; Ori et al., 2002). The blood flow in an AVF is between 400 and 4000 mL/min, which is a huge increment compared to the blood flow in a normal cephalic vein of approximately 30 mL/min. A relatively infrequent but important complication of AVF is progressive high-output cardiac failure, despite preserved LV systolic function (Ahearn & Maher, 1972; Anderson et al., 1976; MacRae et al., 2004). This has been shown to be more common with fistula flows greater than 2 L/min. Upper arm fistulas tend to have the highest blood flow rates and in fact, access flow has been shown to be up to twice as high in upper arm compared with lower arm fistulas (1,336 ± 689 vs. 645 ± 332 mL/min) (Begin et al., 2002). A combination of increased cardiac output as well as altered diastolic filling parameters has been shown to precipitate heart failure in this population.

Six weeks is the minimum time for a new AVF to mature sufficiently to allow successful needling and adequate blood flow for efficient hemodialysis. Parallel to the vascular

remodelling in the fistula arm, creation of a non-physiologic shunt initiates a cascade of haemodynamic and structural changes in the heart muscle. There is a pervasive belief that it takes a substantial amount of time for fistulas to mature enough to reach their maximum flow and similarly changes in LV mass and cardiac indexes occur gradually over a long period of time following AVF creation. Furthermore, it is thought that high-output failure is relevant only with fistulas of long-standing duration. But AVFs have been shown to reach their maximum flow as early as 6 weeks after creation (Begin et al., 2002), and we know that AVF creation has immediate cardiac effects, thus, perhaps high-output cardiac failure can occur sooner than thought.

Cardiovascular magnetic resonance imaging is the ‘gold standard’ for evaluation of cardiac structure and function with substantially greater accuracy, prognostic value and reproducibility compared to alternative techniques, such as echocardiography (Edwards et al., 2008; Mark et al., 2008; Nelson et al., 2009). Using CMR in 24 patients, Dundon et al (Dundon et al., 2014) showed a mean increase of 12.7% in LV mass 6 months after creation of an AVF.

Our study hypotheses were that a) LV mass changes occur within weeks after AVF creation and b) changes in LV mass are proportional to the AVF blood flow. To test our hypotheses we conducted a prospective study using CMR to evaluate changes on cardiac structure and function 6 weeks after AVF surgery in patients with ESRD.

7.2 Methods

In this prospective cohort study, patients with ESRD listed for AVF creation underwent cardiac magnetic resonance imaging at baseline and at 6 weeks after AVF surgery. All participants had ultrasound measurements of brachial artery blood flow at 6 weeks, which is traditionally used for estimation of AVF blood flow. The primary outcome was the change in LV mass. Secondary outcomes included changes in LV end-systolic and end-diastolic volumes, left atrial volume, LV ejection fraction, LV global longitudinal strain, cardiac output/index, septal thickness, NT-proBNP and high-sensitivity Troponin I.

7.3 Results

A total of 65 patients were enrolled, of whom 40 patients (mean age 56 ± 11 years; 21 women; 40% with diabetic nephropathy) underwent AVF surgery and had CMR at baseline and 6 weeks after surgery during the period between 12th December 2016 and 30th November 2018. All study participants had US Duplex of their AVF performed at the same time as the repeat CMR. The patients' baseline characteristics are shown in Table 7-1.

The median time between CMR scans was 8.1 weeks (interquartile range, 6.3–9.5 weeks). However, the median time from AVF surgery to the second CMR scan was 6.4 weeks (interquartile range, 5.8–6.9 weeks). This delay was the result of listing patients for AVF surgery after the baseline CMR and scheduling of CMR scans.

Age (y), mean (SD)	56.2 (10.9)
Male, n (%)	19 (47.5)
Race, n (%)	
White	36 (90.0)
Asian	3 (7.5)
Black African	1 (2.5)
Time between first scan and AVF creation (wk), median (IQR)	1.9 (0.9-2.8)
Time between AVF creation and second scan (wk), median (IQR)	6.4 (5.8-6.9)
Cause of ESRD, n (%)	
Diabetes	16 (40.0)
Glomerulonephritis	8 (20.0)
Renovascular	3 (7.5)
Polycystic kidney disease	3 (7.5)
Unknown	7 (17.5)
Other[a]	3 (7.5)
Location of AVF, n (%)	
Forearm	22 (55.0)
Upper arm	18 (45.0)
AVF blood flow, n (%)	
≥ 600 mL/min	22 (55.0)
< 600 mL/min	18 (45.0)
Laboratory values at time of CMR	
Haemoglobin (g/L), mean (SD)	108 (17)
Creatinine (mg/dL), mean (SD)[b]	4.9 (1.4)
eGFR (mL/min/1.73m^2), mean (SD)[b]	11.1 (2.5)
CKD stage, n (%)	
Stage 4	3 (7.5)
Stage 5 - non-dialysis	23 (57.5)
Stage 5 – dialysis	14 (35.0)
At least one previous AV access, n (%)	8 (20.0)
At least one previous CVC, n (%)	17 (42.5)
[a]Obstructive uropathy (n=2), Congenital dysplasia (n=1) [b]Excludes patients on dialysis	
AVF, arteriovenous fistula; ESRD, end-stage renal disease; CMR, cardiac magnetic resonance imaging; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; AV, arteriovenous; CVC, central venous catheterisation	

Table 7-1 Baseline characteristics of study participants.

7.3.1 Primary Outcome

The primary end point showed a mean increase of 7.4 g (95% CI, 1.1–13.7, $p = 0.02$) in LV mass following AVF surgery. To adjust for body surface area, change in LV mass index was also calculated. An increase of 5.1 g/m^2 (95% CI, 1.6–8.6, $p = 0.005$) was found.

In the high flow group the mean increase in LV mass was 15.5 g (95% CI, 7.3–23.8) compared with a small decrease of 2.5 g (95% CI, −10.6 to 5.6) in the low flow group ($p = 0.003$ for comparison) (Figure 7-1). For the LV mass index the mean increase was 9.5 g/m^2 (95% CI, 5.2–14.0) in the high flow group compared with a small decrease of 0.3 g/m^2 (95% CI, −5.2 to 4.6) in the low flow group ($p = 0.003$ for comparison) (Figure 7-1).

Linear regression analyses undertaken showed that increase in the LV mass and LV mass index was more pronounced in subjects with higher flow fistulas (Figure 7-2) and in subjects with lower LV mass at baseline (Figure 7-3). In the high flow group, increase in LV mass was demonstrated in all except 2 subjects.

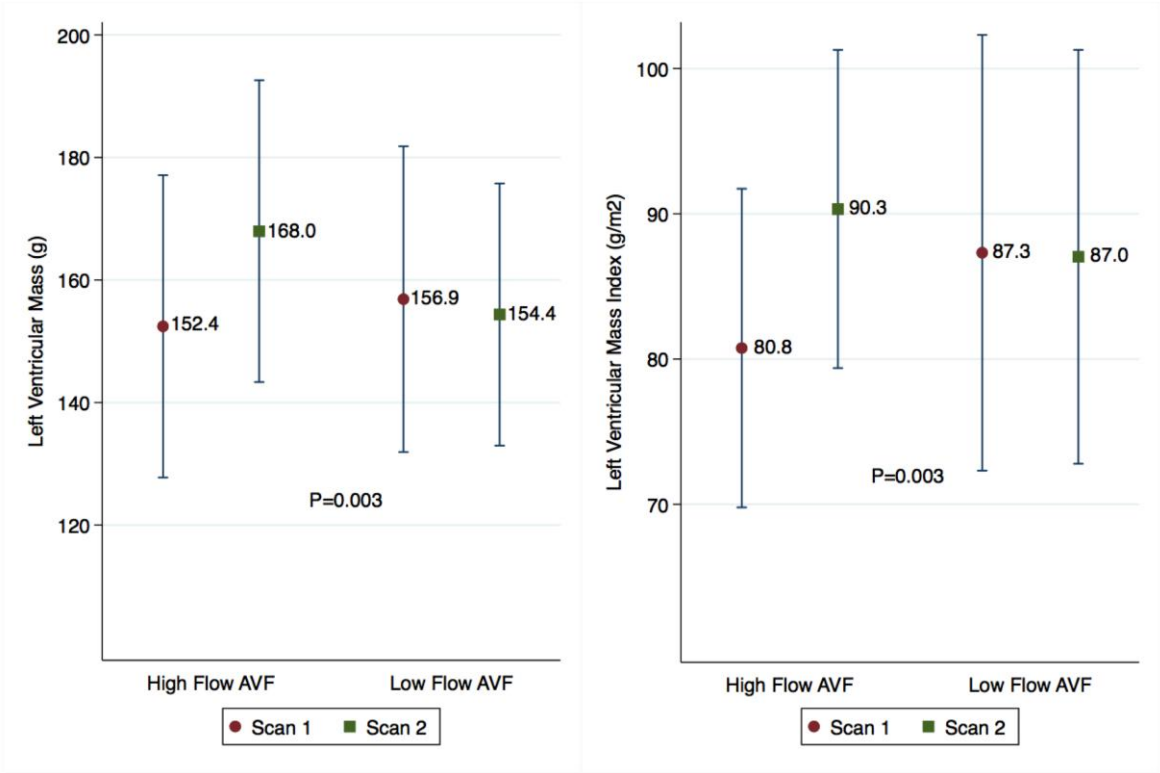


Figure 7-1 Difference in left ventricular (LV) mass and LV mass index between scans per AVF flow groups.

Difference in the means of left ventricular (LV) mass (left) and LV mass index (right) between the 2 scans according to the brachial artery blood flow (p = 0.003 for the difference between groups). This figure shows the means in 40 subjects who completed the second cardiac magnetic resonance scan, 22 in the high flow group (≥ 600mL/min) and 18 in the low flow group (< 600mL/min). Change in means and the 95% CI show a significant statistical difference between groups (p = 0.003) with an independent t test.

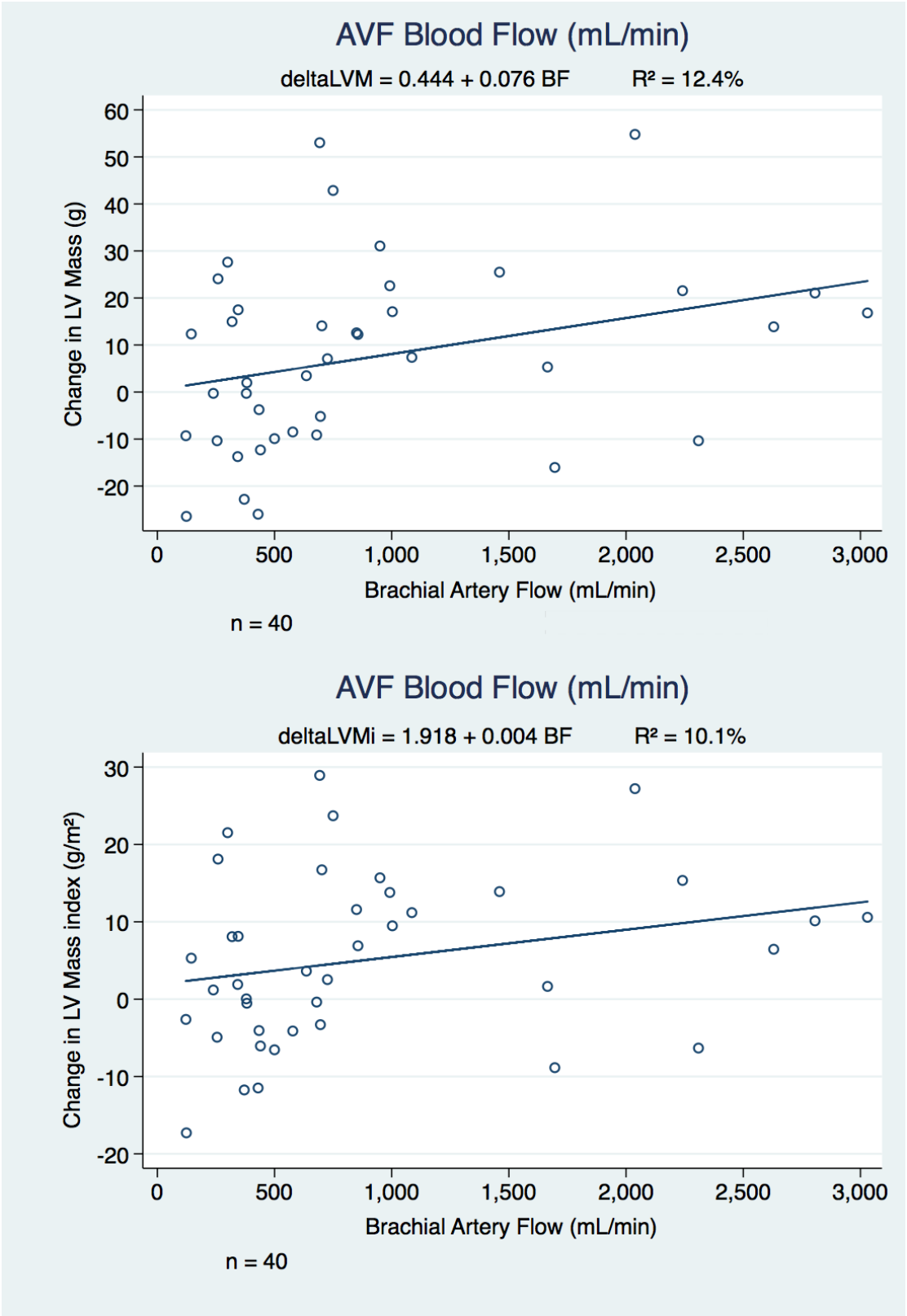


Figure 7-2 Linear regression analysis of left ventricular (LV) mass and LV mass index change according to brachial artery blood flow.

Effect of arteriovenous fistula (AVF) creation based on AVF blood flow. Linear regression analysis looking at change in LV mass (above) and LV mass index (below) in study participants with AVF creation. Increases in LV mass and LV mass index were more pronounced in those with higher fistula flows at 6 weeks after surgery.

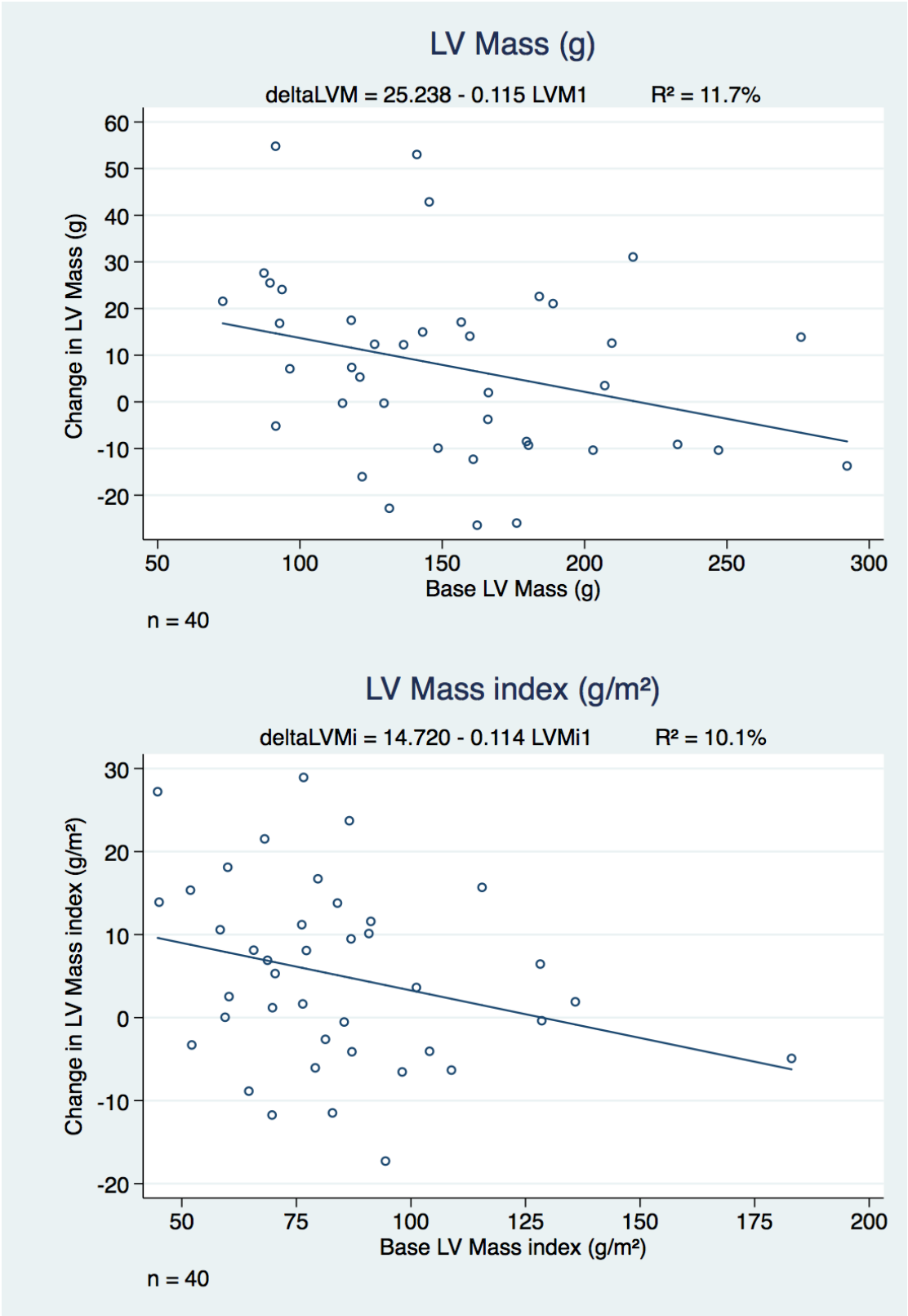


Figure 7-3 Linear regression analysis of left ventricular (LV) mass and LV mass index change according to baseline LV mass and index.

Effect of arteriovenous fistula (AVF) creation based on baseline LV mass and LV mass index. Linear regression analysis looking at change in LV mass (above) and LV mass index (below) in study participants with AVF creation. Increases in LV mass and LV mass index were more pronounced in those with lower LV mass and LV mass index in the baseline cardiac magnetic resonance imaging.

7.3.2 Secondary Outcomes

Table 7-2 shows the changes observed for other cardiac indexes, including LV end-diastolic volume, LV end-systolic volume, ejection fraction, cardiac output, cardiac index, LV global longitudinal strain, left atrial volume, left atrial volume index and septal thickness. The mean NT-proBNP levels for all subjects were elevated at baseline (Table 7-2) and increased further in the higher flow AVF group ($p = 0.05$ for comparison; Figure 7-4). There was a drop in diastolic blood pressure between CMR scans ($p = 0.03$) but no changes in systolic blood pressure, body weight and haematocrit were observed (Table 7-2).

	All (n=40)			AVF flow ≥600 mL/min (n=22)			AVF flow <600 mL/min (n=18)		
	Baseline	Follow-up	p value	Baseline	Follow-up	p value	Baseline	Follow-up	p value
LV mass, g	154.4 ± 52.6*	161.8 ± 50.2	0.02	152.4 ± 55.6*	168.0 ± 55.6	<0.001	156.9 ± 50.2	154.4 ± 43.0	0.52
LV mass index, g/m^2	83.7 ± 27.1	88.8 ± 26.2	0.005	80.8 ± 24.7	90.3 ± 24.7	<0.001	87.3 ± 30.2	87.0 ± 28.6	0.91
LV end-diastolic volume, mL	155.8 ± 55.1	165.3 ± 49.6	0.04	167.5 ± 58.7	182.0 ± 54.5	0.03	141.5 ± 48.2	145.0 ± 34.2	0.61
LV end-systolic volume, mL	51.3 ± 27.6	55.4 ± 27.1	0.12	57.2 ± 31.7	63.5 ± 32.8	0.10	44.1 ± 20.0	45.5 ± 13.0	0.70
LV ejection fraction, %	67.9 ± 7.8	67.1 ± 7.2	0.52	66.7 ± 8.1	66.1 ± 7.4	0.66	69.2 ± 7.6	68.4 ± 7.0	0.65
LV cardiac output, L/min	6.9 ± 2.1	7.5 ± 2.0	0.02	7.2 ± 1.9	8.2 ± 1.9	0.007	6.5 ± 2.2	6.8 ± 1.8	0.61

LV cardiac index, L/min/m^2	3.8 ± 1.1	4.2 ± 1.1	0.009	3.9 ± 1.0	4.5 ± 1.2	0.002	3.6 ± 1.1	3.8 ± 0.9	0.53
LV global longitudinal strain, %	-15.3 ± 2.3	-15.7 ± 2.5	0.21	-15.9 ± 1.9	-16.0 ± 2.0	0.93	-14.5 ± 2.6	-15.2 ± 3.1	0.04
LA volume, mL	85.9 ± 40.1	93.4 ± 34.7	0.10	86.6 ± 43.3	99.3 ± 37.8	0.05	84.9 ± 37.0	86.2 ± 30.1	0.85
LA volume index, mL/m^2	46.9 ± 21.0	52.1 ± 20.0	0.04	46.6 ± 21.9	54.5 ± 19.9	0.03	47.3 ± 20.6	49.2 ± 20.4	0.59
Septal thickness, mm	9.0 ± 2.9	8.5 ± 2.9	0.33	8.5 ± 2.9	7.8 ± 3.0	0.23	9.5 ± 2.9	9.5 ± 2.6	0.90
Body weight, kg	74.7 ± 16.7	73.3 ± 15.2	0.74	75.3 ± 17.2	73.6 ± 15.2	0.76	73.9 ± 16.7	73 ± 15.7	0.89
Systolic BP, mmHg	154.3 ± 29.8	147 ± 30.0	0.35	149.8 ± 24.0	146.2 ± 21.1	0.64	160.1 ± 36.3	148.2 ± 39.7	0.43
Diastolic BP, mmHg	76.3 ± 13.9	69.4 ± 10.5	0.03	77.3 ± 14.9	70.2 ± 12.2	0.14	74.9 ± 12.9	68.4 ± 8.0	0.13
Hematocrit, %	32.7 ± 5.2	32.4 ± 4.3	0.85	32.0 ± 4.5	31.5 ± 4.0	0.70	33.4 ± 5.9	33.6 ± 4.5	0.93
Serum creatinine, μmol/L[#]	458 ± 127	487 ± 161	0.53	486 ± 140	521 ± 180	0.57	394 ± 56	408 ± 53	0.65
Estimated GFR, mL/min/1.73m^2[#]	11.5 ± 2.6	10.3 ± 4.0	0.25	11.1 ± 2.3	9.5 ± 4.3	0.26	12.6 ± 3.0	11.9 ± 2.6	0.71
NT-proBNP,	2,390 ±	3,114	0.08	1,647 ±	3,174	0.02	2,948 ±	3,069	0.82

pg/mL	2,513	± 2.360		1,401	± 2,439		3,043	± 2,408	
hs-cTnI, pg/mL[§]	13.1 (8.1-18.2)	12.0 (7.8-16.1)	0.36	12.4 (3.1-21.8)	12.7 (5.9-19.5)	0.89	13.7 (6.7-20.6)	11.4 (5.3-17.5)	0.21

AVF, arteriovenous fistula; LA, left atrial; LV, left ventricular; BP, blood pressure; GFR, glomerular filtration rate calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) formula; NT-proBNP, N-Terminal-pro B-type Natriuretic Peptide; hs-cTnI, high-sensitivity cardiac Troponin I

*Plus-minus values are mean ± SD

[#]Includes 23 non-dialysis participants

Table 7-2 Summary of changes in cardiac magnetic resonance–derived cardiac indexes, clinical and laboratory parameters.

Summary of changes from baseline to 6 weeks in the overall population and in AVF blood flow subgroups

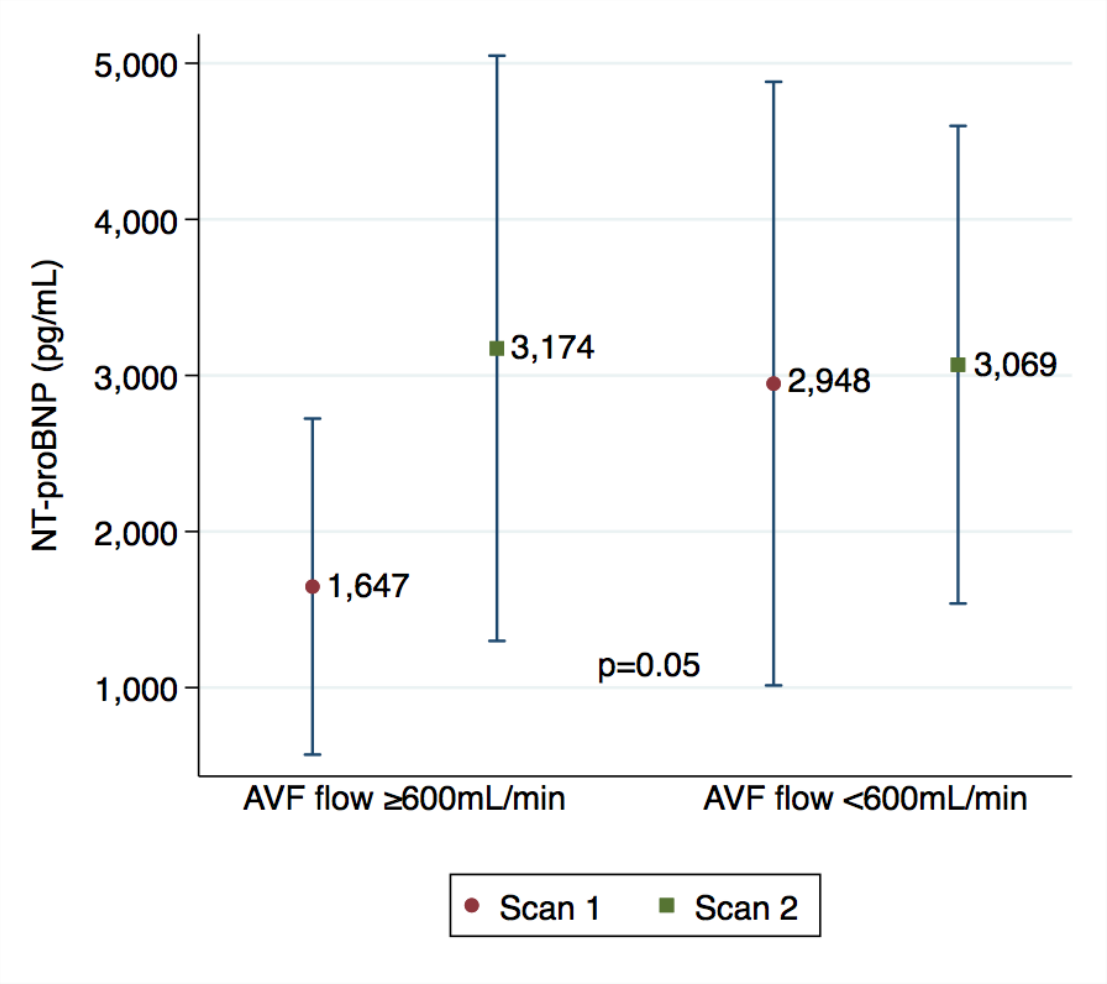


Figure 7-4 Changes of N-terminal-pro B-type natriuretic peptide (NT-proBNP) between the high and low AVF flow groups.

Effect of arteriovenous fistula (AVF) creation on NT-proBNP levels. Changes in the blood NT-proBNP levels (picograms per millilitre) performed at the time of cardiac magnetic resonance scans according to the brachial artery blood flows (≥600 mL/min vs <600 mL/min), showing a significant increase in the higher flow group compared with the lower flow AVF group (p=0.05).

7.4 Discussion

We have examined the immediate effect of AVF surgery in patients with advanced CKD using gold standard CMR-derived LV mass. There was a substantial increase in LV mass observed on the second CMR scan after AVF surgery. The effect was proportional to the blood flow of the AVF, with a significant increase in CMR-derived LV mass in the high flow compared with a small decrease in the low flow group.

The haemodynamic effects of a left-to-right shunt have been well described (Abassi et al., 2003; GUYTON & SAGAWA, 1961; MacRae et al., 2004). Vascular access blood flow is

necessary for dialysis adequacy and small solute clearance. On the one hand, low blood flow is indicative of access dysfunction; on the other hand, high blood flow is associated with increased cardiac output and high-output cardiac failure, especially in patients with pre-existing cardiac disease. A 6-fold increase in mean blood flow is observed on the AVF side compared with the contralateral side (Girerd et al., 1996). It has been advocated that cardiac adaptations occur gradually following surgery relative to the increase in AVF blood flow. However, data show that the mean brachial artery flow increases from 56 mL/min before to 365 ml/min 1 day after and to 720 ml/min 28 days after the creation of an AVF (Lomonte et al., 2005). The novel finding of our prospective study is the demonstration of early changes in cardiac indexes, where 4.8% increase in LV mass occurred after an average time of 6.4 weeks post-AVF creation. Notably, the change was more prominent in AVF with blood flows exceeding 600 mL/min, where an increase of 10.2% in LV mass was observed.

In a prospective short-term echocardiographic study, a significant increase in cardiac output (15%), LV end-diastolic diameter (4%), and fractional shortening (8%) occurred 14 days after the creation of an AVF(Iwashima et al., 2002). Other echocardiographic studies have demonstrated the potential for increased LV mass and LV dilatation following AVF-creation (Iwashima et al., 2002; Ori et al., 2002). In another prospective study of 24 patients with stage 5 CKD undergoing AVF creation, CMR was undertaken at baseline, and 6 months following AVF creation. At follow up, LV mass was increased by 12.7%, mean cardiac output by 25%, LV end-systolic volumes by 21%, and LA area by 11%. In our study, LV end-diastolic volume was increased by 6.1%, cardiac output by 8.7%, and LA volume index by 11.1% (Dundon et al., 2014) six weeks following AVF creation showing that changes in cardiac structure occur early after AVF creation.

As demonstrated by our study, elective AVF surgery is associated with adaptive cardiac remodeling, necessary to accommodate the increase in cardiac output sufficient to service the fistula, whilst maintaining systemic blood supply. Maladaptive cardiac remodeling and, in particular, increased LV mass is an independent predictor of adverse cardiovascular events and has been used extensively as a surrogate end point. Both eccentric and concentric patterns of LV hypertrophy carry prognostic implications in a number of disease states (Paoletti et al., 2005; Velagaleti et al., 2014). In a prospective study of 96 patients with AVF (65 with lower and 31 with upper arm AVFs), blood flow exceeding 2 L/min was predictive of heart failure (Basile et al., 2008). Left ventricular hypertrophy, dilatation,

and dysfunction are negative prognostic factors in ESRD patients commencing dialysis (Parfrey et al., 1996). On the contrary, London et. al have demonstrated a prognostic benefit of therapeutic interventions that successfully reduce LV mass by at least 10% in ESRD patients. These were associated with a 22% reduction in all-cause mortality and a 28% reduction in cardiovascular event-free survival (London et al., 2001).

The accuracy and reproducibility of 3D techniques, such as CMR, to reliably identify small changes in LV mass, such as were seen in this study has been shown in previous clinical trials and ex vivo studies. CMR has been used in clinical trials to identify very small differences in LV mass between groups: differences between 7 to 11 g/m^2 in LV mass have been shown in studies with 15 to 40 subjects per group (Gaudio et al., 1998; Johnson et al., 1997; Myerson et al., 2001). The accuracy of CMR measurements of LV mass has been validated using post-mortem human hearts, imaged ex vivo, which showed excellent agreement between the CMR-obtained and true LV masses, with SD of the difference of 8 g (95% CI, 15 g) (Katz et al., 1988) and a mean bias between 3D-CMR and pathology measures for LV mass of -16 g (Farber et al., 2014).

This prospective observational study, using the gold standard imaging modality (CMR) for evaluation of cardiac structure and function, demonstrates that AVF creation causes an increase in LV mass. Because of the short interval between the scans (median 8.3 weeks), the increase in LV mass observed is unlikely to be resulting from worsening of uraemia, plasma volume overload or changes in haematocrit and in fact serum creatinine, body weight and haematocrit did not change significantly between the scans. The clinical implications of this abrupt increment in LV mass within weeks after shunt surgery are not known. Nonetheless, there was an increase in NT-proBNP and high-sensitivity Troponin I in subjects following AVF surgery, although the magnitude of the change was not significant. But the significant increase in brain natriuretic peptide in the high AVF flow group argues for a physiological deleterious impact of the procedure. In addition, the minimal changes in LV mass, NT-proBNP and high-sensitivity Troponin I in the low AVF flow group are physiologically plausible and further strengthen our findings.

Brain natriuretic peptide and its inactive N-terminal fragment have been studied extensively in patients with heart failure, and both markers have been shown to be strong predictors of morbidity and mortality (de Lemos et al., 2003; Kragelund et al., 2005). They are thought to be secreted in greater quantities in response to increases in myocardial wall

stretch (Wang et al., 2005). Population-based studies suggest that plasma levels of brain natriuretic peptide and NT-proBNP are useful screening tests for heart failure and asymptomatic LV dysfunction (Iwashima et al., 2002). Similarly, in patients with CKD, high-sensitivity Troponin T was strongly associated with alterations of LV structure and diastolic dysfunction, regardless of eGFR strata (Kang et al., 2019). In a study of multiple biomarker monitoring in ESRD patients, increased plasma hs-CRP, Troponin T, and Troponin I were all independently predictive of subsequent death (Apple et al., 2004). The combination of an increase in cardiac biomarkers and cardiac structural changes suggests that observed changes could translate into clinical outcomes.

These results potentially have significant implications for the management of cardiovascular risk in CKD, given that AVF creation, which is the cornerstone of haemodialysis treatment, has the potential to provide substantial cardiovascular risks. This is particularly important for CKD patients with underlying cardiovascular disease. In addition, when AVF is compared to other types of access to the circulation, such as CVC, cardiovascular end-points are rarely used as surrogate outcomes, and the focus is on patency and infection outcomes.

The strengths of this study include a prospective consecutive design, use of a gold standard cardiac imaging modality, and a study group that represents the typical CKD population referred for AVF creation. The study limitations include a limitation in power to detect clinically significant differences in cardiovascular events and patient survival. Due to time constrains, the right heart was not assessed, but the study was adequately powered to examine LV mass, which was our primary outcome. To build on this study, a larger-scale multicenter study powered for clinical outcomes for cardiovascular morbidity and mortality is warranted.

7.5 Conclusions

This study shows that AVF creation is associated with a significant increase in CMR-derived LV myocardial mass. Furthermore, surgical AVF creation is associated with increments in cardiac chamber dimensions and an increase in NT-proBNP and high-sensitivity Troponin I levels. The changes are more pronounced in high blood flow arteriovenous fistulas. Because these surrogate markers are strongly associated with

important clinical outcomes, these data support further investigation of the impact of routine AVF creation in CKD patients on clinical outcomes.

Chapter 8. DISCUSSION

8.1 Principle findings

8.1.1 FeMRA vs CTA for assessment of kidney transplant candidates

The usually employed methods for non-invasive vascular imaging using MRI or CT carry potential risks for kidney disease patients. Computed tomography angiography requires radiation and nephrotoxic iodinated contrast, which may precipitate significant worsening of renal function and even prompt the need for institution of dialysis. Magnetic resonance angiography in patients with advanced CKD using linear chelate gadolinium-based contrast agents has been associated with the rare disease 'nephrogenic systemic fibrosis'. To overcome challenges in evaluation of the iliac vasculature prior to kidney transplantation with currently used imaging techniques, we assessed the clinical utility of ferumoxytol-enhanced magnetic resonance angiography.

In a prospective study of 36 kidney transplant candidates, 216 vascular cross-sections were examined with FeMRA and CTA. FeMRA was compared with CTA for assessment of arterial and vein diameter, calcification, and signal. FeMRA showed excellent intra- and inter-reader repeatability (ICC 0.79 – 0.99) for arterial and vein diameter, calcification and signal intensity. Between FeMRA and CTA there were no significant differences in arterial diameter and calcification (-0.36 – 0.89 mm and -0.05 – 0.06 mm^2, respectively), but vein diameter differed (1.53 – 2.44 mm, p <0.001) due to poor venous enhancement with CTA. In a separate analysis, two transplant surgeons identified vein abnormalities in 11% of patients with FeMRA.

Ferumoxytol-enhanced MR angiography was comparable to CT angiography for evaluating arterial lumen and calcification and offered improved venous depiction. The value of FeMRA in identifying under-recognised venous disease is essential in preoperative planning, especially in patients with prior abdominal or pelvic surgery, transplant procedures, venous thromboembolic events, or venous dialysis catheters.

Ferumoxytol-enhanced MR angiography may complement CTA or other non-invasive imaging studies used for evaluation of the vasculature in CKD patients with PAD considered for kidney transplantation. Its applicability in predialysis patients fills unmet

clinical needs and ferumoxytol's favorable pharmacokinetics offer a safe and robust technique decisive to timely transplant listing.

8.1.2 Ferumoxytol MR angiography vs Duplex ultrasound for vascular mapping before arteriovenous fistula surgery for haemodialysis

Preoperative mapping of arm vessels is essential for creating permanent haemodialysis access and used for both arterial and venous evaluation to optimise AVF placement for avoiding unsuccessful surgery. Duplex ultrasound is performed routinely for vascular mapping prior to AVF creation but cannot visualise the central vasculature. Contrast-enhanced MR angiography provides excellent visualisation of both central and upper extremity vessels but entails the risk of nephrogenic systemic fibrosis in advanced CKD. Ferumoxytol has been increasingly used for MR angiography, particularly for patients with CKD. To minimise unnecessary surgical procedures, the clinical utility of ferumoxytol-enhanced MR angiography for pre-operative vascular mapping was assessed using anatomical parameters predictive of fistula outcome.

In a prospective study of 59 (mean age 59 years) CKD patients, FeMRA was compared with Duplex US to evaluate suitability for AVF surgery. Fifty-one AVF were created. FeMRA showed excellent inter- and intra-reader repeatability (interclass correlation coefficients 0.84 - 0.99). In addition to identifying 15 central vasculature stenoses, FeMRA characterised 37% of the arterial sections examined as unsuitable for AVF creation compared to 26% with Duplex US ($p = 0.01$). Prediction models of AVF outcome were created based on an algorithm relying on mapping findings. On multivariable regression analyses FeMRA mapping independently predicted AVF success in models including [OR: 6.49 (95% CI 1.70-24.79); $p = 0.006$] and excluding information on the central vasculature [OR: 4.58 (95% CI 1.25-16.83); $p = 0.02$].

Ferumoxytol-enhanced MR angiography is fast, operator-independent, reliable in the detection of central vein stenosis, and more accurate for visualisation of the arm vessels compared with Duplex ultrasound. FeMRA promises to set a new standard for non-invasive, high-resolution arterial and venous imaging, provides a viable option for selected patients in whom advanced imaging beyond Duplex US is required and can minimise unnecessary surgical procedures.

8.1.3 Effects of haemodialysis arteriovenous fistula creation on cardiac structure and function

Arteriovenous fistula is considered the preferred type of access for maintenance haemodialysis. The creation of an AVF may contribute to maladaptive cardiovascular remodelling. We conducted a study to evaluate the effect of AVF creation on cardiac structure and function in patients with ESRD.

In this prospective cohort study, patients with ESRD listed for AVF creation underwent cardiac magnetic resonance imaging at baseline and at 6 weeks. All participants had ultrasound measurements of brachial artery blood flow at 6 weeks. The primary outcome was the change in LV mass. Secondary outcomes included changes in LV volumes, left atrial volume, LV ejection fraction, LV global longitudinal strain, cardiac output/index, septal thickness, NT-proBNP and high-sensitivity Troponin I.

A total of 65 patients were enrolled, of whom 40 had an AVF creation and completed both scans. The median time from AVF surgery to the second CMR scan was 6.4 weeks (interquartile range, 5.8–6.9 weeks). Patients were divided into two groups based on AVF blood flows: 22 in the high flow group (≥ 600mL/min) and 18 in the low flow group (< 600mL/min). On the second cardiac magnetic resonance scan, a mean increase of 7.4 g (95% CI, 1.1–13.7, P=0.02) was observed in LV mass; in the high flow group the mean increase was 15.5 g (95% CI, 7.3–23.8) compared with a small decrease of 2.5 g (95% CI, −10.6 to 5.6) in the low flow group ($p = 0.003$). Significant increases in LV end-diastolic volumes, cardiac output, and cardiac index were also seen after AVF creation ($p < 0.04$). No significant changes were observed in LV ejection fraction ($p = 0.52$), LV end-systolic volumes ($p = 0.12$), LV global longitudinal strain ($p = 0.21$), NT-proBNP ($p = 0.12$) and high-sensitivity Troponin I ($p = 0.29$).

Creation of AVF in adults with ESRD resulted in significant increase of LV myocardial mass and increments in cardiac chamber dimensions 6 weeks after surgery. The changes were more pronounced in high blood flow arteriovenous fistulas. These data support further investigation of the impact of routine AVF creation in CKD patients on clinical outcomes.

8.2 Limitations and criticism

8.2.1 Ferumoxytol use in clinical practice and cost

There are limitations pertaining to translation of our study protocols to clinical practice. Ferumoxytol was approved for parenteral treatment of iron deficiency anaemia in patients with CKD in June 2009 and in February 2018, a broad label was granted across all conditions associated with lack of iron in adults who were intolerant of or had an inadequate response to oral iron. However, it is not yet licensed as a contrast agent for MRI and it is only used off-label by clinicians and researchers for a wide range of applications.

Emerging issues with trace gadolinium retention in biologic tissues (Radbruch et al., 2015; United States Food and Drug Administration, September 8, 2017) have given rise to new controversies about the use of GBCAs in MRI and have generated calls for new contrast agent classes. To date, a growing number of imaging studies with ferumoxytol are underway. In addition, a wide range of iron-based USPIOs have been investigated in many biological applications, both in vitro and in vivo, however most of them are pre-clinical imaging agents used for animal studies.

Costing remains a major obstacle and ferumoxytol's current commercial price (approximately $700 per 17 mL vial compared to less than $100 per vial for GBCAs) is not realistic for a routine deployment, limiting translation of our study protocol to clinical practice. Also it is recommended than once a vial is opened, this should be used immediately or alternatively stored at controlled room temperature (25 °C ± 2 °C) for up to 4 hours or refrigerated (2-8 °C) for up to 48 hours. This is because ferumoxytol does not contain antimicrobial preservatives. In practice, the unused portion of each vial is discarded. For an average 70 kg individual, a dose equivalent to 210 mg is required for diagnosis, which translates in wastage of > 50% of the remaining contrast. It is anticipated that when ferumoxytol is licensed as a contrast agent, the cost of each vial will be substantially less than its current price for therapeutic use.

Moreover, our scans were performed on a 3.0 T research MRI scanner and translation of our protocols to 1.5 T needs to be studied. But other studies have shown that ferumoxytol-enhanced MRI is feasible at both 1.5 T and 3 T with refinements to echo-time acquisition, post-processing and analysis techniques to ensure reliable and robust quantification of tissue enhancement (Knobloch et al., 2018; Stirrat et al., 2016).

8.2.2 Ferumoxytol administration

We administered diluted ferumoxytol as an intravenous infusion over a minimum of 15 minutes, and applied haemodynamic monitoring up to 30 minutes after infusion to comply with FDA recommendations. This is in contrast to the originally advocated bolus injection over 17 seconds to avoid potentially life-threatening allergic reactions. All images in our studies were acquired in steady state (i.e. after all contrast has been delivered). Although there is no evidence that small bolus injections carry a higher risk of adverse events, rapid injection of ferumoxytol is not currently recommended by the FDA.

Given the recommendations for slow administration of the agent, its use as a contrast agent may be impractical in clinical practice. However due to ferumoxytol's delayed extravasation it can be given before the patient is transferred to the MRI suite or whilst in the MRI waiting room. In addition, slow infusion is not ideal for arterial phase dynamic imaging. We should note here that while slow infusion is applicable for the therapeutic dose of 510mg (approximately 7 mg/kg for a 70 kg adult), the prorated infusion time for the diagnostic dose of 3 mg/kg would be about 6.5 minutes, while still staying within the recommended FDA limits. This is supported by data from a multicenter safety report on diagnostic use of ferumoxytol in MRI from 11 institutions worldwide (including our center), which demonstrated no serious adverse events and few (< 2%) minor adverse reactions following 4,240 ferumoxytol injections using various infusion rates (from < 0.6 to 45 mg of iron per second) (Nguyen et al., 2019b). In addition, there was paucity of adverse events in our preliminary studies, where faster divided controlled infusions (aliquots) were administered until the maximum dose of 4 mg/kg was delivered (Stoumpos, Hennessy, et al., 2019b). The infusion time for each aliquot ranged from 6 to 18 seconds (depending on body weight and volume of the infusion) and was delivered with a minimum interval of 5 minutes between them to comply with the FDA recommendations.

Lastly, we have examined dose based upon body weight; however, theoretically, the dose should be based upon the patient's intravascular blood volume, which does not linearly increase with body weight; hence, a relatively lower dose may be appropriate for larger patients.

8.2.3 Participants and recruitment

Our studies were performed in a single center reflecting local referring patterns and practices; nevertheless the inclusion and classification criteria we have used (for instance to create our predictive models or to ascertain specific outcomes) are universally acceptable and in agreement with national and international guidelines.

The sample sizes in our studies were relatively modest with respect to absolute participant numbers, but for all our analyses we used multiple vascular sections assessed by different imaging techniques and readers. This generated large datasets and improved the power of our studies. Also we have used a sequential design to eliminate variations in demographic and clinical factors and detect changes in signal after studying relatively small sets of patients.

8.2.4 Ferumoxytol-enhanced venography for assessment of kidney transplant candidates

Non-contrasted CT offers a cost-effective assessment of excessive calcification, which is a primary surgical factor excluding a candidate for transplant and it could be argued that angiographic studies are not necessary for pre-transplant assessment. Also, conventional CT venography was not performed, which limits the comparison between FeMRA and CT venography when CT, the standard comparator, does not provide adequate opacification.

Performing comprehensive aortoiliac imaging in this group of patients is challenging and to date no modality is perfect. It is true that non-contrast CT is accepted for assessment of arterial calcification, however non-contrast CT does not provide adequate luminal assessment of arterial or venous structures. CT venography is not used routinely in evaluation of kidney transplant candidates and most published CT venography protocols require significantly higher doses of contrast than that required purely for arterial assessment, which is a clear problem in patients in whom residual renal function could be compromised. Furthermore, the timing of optimal CT venography for the iliac veins is difficult to predict such that multiphase examinations may be required with a radiation dose penalty for each. On the contrary, ferumoxytol-enhanced MR venography is part of ferumoxytol’s inherent properties and does not require additional time in the scanner, higher doses of contrast or complex angiographic protocols.

8.3 Future directions and applications

Ultrasmall superparamagnetic iron oxide nanoparticles have been used for clinical imaging for more than 20 years (Jung & Jacobs, 1995; Ros et al., 1995; Stark et al., 1988). With its unique pharmacological, metabolic and imaging properties, and favorable safety profile ferumoxytol may play a crucial role in future MR imaging, especially in patients with impaired renal function. Initially, ferumoxytol was developed as an MRI contrast agent due to its effectiveness in shortening T1 and T2 relaxation times. Licensing the drug as a therapeutic iron supplement was likely a strategic decision but this compound still holds great potential as an MRI contrast agent. Satisfactory contrast-enhanced imaging can be performed with doses lower than 1 mg/kg and as high as a 510 mg total dose.

Ferumoxytol provides long-lasting blood pool enhancement, which can be used for any MRI examination that requires detailed and/or long-lasting vessel delineation such as MR angiographies, tissue perfusion studies, and whole-body tumor staging with MR and positron emission tomography/MR imaging. There are three district intravascular phases of ferumoxytol; the dynamic, the blood pool, and the delayed phase, all serving different image acquisition protocols.

The arterial or venous dynamic phase is appropriate for dynamic susceptibility contrast perfusion imaging in the brain (Gahramanov et al., 2013), cardiovascular and peripheral vascular investigations. Ferumoxytol has been used in various vascular beds, and recently there is a growing interest for use of dynamic imaging in assessment of the coronary arteries in patients with an eGFR <30mL/min (NCT02954510). The blood pool phase is suitable for identification of tumours (Christen et al., 2013) and steady state angiography of the peripheral vessels. The delayed phase of the contrast is useful for early recognition of brain lesions and nodal metastases. In early brain lesions, slow leakage of ferumoxytol through the disrupted blood-brain barrier results in MRI signal changes, which are peaking around 24 hours after ferumoxytol administration (Neuwelt et al., 2007). Intracellular uptake of ferumoxytol in abdominal organs, lymph nodes and vascular walls can be used to effectively delineate pathology in these areas (Harisinghani et al., 2007; Hedgire et al., 2014).

More specifically, ferumoxytol can be useful for early recognition of nodal disease and efficacy of cancer therapies. Iron oxide particles are taken up by and retained in normal

lymph nodes, resulting in signal loss on T2- and T2*- weighted images (Anzai et al., 2003). When nodes are infiltrated with malignant cells, nodal ferumoxytol uptake capacity reduces and malignant nodes retain high signal intensity on T2*-weighted images. Optimal node T2*-weighted imaging contrast with ferumoxytol can be achieved 24 – 48 hours post-injection. Ferumoxytol is slowly phagocytosed by macrophages in the reticuloendothelial system, making them ideal for MR imaging detection of tumors in the liver, spleen, lymph nodes, and bone marrow. Similarly, ferumoxytol is slowly phagocytosed by tumor-associated macrophages in the tumor microenvironment; this could be leveraged to grade tumor associated inflammation and monitor the efficacy of new cancer immunotherapies.

Since ferumoxytol is taken up by the macrophages, it has the potential to serve as a tool for measuring macrophage dysfunction. Quantitative measures of macrophage function, as estimated from dynamic imaging of ferumoxytol uptake in the kidney, may prove to be useful predictors of graft dysfunction and rejection. In a study of paediatric kidney allograft recipients, allografts undergoing acute rejection showed prolonged T2* values on ferumoxytol-enhanced MR images (Aghighi et al., 2018). This can be explained by glomerular vasospasm, reduced perfusion, and oedema of rejecting allografts as compared to non-rejecting allografts, which leads to diminished ferumoxytol perfusion.

Focal inflammation is one of the major applications of ferumoxytol. By labelling macrophages with ferumoxytol in vivo, macrophage trafficking can be detected and inflammatory lesions can be localised (Hasan et al., 2012; Wagner et al., 2013). Ferumoxytol-enhanced MRI is promising for assessing rheumatologic diseases, differentiating acute from chronic inflammatory kidney disease (Budjan et al., 2016; Neuwelt et al., 2017), diagnosing osteomyelitis in the feet of patients with diabetes (Neuwelt et al., 2017) as well as detecting the activity of Crohn’s disease (Moy et al., 2016).

Ferumoxytol can be used for tissue perfusion studies, where measurement of the blood volume in tissues can carry important information about the level of vascularisation. Small molecular weight contrast agents can only estimate blood volume using dynamic first pass technique. But intravascular contrast agents allow measuring the blood volume using the steady state technique, by calculating signal differences between pre- and post-contrast (intravascular) images. This has the benefit of high spatial resolution, since no rapid acquisition is necessary.

8.4 Conclusions

Ferumoxytol-enhanced MR angiography was established as a robust method for vascular mapping of patients with advanced CKD, with similar or higher yield compared with the currently employed imaging techniques. Ferumoxytol-enhanced MR angiography is fast, operator independent, reliable in imaging of the central and peripheral arterial and venous vasculature and has an established safety profile.

Publications containing work undertaken for this thesis

"Ferumoxytol MR angiography vs Duplex ultrasound for vascular mapping before arteriovenous fistula surgery for hemodialysis." **Sokratis Stoumpos,** Alfred Tan, Pauline Hall Barrientos, Karen Stevenson, Peter Thomson, Ram Kasthuri, Aleksandra Radjenovic, David Kingsmore, Giles Roditi, Patrick Mark. *Radiology.* (In Press).

"Ferumoxytol MR Angiography: A Novel Technique for Assessing Iliac Vasculature in Potential Kidney Transplant Recipients." **Stoumpos S,** Hall Barrientos P, Black DH, Stevenson K, Hennessy M, Vesey AT, Strauss W, Kasthuri R, Radjenovic A, Kingsmore DB, Roditi G, Mark PB. *JACC Cardiovasc Imaging.* 2020 May 8:S1936-878X(20)30268-0. doi: 10.1016/j.jcmg.2020.02.032.

"Multicenter Safety and Practice for Off-Label Diagnostic Use of Ferumoxytol in MRI." Nguyen KL, Yoshida T, Kathuria-Prakash N, Zaki IH, Varallyay CG, Semple SI, Saouaf R, Rigsby CK, **Stoumpos S,** Whitehead KK, Griffin LM, Saloner D, Hope MD, Prince MR, Fogel MA, Schiebler ML, Roditi GH, Radjenovic A, Newby DE, Neuwelt EA, Bashir MR, Hu P, Finn JP. *Radiology.* 2019 Dec;293(3):554-564. doi: 10.1148/radiol.2019190477.

"Should We Ligate Arteriovenous Fistulas in Asymptomatic Patients After Kidney Transplantation?" **Stoumpos S,** Mark PB. *Circulation.* 2019 Jun 18;139(25):2819-2821. doi: 10.1161/CIRCULATIONAHA.119.040361.

"Ferumoxytol magnetic resonance angiography: a dose-finding study in patients with chronic kidney disease." **Stoumpos S,** Hennessy M, Vesey AT, Radjenovic A, Kasthuri R, Kingsmore DB, Mark PB, Roditi G. *Eur Radiol.* 2019 Jul;29(7):3543-3552. doi: 10.1007/s00330-019-06137-4.

"Ferumoxytol-enhanced magnetic resonance angiography for the assessment of potential kidney transplant recipients." **Stoumpos S,** Hennessy M, Vesey AT, Radjenovic A, Kasthuri R, Kingsmore DB, Mark PB, Roditi G. *Eur Radiol.* 2018 Jan;28(1):115-123. doi: 10.1007/s00330-017-4934-5.

Presentations to learned societies, of work undertaken for this thesis

"Ferumoxytol MR Angiography vs. Doppler Ultrasound for Vascular Mapping Before Hemodialysis Arteriovenous Fistula Creation." *2019 ASN Kidney Week*, Washington, DC, Nov 05-10, 2019, TH-OR139 (**Oral Presentation**, International Meeting)

"Ferumoxytol MR angiography: a novel imaging technique for the assessment of potential kidney transplant recipients." *19th ESOT Congress*, Copenhagen, Sep 15-18, 2019, Full Oral Presentation OS132 (**Oral Presentation**, International Meeting)

"Ferumoxytol MR Angiography vs Doppler US for vascular mapping before haemodialysis arteriovenous creation." *31st SMRA Annual Conference*, Nantes, Aug 28-30, 2019, Free Communication (**Oral Presentation**, International Meeting)

"Ferumoxytol MR angiography vs CT angiography for the assessment of potential kidney transplant recipients." *56th ERA-EDTA Congress*, Budapest, Jun 13-16, 2019, Free Communication FO039 (**Oral Presentation**, International Meeting)

"Ferumoxytol MR angiography vs Doppler US for vascular mapping before haemodialysis AVF creation." *56th ERA-EDTA Congress*, Budapest, Jun 13-16, 2019, Free Communication FO019 (**Oral Presentation**, International Meeting)

"Ferumoxytol-Enhanced MR Angiography (FeMRA) vs CT Angiography (CTA) for the Assessment of Potential Kidney Transplant Recipients." *2018 ASN Kidney Week*, San Diego, California, Oct 23-28, 2018, SA-PO093 (**Poster Presentation**, International Meeting)

"CT angiography (CTA) vs ferumoxytol-enhanced MR angiography (FeMRA) for the assessment of potential kidney transplant recipients." *30th SMRA Annual Conference*, Glasgow, Aug 29-31, 2018, A80 (**Oral Presentation**, International Meeting)

"Safety profile of ferumoxytol as contrast for MR angiography in patients with chronic kidney disease." *30th SMRA Annual Conference*, Glasgow, Aug 29-31, 2018, A27 (**Poster Presentation**, International Meeting)

“Ferumoxytol-enhanced magnetic resonance angiography (FeMRA) for the assessment of patients with complex anatomy due for vascular access creation.” *VASBI Annual Meeting 2017*, Belfast, Sep 28-29, 2017, Free Communication (**Oral Presentation**, National Meeting)

“Ferumoxytol-enhanced magnetic resonance angiography for the assessment of potential kidney transplant recipients.” *UK Kidney Week 17*, ACC Liverpool, Jun 19-21, 2017, PO-107 (**Poster Presentation**, National Meeting)

“Ferumoxytol-enhanced magnetic resonance angiography for the assessment of patients with complex anatomy due for vascular access creation.” *54th ERA-EDTA Congress*, Madrid, Jun 03-05, 2017, Free Communication MO050 (**Oral Presentation**, International Meeting)

“Ferumoxytol-enhanced magnetic resonance angiography for the assessment of potential kidney transplant recipients.” *54th ERA-EDTA Congress*, Madrid, Jun 03-05, 2017, MP817 (**Poster Presentation**, International Meeting)

“Ferumoxytol-enhanced MRA for the assessment of patients with complex anatomy due for vascular access creation.” *10th Congress of Vascular Access Society*, Ljubljana, Apr 05-08, 2017, Free Communication (**Oral Presentation**, International Meeting)

“Developing a new imaging service for renal failure patients with ferumoxytol-enhanced magnetic resonance angiography.” *Scottish Renal Association Meeting 2016*, Inverness, Oct 27-28, Free Communication (**Oral Presentation**, National Meeting)

Appendix 1

Participant Information Sheets

Participant Information Sheet (Pre-transplant assessment cohort)

Title of Study

Use of Ferumoxytol enhanced Magnetic Resonance Angiography for cardiovascular assessment in late-stage Chronic Kidney Disease: The **FeMRA in CKD** study.

Name of Researcher

Chief Investigator: *Dr Sokratis Stoumpos*

Principal Investigators: *Dr Patrick Mark, Mr David Kingsmore, Dr Giles Roditi, Dr Alexandra Radjenovic*

Details of Study

You are being invited to participate in a clinical study at the Cardiovascular Research Centre, University of Glasgow. We have asked you to take part as your Consultant kidney specialist has recommended that you undergo a test called a CT angiogram as part of your preparation for potential kidney transplantation. This study will form part of a higher degree for Dr Stoumpos. Before you decide whether or not to take part it is important for you to understand why the research is being carried out and what it involves. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is unclear or if you would like more information. Take your time to decide whether or not you would like to take part.

Background

A large number of potential kidney transplant recipients with kidney failure have peripheral vascular disease. Peripheral vascular disease causes a narrowing of blood vessels that carry blood to the legs or organs such as the kidney. Doctors often need

to perform additional tests to visualise the vessels to help decide if a patient is suitable to receive a kidney transplant. A CT angiogram is a standard test that allows doctors to visualise the vessels of the aorta and leg vessels. A CT angiogram involves a contrast medium (sometimes known as a 'dye') being injected into the arm and the patient then lying on a bed which passes through a doughnut-shaped opening in a CT scanner. Using the contrast provides better images of the vessels. The images of the vessels allow doctors to view the exact anatomy of the vessels and the presence of calcifications (deposit of calcium salts). One of the problems with performing a CT angiogram is that the contrast used for CT angiography can sometimes harm the kidneys. Other methods to examine the blood vessels also have potential risks in patients with kidney problems.

In this study we aim to examine if an MRI angiogram using an alternative contrast agent provides better images than the routine CT angiogram.

Do I have to take part?

Participation in this study is entirely voluntary and you are free to refuse to take part or withdraw from the study at any time (without having to give a reason) and without this in any way affecting your future medical care or your relationship with medical staff looking after you. You should check that participation in this research does not affect any policy you might be thinking about taking out or any existing policy.

Impact on Insurance

Participation in this study might affect any insurance cover that you may have [for example, travel insurance, protection insurance (life insurance, income protection, critical illness cover) and private medical insurance] and you are advised to seek expert advice as to whether this will affect you.

What is involved in the study?

This study requires a single visit in hospital. **One MRI scan and one blood sample are required for your participation in the study** over and above your standard care procedures**.**

This study is a single-centre study conducted in NHS Greater Glasgow & Clyde. You will be given an alternative iron-based contrast agent called Ferumoxytol when you are having the MRI scan. Ferumoxytol was previously approved in the UK as a treatment for iron deficiency in patients with kidney failure. However, in 2015 the company responsible for manufacturing Ferumoxytol decided for commercial reasons to withdraw the medicine in the UK and Europe. Ferumoxytol is therefore only available in the UK as an unlicensed medicine. Ferumoxytol is still available in other countries such as Canada and the USA. The typical dose used in this study will be about 15-50% of that used for treatment of iron deficiency.

Before you are enrolled in the study the doctor will do a screening visit to check you are eligible for the study. A summary of the tests done is included in a diagram at the end of this information sheet.

Screening visit

This visit takes place at the same time and place as one of your planned outpatient visits. We will notify you in advance (usually by phone) before we meet you at the clinic. During this visit, the doctor assesses your suitability for the study.

At the screening visit the doctor will check your medical history, medications, allergies and body weight.

If you are eligible to participate in the study you will be asked to return for an MRI Scan - a special scan of your legs and heart. A blood sample will also be taken at the same time.

A CT angiogram of your aorta and legs will be performed as part of your routine preparation for potential kidney transplantation. This means you will have the CT angiogram scan irrespective of your participation in the study. This is to look at the arteries and veins in your legs and aids our decision on your suitability for, and the best site for placement of, a kidney graft. The results of this scan will be used for the study.

Study visit: MRI Scan

For the MRI scan you will receive an appointment either by telephone call, letter or e-mail and be sent directions to attend the Research MRI department which is located at the Neurosciences Building, Queen Elizabeth University Hospital in Glasgow. The scan will take place within two to four weeks after your written consent on a day and time that are convenient for you. If you are female and it is possible that you could be pregnant then a pregnancy test will be performed before you continue any further in

the study.

An MRI scan uses a powerful magnetic field and a computer to visualise the vessels. The magnetic field is not harmful but the MRI scan may not be suitable for you if you have any medical devices or metal in your body. Before your MRI scan you will meet one of the research team members who will check that you are still eligible to participate in the study and the radiographer, the person taking your scan, will go through a checklist to ensure that it is safe for you to be scanned.

With your consent, we will write to your GP informing them of your MRI safety status, as this information may be of benefit for your future health care needs.

You will then be asked to change into a gown for the scan. We will place an intravenous cannula (a small plastic tube, most usually into an arm vein) to infuse the contrast - this is no different from any other scan where contrast is used. A blood sample will be taken when the cannula is placed in your arm. Approximately 2 tablespoons (30ml) of blood will be collected. You will be asked to lie on the scanning table, which will then be moved into the centre of the scanner (the scanner is shaped like a big doughnut). During the scan, which takes around 45 minutes, you will be able to speak to the radiographer. The scan will take pictures of your body, particularly your heart and blood vessels. As the scan is noisy you will be wearing hearing protection and listen to the music of your preference if you wish. During the scan Ferumoxytol will be given into the vein in five small injections. Each injection will last up to 20 seconds followed by a break of at least 5 minutes during which time the scanner will collect the images. This method of giving Ferumoxytol is different compared to how Ferumoxytol is usually given. Each injection will be given a little faster than has been recommended when used for treatment of anaemia which means you will receive a higher peak of drug at each injection. We are doing this to obtain better quality pictures. This may increase slightly the risk of adverse reactions. However, the total dose will be less than used for the treatment of anaemia, delivered in total over a longer period and you will be very closely monitored during the infusions. At the time of preparation of this information sheet we have treated 58 patients at Queen Elizabeth University Hospital using the same Ferumoxytol regime and no patients have experienced any side effects. You will be monitored both during the scan and for at least 30 minutes following injection of the contrast. You will then be free to go home. You can drive if you do not feel drowsy or dizzy or if you prefer a taxi can be arranged to take you to and from the hospital. A specialist will examine

your study MRI scan at a later date but the results will not be known to your surgeon unless a major problem is identified.

The blood taken will be tested for a number of different biomarkers. With your permission a small amount of the blood taken will be stored for future ethically approved testing of novel biomarkers or gene expression i.e. the process by which information from a gene is used to direct protein synthesis. This sample will be anonymised and stored in the secure laboratory within BHF Cardiovascular Research Building. The results of any future tests would not be linked to your records and you would not receive any information about the results. **You can opt not to have this done without affecting your participation in the study.**

This visit should take no longer than one hour.

You may be asked if you are willing to have another MRI scan to look at your coronary arteries (the arteries supplying blood to your heart) as part of a sub-study. This will take place two to four hours after the first scan at the MRI scanner sited at the University of Glasgow. No additional contrast administration is required for this scan and it will take approximately 60 minutes to complete. If you agree to have the second scan, lunch and transport to the University site will be offered. **This extra scan is optional. You can opt not to have this done without affecting your participation in the study.**

Following the scan, no further study visits are required. With your permission data will be collected from your medical notes for up to 2 years to assess your kidney transplant function, if you eventually receive one.

If your capacity to consent is lost during the study, you will be withdrawn from the study but identifiable data or blood already collected with consent will be retained and used in the study.

Can I take part in this study if I am pregnant or breastfeeding?

If taken during pregnancy, Ferumoxytol may affect an unborn baby therefore it is important that you do not become pregnant during the study. You must not take part in the study if you are breastfeeding, pregnant, planning pregnancy or not using a reliable method of contraception. We will advise you about contraception before you decide if you wish to take part in the study and for how long contraception should continue after treatment with Ferumoxytol. A pregnancy test will be done prior to each MRI scan in all women who have the potential to become pregnant.

What are the discomforts, risks and side effects?

Cannulation: Placing a cannula (small plastic tube in the vein) can cause a little discomfort and can lead to some bruising. An experienced radiographer or doctor will perform this. The cannula will only be in place for an hour or so and be removed following the MRI scan, thus rendering negligible any potential complications relating to infection. Blood samples will be taken at the time of cannula insertion to avoid further venepuncture.

MRI scanning: This type of scan is very safe and does not use radiation. Some people, when being scanned, may feel a bit closed in but you will be in constant contact with the person performing the scan and you can come out at any time. The scanner is a bit noisy but you will be given ear protection which also plays music.

Ferumoxytol: Like many drugs in some instance, serious complications, such as anaphylaxis might occur when using Ferumoxytol. Anaphylaxis is a severe, potentially life-threatening allergic reaction. The rate of anaphylaxis is roughly 1 in 10,000, and death can occur in 1 in 50,000. Patients who have received Ferumoxytol have died despite immediate medical care and attempts to revive them. 4 in 100 people taking this drug may show symptoms associated with allergy (e.g. skin reactions, rash, wheezing), and 2 in 100 may develop low blood pressure.

It is important to know that the side effects of Ferumoxytol (including death) have occurred under different conditions than proposed for this study. For example, they may have involved higher doses of Ferumoxytol, injection of more concentrated forms (we are using very dilute doses) and in patients with different diseases. Side effects observed in one clinical study of a drug may not accurately predict the side effects observed in other studies. However we do not know for certain if giving you Ferumoxytol like this may cause more, less or any side effects to occur or how severe those side effects might be. Reassuringly, the same regime is used in other centres around the world and no serious side effects have been reported in the literature so far, when Ferumoxytol is used for imaging.

You should not be given Ferumoxytol if you have a known allergy to it or any of its components, if you have a history of allergic reactions to any intravenous iron product, or if you have allergy to other drugs. If you tell us that you have any conditions associated with iron overload (e.g. haemochromatosis, chronic liver disease, or blood disorders requiring frequent blood transfusions), we will not administer Ferumoxytol because it might result in excess iron in the body.

All CT and MRI scans with contrast injections are performed in facilities with trained staff and equipment to treat any reactions to contrast administration immediately, and you will be carefully monitored during and for at least 30 minutes after administration of Ferumoxytol to determine whether you might be having a reaction.
Common side effects (may affect up to 1 in 10 people) are bleeding, and pain or irritation at the injection site. Uncommon side effects (may affect up to 1 in 100 people) include dizziness, low blood pressure, feeling weak, tired or drowsy, skin rash, and stomach upset (feeling sick, vomiting, bloating or pain). If you feel tired or drowsy then you should not drive or use any tools or machinery until this has passed.

You will be provided with an Alert Card which you should carry with you at all times while you are participating in the study. Please show the Alert Card to any Health Care Professional including doctor, nurse or pharmacist, who is caring for you.

What are the benefits of taking part in the study?

The MRI scan will give us information about the anatomy and function of your heart and leg vessels. If the MRI scan reveals any significant new abnormality we will either discuss this with your kidney consultant or refer you to a specialist clinic (whichever seems most appropriate). Taking this into consideration, it is likely that a small number of participants may directly benefit from the study. In due course we hope that the results from this study may help us develop a new imaging technique, allowing better assessment in the future of the vessels in patients with kidney failure who are undergoing assessment for transplant listing like you.

What are my rights?

If you wish the results of the study can be made available to you or your GP when the study is complete.
Any complaint about the way you have been dealt with during the study or any possible harm you may suffer will be addressed. In the first instance you should talk to the investigator involved in your care. You can ask to speak to a senior member of the Cardiovascular Research Centre, University of Glasgow or contact the NHS Greater Glasgow and Clyde complaints service.

Phone: 0141 201 4500

E-mail: complaints@ggc.scot.nhs.uk

In the event that something goes wrong and you are harmed during the study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Glasgow or NHS Greater Glasgow and Clyde but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will the research influence the treatment I receive?

The research will not alter the regular treatments you receive.

Will my taking part in the study be kept confidential?

With your permission, identifiable information about you and data collected during the study will be held by the Cardiovascular Research Centre, University of Glasgow and NHS Greater Glasgow and Clyde. All data collected in this study will be coded and stored on a computer system protected by a password only available to the researchers. No one outside the research team will have access to any identifiable information and all identifiable information and data will be kept securely. Your data will be archived securely for at least five years after the end of study. With your permission, we will inform your GP of your participation in this study. It is a requirement of the regulators that your records in this study, together with any other relevant medical records, be made available for scrutiny by appropriate staff from NHS Greater Glasgow and Clyde, University of Glasgow (or their appointed third party) and the regulatory authorities.

Additionally there will be two sets of information obtained after you have had your MRI scan. One set will be the MRI scan images and the other, the research data obtained from those images. The MRI images obtained will be stored indefinitely using your name and unique hospital record number within the NHS clinical system and can be made available to specialist doctors for your future health care needs. Your research data will be stored using a unique study code which is non-identifiable and held on password protected University of Glasgow secure databases. Only

individuals directly involved with the study will have access to this information. Anonymised images obtained may be used for illustrating reports on the study and teaching.

Expenses

Taxi transport, or reasonable costs to cover your travel costs, will be provided for any extra visits to the hospital for the purposes of this study.

Who has reviewed this study?

This study has been reviewed by the North of Scotland Research Ethics Committee (2).

It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from The University of Glasgow, NHS Greater Glasgow and Clyde and by the Regulatory Authorities, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

If you are worried at any time about the research or wish to discuss things generally further, please do not hesitate to contact:

Dr Sokratis Stoumpos
Clinical Research Fellow
British Heart Foundation
Cardiovascular Research Centre
126 University Place
University of Glasgow
Glasgow G12 8TA
Tel: 0141 330 2079
E-mail – sstoumpos@nhs.net

Contact Numbers

If during the study you become unwell or are concerned, you can contact the study team during normal working hours on 0141 330 2079. If you are unwell and need urgent advice or assistance do not delay in seeking further advice or treatment as usual through the NHS services such as NHS24 or by contacting your GP who will

have received details of your participation in this study should you agree to them being informed.

Thank you for reading this information sheet and considering taking part in this study. If you would like more information or want to ask questions about the study please contact the study team on the number above.

What will happen to me during the study?

The following is the programme involved in this study. The screening visit will occur at one of your scheduled clinic appointments or hospital attendances as part of your routine care.

GROUP A		
STUDY VISIT	**Screening visit**	**Visit 1**
	At clinic after notification	2-4 weeks after consent
Informed consent	**X**	
Doctor check inclusion/exclusion criteria	**X**	
Demographics	**X**	
Medical history	**X**	
Medications	**X**	**X**
Allergies	**X**	**X**
Body weight		**X**
Pregnancy test (for women who may be pregnant)		**X**
FeMRA[#]		**X**
CTA*		**X**
[#]Only if eligible after screening *Standard clinical care		

Contact for further information

For further information about this study, please contact Dr Sokratis Stoumpos on 0141 330 2079. If you would like independent advice regarding this study you can

contact Dr Marie Freel, Consultant Physician, 0141 330 3412. She can be contacted at the above number and will be able to get back to you.

Finally thank you for taking the time to read this information leaflet and taking part in the study. If you wish to take part in the study you will be given a copy of this to keep and asked to sign a consent form.

Participant Information Sheet (Vascular access mapping cohort)

Title of Study

Use of Ferumoxytol enhanced Magnetic Resonance Angiography for cardiovascular assessment in late-stage Chronic Kidney Disease: The **FeMRA in CKD** study.

Name of Researcher

Chief Investigator: *Dr Sokratis Stoumpos*

Principal Investigators: *Dr Patrick Mark, Mr David Kingsmore, Dr Giles Roditi, Dr Alexandra Radjenovic*

Details of Study

You are being invited to participate in a clinical study at the Cardiovascular Research Centre, University of Glasgow. We have asked you to take part as your Consultant kidney specialist has recommended that you have a fistula created for dialysis in the near future. This study will form part of a higher degree for Dr Stoumpos. Before you decide whether or not to take part it is important for you to understand why the research is being carried out and what it involves. Please take time to read the following information carefully and discuss it with others if you wish. Please ask if there is anything that is unclear or if you would like more information. Take your time to decide whether or not you would like to take part.

Background

Fistulas created to be used for dialysis commonly fail. This means a large number of unnecessary surgical procedures. One of the problems is that we cannot predict which of the fistulas will develop adequately to be used for dialysis. We know though that nearly 100% of fistulas that present with failure have an anatomic problem of

some type, usually narrowing or blockage of the vessels. In this study we aim to find out if there are any anatomical predictors of poor fistula outcomes using new imaging techniques. As all current imaging methods used to visualise your blood vessels can be non-diagnostic or sometimes harm the kidneys, we would like to perform an angiogram called a MRI angiogram using an alternative contrast agent, which will be performed as part of the research.

Do I have to take part?

Participation in this study is entirely voluntary and you are free to refuse to take part or withdraw from the study at any time (without having to give a reason) and without this in any way affecting your future medical care or your relationship with medical staff looking after you. You should check that participation in this research does not affect any policy you might be thinking about taking out or any existing policy.

Impact on Insurance

Participation in this study might affect any insurance cover that you may have [for example, travel insurance, protection insurance (life insurance, income protection, critical illness cover) and private medical insurance] and you are advised to seek expert advice as to whether this will affect you.

What is involved in the study?

This study takes up to 6 weeks for you to complete and will only need two visits in hospital. **Two MRI scans and two blood samples are required for your participation in the study** over and above your standard care procedures**.**

This study is a single-centre study conducted in NHS Greater Glasgow & Clyde. You will be given an alternative iron-based contrast agent called Ferumoxytol when you are having the MRI scan. Ferumoxytol was previously approved in the UK as a treatment for iron deficiency in patients with kidney failure. However, in 2015 the company responsible for manufacturing Ferumoxytol decided for commercial reasons to withdraw the medicine in the UK and Europe. Ferumoxytol is therefore only available in the UK as an unlicensed medicine. Ferumoxytol is still available in

other countries such as Canada and the USA. The typical dose used in this study will be about 15-50% of that used for treatment of iron deficiency.

Before you are enrolled in the study the doctor will do a screening visit to check you are eligible for the study. A summary of the tests done is included in a diagram at the end of this information sheet.

Screening visit

This visit takes place at the same time and place as one of your planned outpatient visits. We will notify you in advance (usually by phone) before we meet you at the clinic. During this visit, the doctor assesses your suitability for the study.

At the screening visit the doctor will check your medical history, medications, allergies and body weight.

If you are eligible to participate in the study you will be asked to return for an MRI Scan - a special scan of your arms and heart – before your fistula is created. A second MRI will be performed 6 weeks after your fistula is created. Blood samples will be taken in both occasions.

An ultrasound scan of your arms (US vascular mapping) will be performed as part of your routine preparation for fistula creation. This means you will have the ultrasound scan irrespective of your participation in the study. This is to look at the arteries and veins in your arms and aids our decision on the best site for placement of a fistula. A second ultrasound scan of your fistula arm (similar to the first one) will be performed as part of your routine follow up 6 weeks after fistula creation. This means you will have the ultrasound scan irrespective of your participation in the study. This is to look if your fistula is growing sufficiently to be used for dialysis. The results of both scans will be used for the study.

Study visit 1: Baseline MRI Scan

For the MRI scan you will receive an appointment either by telephone call, letter or e-mail and be sent directions to attend the Research MRI department which is located at the Neurosciences Building, Queen Elizabeth University Hospital in Glasgow. The scan will take place within two weeks after your written consent and before you have your fistula created on a day and time that are convenient for you. If you are female and it is possible that you could be pregnant then a pregnancy test will be performed before you continue any further in the study.

An MRI scan uses a powerful magnetic field and a computer to visualise the vessels. The magnetic field is not harmful but the MRI scan may not be suitable for you if you

have any medical devices or metal in your body. Before your MRI scan you will meet one of the research team members who will check that you are still eligible to participate in the study and the radiographer, the person taking your scan, will go through a checklist to ensure that it is safe for you to be scanned.

With your consent, we will write to your GP informing them of your MRI safety status, as this information may be of benefit for your future health care needs.

You will then be asked to change into a gown for the scan. We will place an intravenous cannula (a small plastic tube, most usually into an arm vein) to infuse the contrast - this is no different from any other scan where contrast is used. A blood sample will be taken when the cannula is placed in your arm. Approximately 2 tablespoons (30ml) of blood will be collected. You will be asked to lie on the scanning table, which will then be moved into the centre of the scanner (the scanner is shaped like a big doughnut). During the scan, which takes around 45 minutes, you will be able to speak to the radiographer. The scan will take pictures of your body, particularly your heart and blood vessels. As the scan is noisy you will be wearing hearing protection and listen to the music of your preference if you wish. During the scan Ferumoxytol will be given into the vein in five small injections. Each injection will last up to 20 seconds followed by a break of at least 5 minutes during which time the scanner will collect the images. This method of giving Ferumoxytol is different compared to how Ferumoxytol is usually given. Each injection will be given a little faster than has been recommended when used for treatment of anaemia which means you will receive a higher peak of drug at each injection. We are doing this to obtain better quality pictures. This may increase slightly the risk of adverse reactions. However, the total dose will be less than used for the treatment of anaemia, delivered in total over a longer period and you will be very closely monitored during the infusions. At the time of preparation of this information sheet we have treated 58 patients at Queen Elizabeth University Hospital using the same Ferumoxytol regime and no patients have experienced any side effects. You will be monitored both during the scan and for at least 30 minutes following injection of the contrast. You will then be free to go home. You can drive if you do not feel drowsy or dizzy or if you prefer a taxi can be arranged to take you to and from the hospital. A specialist will examine your study MRI scan at a later date but the results will not be known to your surgeon unless a major problem is identified.

The blood taken will be tested for a number of different biomarkers. With your permission a small amount of the blood taken will be stored for future ethically approved testing of novel biomarkers or gene expression i.e. the process by which information from a gene is used to direct protein synthesis. This sample will be anonymised and stored in the secure laboratory within BHF Cardiovascular Research Building. The results of any future tests would not be linked to your records and you would not receive any information about the results. **You can opt not to have this done without affecting your participation in the study.**

This visit should take no longer than one hour.

You may be asked if you are willing to have another MRI scan to look at your coronary arteries (the arteries supplying blood to your heart) as part of a sub-study. This will take place two to four hours after the first scan at the MRI scanner sited at the University of Glasgow. No additional contrast administration is required for this scan and it will take approximately 60 minutes to complete. If you agree to have the second scan, lunch and transport to the University site will be offered. **This extra scan is optional. You can opt not to have this done without affecting your participation in the study.**

Study visit 2: 6-week MRI Scan

A repeat MRI scan of your fistula arm and your heart will be performed approximately 6 weeks after your fistula is created. A blood sample will be taken when the intravenous cannula is placed in your arm to infuse the contrast. The process followed for the scan will be the same to the previous scan. This will be compared with the ultrasound scan done near the same time as part of your routine care. If you are female and it is possible that you could be pregnant then a pregnancy test will be performed before you continue any further in the study.

Following the scan, no further study visits are required. With your permission data will be collected from your medical notes for up to 2 years to assess if your fistula is still working.

If your capacity to consent is lost during the study, you will be withdrawn from the study but identifiable data or blood already collected with consent will be retained and used in the study.

Can I take part in this study if I am pregnant or breastfeeding?

If taken during pregnancy, Ferumoxytol may affect an unborn baby therefore it is important that you do not become pregnant during the study. You must not take part

in the study if you are breastfeeding, pregnant, planning pregnancy or not using a reliable method of contraception. We will advise you about contraception before you decide if you wish to take part in the study and for how long contraception should continue after treatment with Ferumoxytol. A pregnancy test will be done prior to each MRI scan in all women who have the potential to become pregnant.

What are the discomforts, risks and side effects?

Cannulation: Placing a cannula (small plastic tube in the vein) can cause a little discomfort and can lead to some bruising. An experienced radiographer or doctor will perform this. The cannula will only be in place for an hour or so and be removed following the MRI scan, thus rendering negligible any potential complications relating to infection. Blood samples will be taken at the time of cannula insertion to avoid further venepuncture.

MRI scanning: This type of scan is very safe and does not use radiation. Some people, when being scanned, may feel a bit closed in but you will be in constant contact with the person performing the scan and you can come out at any time. The scanner is a bit noisy but you will be given ear protection which also plays music.

Ferumoxytol: Like many drugs in some instance, serious complications, such as anaphylaxis might occur when using Ferumoxytol. Anaphylaxis is a severe, potentially life-threatening allergic reaction. The rate of anaphylaxis is roughly 1 in 10,000, and death can occur in 1 in 50,000. Patients who have received Ferumoxytol have died despite immediate medical care and attempts to revive them. 4 in 100 people taking this drug may show symptoms associated with allergy (e.g. skin reactions, rash, wheezing), and 2 in 100 may develop low blood pressure.

It is important to know that the side effects of Ferumoxytol (including death) have occurred under different conditions than proposed for this study. For example, they may have involved higher doses of Ferumoxytol, injection of more concentrated forms (we are using very dilute doses) and in patients with different diseases. Side effects observed in one clinical study of a drug may not accurately predict the side effects observed in other studies. However we do not know for certain if giving you Ferumoxytol like this may cause more, less or any side effects to occur or how severe those side effects might be. Reassuringly, the same regime is used in other centres

around the world and no serious side effects have been reported in the literature so far, when Ferumoxytol is used for imaging.

You should not be given Ferumoxytol if you have a known allergy to it or any of its components, if you have a history of allergic reactions to any intravenous iron product, or if you have allergy to other drugs. If you tell us that you have any conditions associated with iron overload (e.g. haemochromatosis, chronic liver disease, or blood disorders requiring frequent blood transfusions), we will not administer Ferumoxytol because it might result in excess iron in the body.

All CT and MRI scans with contrast injections are performed in facilities with trained staff and equipment to treat any reactions to contrast administration immediately, and you will be carefully monitored during and for at least 30 minutes after administration of Ferumoxytol to determine whether you might be having a reaction.

Common side effects (may affect up to 1 in 10 people) are bleeding, and pain or irritation at the injection site. Uncommon side effects (may affect up to 1 in 100 people) include dizziness, low blood pressure, feeling weak, tired or drowsy, skin rash, and stomach upset (feeling sick, vomiting, bloating or pain). If you feel tired or drowsy then you should not drive or use any tools or machinery until this has passed.

You will be provided with an Alert Card which you should carry with you at all times while you are participating in the study. Please show the Alert Card to any Health Care Professional including doctor, nurse or pharmacist, who is caring for you.

What are the benefits of taking part in the study?

Your fistula will be monitored closely during the study. The MRI scans will give us information about the anatomy and function of your fistula and heart. If the MRI scans reveal any significant new abnormality we will either discuss this with your kidney consultant or refer you to a specialist clinic (whichever seems most appropriate). Taking this into consideration, it is likely that a small number of participants may directly benefit from the study. In due course we hope that the results from this study may help us develop a new imaging technique, allowing better assessment in the future of the vessels in patients having a fistula created for dialysis like you.

What are my rights?

If you wish the results of the study can be made available to you or your GP when the study is complete.

Any complaint about the way you have been dealt with during the study or any possible harm you may suffer will be addressed. In the first instance you should talk to the investigator involved in your care. You can ask to speak to a senior member of the Cardiovascular Research Centre, University of Glasgow or contact the NHS Greater Glasgow and Clyde complaints service.

Phone: 0141 201 4500

E-mail: complaints@ggc.scot.nhs.uk

In the event that something goes wrong and you are harmed during the study there are no special compensation arrangements. If you are harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against the University of Glasgow or NHS Greater Glasgow and Clyde but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will the research influence the treatment I receive?

The research will not alter the regular treatments you receive.

Will my taking part in the study be kept confidential?

With your permission, identifiable information about you and data collected during the study will be held by the Cardiovascular Research Centre, University of Glasgow and NHS Greater Glasgow and Clyde. All data collected in this study will be coded and stored on a computer system protected by a password only available to the researchers. No one outside the research team will have access to any identifiable information and all identifiable information and data will be kept securely. Your data will be archived securely for at least five years after the end of study. With your permission, we will inform your GP of your participation in this study. It is a requirement of the regulators that your records in this study, together with any other relevant medical records, be made available for scrutiny by appropriate staff from

NHS Greater Glasgow and Clyde, University of Glasgow (or their appointed third party) and the regulatory authorities.

Additionally there will be two sets of information obtained after you have had your MRI scan. One set will be the MRI scan images and the other, the research data obtained from those images. The MRI images obtained will be stored indefinitely using your name and unique hospital record number within the NHS clinical system and can be made available to specialist doctors for your future health care needs. Your research data will be stored using a unique study code which is non-identifiable and held on password protected University of Glasgow secure databases. Only individuals directly involved with the study will have access to this information. Anonymised images obtained may be used for illustrating reports on the study and teaching.

Expenses

Taxi transport, or reasonable costs to cover your travel costs, will be provided for any extra visits to the hospital for the purposes of this study.

Who has reviewed this study?

This study has been reviewed by the North of Scotland Research Ethics Committee (2).

It is a requirement that your records in this research, together with any relevant medical records, be made available for scrutiny by monitors from The University of Glasgow, NHS Greater Glasgow and Clyde and by the Regulatory Authorities, whose role is to check that research is properly conducted and the interests of those taking part are adequately protected.

If you are worried at any time about the research or wish to discuss things generally further, please do not hesitate to contact:

Dr Sokratis Stoumpos
Clinical Research Fellow
British Heart Foundation
Cardiovascular Research Centre
126 University Place
University of Glasgow

Glasgow G12 8TA
Tel: 0141 330 2079
E-mail – sstoumpos@nhs.net

Contact Numbers

If during the study you become unwell or are concerned, you can contact the study team during normal working hours on 0141 330 2079. If you are unwell and need urgent advice or assistance do not delay in seeking further advice or treatment as usual through the NHS services such as NHS24 or by contacting your GP who will have received details of your participation in this study should you agree to them being informed.

Thank you for reading this information sheet and considering taking part in this study. If you would like more information or want to ask questions about the study please contact the study team on the number above.

What will happen to me during the study?

The following is the programme of visits involved in this study. The screening visit will occur at one of your scheduled clinic appointments or hospital attendances as part of your routine care.

GROUP B			
STUDY VISIT	**Screening visit**	**Visit 1**	**Visit 2**
	-1 to -4 weeks	-1 to -4 weeks	-3 to +3 days
Informed consent	**X**		
Doctor check inclusion/exclusion criteria	**X**		
Demographics	**X**		
Medical history	**X**		
Medications	**X**	**X**	**X**
Allergies	**X**	**X**	**X**
Body weight		**X**	**X**
Pregnancy test (for women who may be pregnant)		**X**	
FeMRA[#]		**X**	
CMR*		**X**	**X**
Duplex US^		**X**	**X**
Blood samples[$]		**X**	**X**
[#] *Only if eligible after screening ^1st scan as part of standard clinical care, 2nd scan to assess AVF maturation (research) [$]To test biomarkers of cardiac function (NT-proBNP and high-sensitivity Troponin I)			

Contact for further information

For further information about this study, please contact Dr Sokratis Stoumpos on 0141 330 2079. If you would like independent advice regarding this study you can contact Dr Marie Freel, Consultant Physician, 0141 330 3412. She can be contacted at the above number and will be able to get back to you.

Finally thank you for taking the time to read this information leaflet and taking part in the study. If you wish to take part in the study you will be given a copy of this to keep and asked to sign a consent form.

Appendix 2

Ethics Committee and NHS Board Correspondence

Favourable Ethics Opinion

North of Scotland Research Ethics Committee
Summerfield House
2 Eday Road
Aberdeen
AB15 6RE

Telephone: 01224 558458
Facsimile: 01224 558609
Email: nosres@nhs.net

14 October 2016

Dr Sokratis Stoumpos
Clinical Research Fellow and Specialist Registrar in Renal Medicine
University of Glasgow
British Heart Foundation
Cardiovascular Research Centre
126 University Place
GLASGOW
G12 8TA

Dear Dr Stoumpos

Study title:	**Use of Ferumoxytol enhanced Magnetic Resonance Angiography (FeMRA) for cardiovascular assessment in late-stage chronic kidney disease (CKD)**
REC reference:	**16/NS/0099**
IRAS project ID:	**211105**

Thank you for your letter of 12 September 2016, responding to the Committee's request for further information on the above research, and for e-submitting your revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact the Assistant Ethics Coordinator, Ms Sarah Lorick, nosres@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the

study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	Version	Date
Covering letter on headed paper: FeMRA in CKD Cover		13 October 2016

response letter		
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		04 August 2016
GP/consultant information sheets or letters: FeMRA in CKD GP notification letter	v1.0	22 July 2016
IRAS Checklist XML		14 October 2016
Peer review 1: Reviewed by Dr Emily McQuarrie		03 October 2016
Peer review 2: reviewed by Emma Aitken		13 October 2016
Peer review 3: reviewed by Mr Vlad Shumeyko		13 October 2016
FeMRA Patient Alert Card	v1.0	20 September 2016
Participant consent form: FeMRA in CKD Consent form A	v2.0	13 September 2016
Participant consent form: FeMRA in CKD Consent form B	v2.0	13 September 2016
Participant consent form: FeMRA in CKD Consent form C	v2.0	13 September 2016
Participant information sheet (PIS): FeMRA in CKD PIS A	v2.0	13 September 2016
Participant information sheet (PIS): FeMRA in CKD PIS A - abbreviated 1pg sheet	v1.0	13 September 2016
Participant information sheet (PIS): FeMRA in CKD PIS B	v2.0	13 September 2016
Participant information sheet (PIS): FeMRA in CKD PIS B - abbreviated 1pg sheet	v1.0	13 September 2016
Participant information sheet (PIS): FeMRA in CKD PIS C	v2.0	13 September 2016
Participant information sheet (PIS): FeMRA in CKD PIS C - abbreviated 1pg sheet	v1.0	13 September 2016
REC Application Form	211105/999 167/1/144	18 August 2016
Research protocol or project proposal: FeMRA in CKD Protocol	v2.0	13 September 2016
Summary CV for Chief Investigator (CI): CV Stoumpos		22 July 2016
Summary CV for supervisor (student research): CV Patrick Mark		18 February 2015

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance

on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

16/NS/0099	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

Professor Nigel Webster
Chair

Enclosures: "After ethical review – guidance for researchers" SL-AR2

Copy to: Dr Maureen Travers, NHS Greater Glasgow and Clyde

NHS GGC Board Approval

Coordinator/administrator: Maureen Travers
Telephone Number: 0141 232 1813
E-Mail: Maureen.Travers@ggc.scot.nhs.uk
website www.nhsggc.org.uk/r&d

Clinical Research & Development
West Glasgow ACH
Dalnair Street
Glasgow G3 8SJ
Scotland, UK

06/12/2016

Dr Sokratis Stoumpos
University of Glasgow,
BHF Cardiovascular Research Centre,
126 University Place,
Glasgow G12 8TA

NHS GG&C Board Approval

Dear Dr Sokratis Stoumpos

Study Title:	Use of Ferumoxytol enhanced Magnetic Resonance Angiography for cardiovascular assessment in late-stage chronic kidney disease
Principal Investigator:	Dr Sokratis Stoumpos
GG&C HB site	QEUH and other renal and transplant clinics throughout NHS GG&C
Sponsor	NHS Greater Glasgow and Clyde
R&D reference:	GN16RE117
REC reference:	16/NS/0099
Protocol no: (including version and date)	Version 3.0 (17.11.2016)

I am pleased to confirm that Greater Glasgow & Clyde Health Board is now able to grant **Approval** for the above study.

Conditions of Approval

1. **For Clinical Trials** as defined by the Medicines for Human Use Clinical Trial Regulations, 2004
   a. During the life span of the study GGHB requires the following information relating to this site
      i. Notification of any potential serious breaches.
      ii. Notification of any regulatory inspections.

It is your responsibility to ensure that all staff involved in the study at this site have the appropriate GCP training according to the GGHB GCP policy (www.nhsggc.org.uk/content/default.asp?page=s1411), evidence of such training to be filed in the site file.

2. **For all studies** the following information is required during their lifespan.
   a. Recruitment Numbers on a quarterly basis
   b. Any change of staff named on the original SSI form
   c. Any amendments – Substantial or Non Substantial

d. Notification of Trial/study end including final recruitment figures
e. Final Report & Copies of Publications/Abstracts

Please add this approval to your study file as this letter may be subject to audit and monitoring.

Your personal information will be held on a secure national web-based NHS database.

I wish you every success with this research study

Yours sincerely,

Maureen Travers
Research Co-ordinator

CC: Dr G Rodditi, Dr P Mark, Dr D Kingsmore, Angela Carruth

Substantial amendment 1

North of Scotland Research Ethics Service
Summerfield House
2 Eday Road
Aberdeen
AB15 6RE

Telephone: 01224 558458
Facsimile: 01224 558609
Email: nosres@nhs.net

23 November 2016

Dr Sokratis Stoumpos
Clinical Research Fellow and Specialist Registrar in Renal Medicine
University of Glasgow
British Heart Foundation
Cardiovascular Research Centre
126 University Place
GLASGOW
G12 8TA

Dear Dr Stoumpos

Study title:	**Use of Ferumoxytol enhanced Magnetic Resonance Angiography (FeMRA) for cardiovascular assessment in late-stage chronic kidney disease (CKD).**
REC reference:	**16/NS/0099**
Amendment number:	**Amendment Number 1 (AM01 REC Ref Only)**
Amendment date:	**17 November 2016**
Amendment summary:	**Dosing protocol of Ferumoxytol clarified and described in detail and a table attached as an appendix for further clarification. No actual change to study methods.**
IRAS project ID:	**211105**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Notice of Substantial Amendment (non-CTIMP)	Amendment Number 1 (AM01 REC Ref Only)	17 November 2016

Document	*Version*	*Date*
Participant Consent Form: A - Pre-transplant Assessment Group	2.0	13 September 2016
Participant Consent Form: B - Native Fistula Group	2.0	13 September 2016
Participant Consent Form: C - Synthetic Graft Group	2.0	13 September 2016
Participant Information Sheet (PIS): A - Pre-transplant Assessment Group	3.0	17 November 2016
Participant Information Sheet (PIS): B - Native Fistula Group	3.0	17 November 2016
Participant Information Sheet (PIS): C - Synthetic Graft Group	3.0	17 November 2016
Research protocol or project proposal	3.0	17 November 2016

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

16/NS/0099: Please quote this number on all correspondence

Yours sincerely

pp'd on behalf of
Dr Georgina Hold
Vice-Chair

Enclosures: List of names and professions of members who took part in the review

Copy to: Dr Maureen Travers, NHS Greater Glasgow and Clyde

North of Scotland Research Ethics Committee (2)

Attendance at Sub-Committee of the REC meeting by correspondence

Committee Members:

Name	*Profession*	*Present*	*Notes*
Dr Georgina Hold	Vice-Chair & Senior Lecturer - Gastroenterology	Yes	
Dr Hanne Bruhn	Lay Member - Research Fellow - Psychology	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Mrs Carol Irvine	Senior Ethics Co-ordinator

Substantial amendment 2

North of Scotland Research Ethics Committee
Summerfield House
2 Eday Road
Aberdeen
AB15 6RE

Telephone: 01224 558458
Facsimile: 01224 558609
Email: nosres@nhs.net

18 October 2017

Dr Sokratis Stoumpos
Clinical Research Fellow and Specialist Registrar in Renal Medicine
University of Glasgow
British Heart Foundation
Cardiovascular Research Centre
126 University Place
G12 8TA

Dear Dr Stoumpos

Study title:	**Use of Ferumoxytol enhanced Magnetic Resonance Angiography (FeMRA) for cardiovascular assessment in late-stage chronic kidney disease (CKD).**
REC reference:	**16/NS/0099**
Amendment number:	**Amendment Number 2 (Study Ref) AM02 (REC Ref)**
Amendment date:	**10 October 2017**
IRAS project ID:	**211105**
Amendment Summary	**Increase in recruitment to 100 participants**

The above amendment was reviewed at the meeting of the Sub-Committee held on 17 October 2017 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	Version	Date
Notice of Substantial Amendment (non-CTIMP)	Amendment Number 2 (Study Ref) AM02 (REC Ref)	10 October 2017
Research protocol or project proposal	4	10 October 2017

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

16/NS/0099:	**Please quote this number on all correspondence**

Yours sincerely

Professor Helen Galley
Chair

Enclosures: List of names and professions of members who took part in the review

Copy to: Dr Maureen Travers, NHS Greater Glasgow and Clyde

North of Scotland Research Ethics Committee 2

Attendance at Sub-Committee of the REC meeting by correspondence

Committee Members:

Name	Profession	Present	Notes
Dr Hanne Bruhn	Research Fellow - Psychology	Yes	
Mrs Sophie Welch	Vice-Chair & Coach Practitioner	Yes	

Also in attendance:

Name	Position (or reason for attending)
Miss Karen Gauld	Ethics Administrator

Annual Progress Report 2017

NHS
Health Research Authority

ANNUAL PROGRESS REPORT TO MAIN RESEARCH ETHICS COMMITTEE
(For all studies except clinical trials of investigational medicinal products)

To be completed in typescript and submitted to the main REC by the Chief Investigator. For questions with Yes/No options please indicate answer in bold type.

1. Details of Chief Investigator

Name:	Dr Sokratis Stoumpos
Address:	Cardiovascular Research Centre 126 University Place Glasgow, G12 8TA
Telephone:	0141 330 2079
E-mail:	sstoumpos@nhs.nte
Fax:	-

2. Details of study

Full title of study:	Use of Ferumoxytol enhanced Magnetic Resonance Angiography (FeMRA) for cardiovascular assessment in late-stage chronic kidney disease (CKD)
Name of main REC:	North of Scotland Research Ethics Committee
REC reference number:	16/NS/0099
Date of favourable ethical opinion:	14 October 2016
Sponsor:	Dr Maureen Travers, NHS Greater Glasgow and Clyde

3. Commencement and termination dates

Has the study started?	***Yes*** */ No*
If yes, what was the actual start date?	12/12/2016
If no, what are the reasons for the study not commencing? What is the expected start date?	
Has the study finished? *If yes, complete and submit "Declaration of end of study" form, available at http://www.hra.nhs.uk/?orderby=relevance&results_per_page=10&s=&s=end+of+study&search_type=Documents*	*Yes /* ***No***

Annual progress report (non-CTIMP), version 4.4, dated November 2014

If no, what is the expected completion date? *If you expect the study to overrun the planned completion date this should be notified to the main REC for information.*	31/07/2018
If you do not expect the study to be completed, give reason(s)	

4. Registration

Is the study a 'clinical trial'? (Defined as first 4 categories on the IRAS filter page) (For CTIMP please use CTIMP progress reporting template)	*Yes / **No***
Is the study registered on a publically accessible database? (Registration of clinical trials is a condition of approval for studies approved after 30 September 2013)	**Yes** / No
If yes, please provide the name of the database and the registration number Database: ClinicalTrials.gov Registration number: NCT02997046	
If no: a. What is the reason for non-registration? b. What are your intentions for registration?	

5. Site information

Do you plan to increase the total number of sites proposed for the study? If yes, how many sites do you plan to recruit?	*Yes / **No***

6. Recruitment of participants

In this section, "participants" includes those who will not be approached but whose samples/data will be studied.

Number of participants recruited: 54	*Proposed in original application: 30* *Actual number recruited to date: 27*
Number of participants completing trial: 0	*Actual number completed to date: 14*

Number of withdrawals from study to date due to (a) withdrawal of consent: 0 (b) loss to follow-up: 0 (c) death (where not the primary outcome): 0 Total study withdrawals: 0	
*Number of treatment failures to date (prior to reaching primary outcome) due to: (a) adverse events: n/a (b) lack of efficacy: n/a Total treatment failures: n/a * Applies to studies involving clinical treatment only	
Have there been any serious difficulties in recruiting participants?	Yes / **No**
If Yes, give details:	
Do you plan to increase the planned recruitment of participants into the study? *Any increase in planned recruitment should be notified to the main REC as a substantial amendment for ethical review.*	**Yes** / No

7. Safety of participants

Have there been any related and unexpected serious adverse events (SAEs) in this study?	*Yes / **No***
Have these SAEs been notified to the Committee? *If no, please submit details with this report and give reasons for late notification.*	*Yes / No /**Not applicable***
Have any concerns arisen about the safety of participants in this study? *If yes, give details and say how the concerns have been addressed.*	*Yes / **No***

8. Amendments

Have any substantial amendments been made to the trial during the year?	*Yes / **No***
If yes, please give the date and amendment number for each substantial amendment made.	

9. Serious breaches of the protocol

Have any serious breaches of the protocol occurred during the year?	*Yes / **No***
If Yes, please enclose a report of any serious breaches not already notified to the REC.	*Yes / No*

10. Other issues

Are there any other developments in the study that you wish to report to the Committee?	*Yes / **No***
Are there any ethical issues on which further advice is required?	*Yes / **No***
If yes to either, please attach separate statement with details.	

11. Declaration

Signature of Chief Investigator:	
Print name:	Dr Sokratis Stoumpos
Date of submission:	13/11/2017

Annual Progress Report 2018

NHS
Health Research Authority

ANNUAL PROGRESS REPORT TO MAIN RESEARCH ETHICS COMMITTEE
(For all studies except clinical trials of investigational medicinal products)

To be completed in typescript and submitted to the main REC by the Chief Investigator. For questions with Yes/No options please indicate answer in bold type.

1. Details of Chief Investigator

Name:	Dr Sokratis Stoumpos
Address:	Cardiovascular Research Centre 126 University Place Glasgow, G12 8TA
Telephone:	0141 330 2079
E-mail:	sstoumpo@nhs.net
Fax:	-

2. Details of study

Full title of study:	Use of Ferumoxytol enhanced Magnetic Resonance Angiography (FeMRA) for cardiovascular assessment in late-stage chronic kidney disease (CKD)
Name of main REC:	North of Scotland Research Ethics Committee
REC reference number:	16/NS/0099
Date of favourable ethical opinion:	14/10/2016
Sponsor:	NHS Greater Glasgow and Clyde, Dr Maureen Travers

3. Commencement and termination dates

Has the study started?	***Yes*** */ No*
If yes, what was the actual start date?	12/12/2016
If no, what are the reasons for the study not commencing? What is the expected start date?	
Has the study finished? *If yes, complete and submit "Declaration of end of study" form, available at http://www.nres.npsa.nhs.uk/applications/after-ethical-review/endofstudy/*	*Yes /* ***No***

If no, what is the expected completion date?	15/01/2019

If you expect the study to overrun the planned completion date this should be notified to the main REC for information.	
If you do not expect the study to be completed, give reason(s)	

4. Registration

Is the study a 'clinical trial'? (Defined as first 4 categories on the IRAS filter page) (For CTIMP please use CTIMP progress reporting template)	*Yes / **No***
Is the study registered on a publically accessible database? (Registration of clinical trials is a condition of approval for studies approved after 30 September 2013)	**Yes** / No
If yes, please provide the name of the database and the registration number Database: ClinicalTrials.gov Registration number: NCT02997046	
If no: a. What is the reason for non-registration? b. What are your intentions for registration?	

5. Site information

Do you plan to increase the total number of sites proposed for the study? If yes, how many sites do you plan to recruit?	*Yes / **No***

6. Recruitment of participants

In this section, "participants" includes those who will not be approached but whose samples/data will be studied.

Number of participants recruited: 300	*Proposed in original application: 100* *Actual number recruited to date: 100*
Number of participants completing trial: 0	*Actual number completed to date: 96*
Number of withdrawals from study to date due to: 0	

(a) withdrawal of consent (b) loss to follow-up (c) death (where not the primary outcome) Total study withdrawals: 0
*Number of treatment failures to date (prior to reaching primary outcome) due to: n/a (a) adverse events (b) lack of efficacy Total treatment failures: n/a * Applies to studies involving clinical treatment only

Have there been any serious difficulties in recruiting participants?	Yes / **No**
If Yes, give details:	
Do you plan to increase the planned recruitment of participants into the study? *Any increase in planned recruitment should be notified to the main REC as a substantial amendment for ethical review.*	Yes / **No**

7. Safety of participants

Have there been any related and unexpected serious adverse events (SAEs) in this study?	*Yes / **No***
Have these SAEs been notified to the Committee? *If no, please submit details with this report and give reasons for late notification.*	*Yes / No /**Not applicable***
Have any concerns arisen about the safety of participants in this study? *If yes, give details and say how the concerns have been addressed.*	*Yes / **No***

8. Amendments

Have any substantial amendments been made to the trial during the year?	*Yes / **No***
If yes, please give the date and amendment number for each substantial amendment made.	

9. Serious breaches of the protocol

Have any serious breaches of the protocol occurred during the year?	*Yes / **No***
If Yes, please enclose a report of any serious breaches not already notified to the REC.	*Yes / No*

10. Other issues

Are there any other developments in the study that you wish to report to the Committee?	*Yes / **No***
Are there any ethical issues on which further advice is required?	*Yes / **No***
If yes to either, please attach separate statement with details.	

11. Declaration

Signature of Chief Investigator:	
Print name:	Dr Sokratis Stoumpos
Date of submission:	20/12/2018

End of Study Report 2019

NHS
Health Research Authority

DECLARATION OF THE END OF A STUDY

(For all studies except clinical trials of investigational medicinal products)

To be completed in typescript by the Chief Investigator and submitted to the Research Ethics Committee (REC) that gave a favourable opinion of the research within 90 days of the conclusion of the study or within 15 days of early termination.

For questions with Yes/No options please indicate answer in bold type.

1. Details of Chief Investigator

Name:	**Sokratis Stoumpos**
Address:	**University of Glasgow, BHF Cardiovascular Research Centre**
Telephone:	**0781 874 2133**
Email:	**sstoumpos@nhs.net**
Fax:	**-**

2. Details of study

Full title of study:	**Use of Ferumoxytol enhanced Magnetic Resonance Angiography (FeMRA) for cardiovascular assessment in late-stage chronic kidney disease (CKD).**
Research sponsor:	**NHS Greater Glasgow and Clyde**
Name of REC:	**North of Scotland Research Ethics Service**
REC reference number:	**16/NS/0099**

3. Study duration

Date study commenced:	**12/12/2016**
Date study ended:	**15/01/2019**
Did this study terminate prematurely?	*Yes / **No*** *If yes, please complete sections 4, 5, 6, & 7.* *If no, please go direct to section 8.*

4. Recruitment

Number of participants recruited	**100**
Proposed number of participants to be recruited at	**100**

the start of the study	
If different, please state the reason or this	

5. Circumstances of early termination

What is the justification for this early termination?	**n/a**

6. Temporary halt

Is this a temporary halt to the study?	*Yes / **No***
If yes, what is the justification for temporarily halting the study? When do you expect the study to re-start?	*e.g. Safety, difficulties recruiting participants, trial has not commenced, other reasons.*

7. Potential implications for research participants

Are there any potential implications for research participants as a result of terminating/halting the study prematurely? Please describe the steps taken to address them.	**n/a**

8. Final report on the research

Is a summary of the final report on the research enclosed with this form?	*Yes / **No*** *If no, please forward within 12 months of the end of the study.*

9. Declaration

Signature of Chief Investigator:	
Print name:	**Sokratis Stoumpos**
Date of submission:	**06/02/2019**

Declaration of end of study (non-CTIMP), version 1.3, August 2014

Appendix 3

Research Study Forms and Protocols

Ferumoxytol-enhanced MR Angiography Protocols

Glasgow Clinical Research Imaging Facility

FeMRA Aortoiliacs - GN16RE117

Iron Contrast Angiogram

Radiologist: Giles Roditi (giles.roditi@glasgow.ac.uk)
Clinician: Soktratis Stoumpos (sstoumpos@nhs.net)

Patient Prep	· Confirm patient ID – EP-7 · Check pregnancy status – EP-8 · Safety checklist · Venflon, Gating, Blood Pressure Cuff, Pulse oximeter
Equipment	Spine coil and two Body Arrays
IV Contrast	Ferumoxytol: Weight dependent Ferumoxytol/Normal Saline 0.9% – See dosage chart
	Rate: 1ml/sec

Localisers

- Three plane HASTE localisers
- T2 Trufi axial – apices to below groin
- T1 StarVIBE (to show calcification) – coronal of abdomen: cover SMA to Aortoiliacs

Liver Iron: BH INSP

- T1 Vibe e-dixon to cover whole Liver (inspiration)
- T1 Vibe q-dixon – coverage must match e-dixon. Use e-dixon to place ROI (inspiration)
    - *Red ROI shows up. Click on it and it will disappear, now scroll through images to find a suitable location avoiding vessels and bile ducts. Click again and ROI will reappear.*
- Liver and Spleen – Single Axial slice to include Liver and Spleen – use e-dixon (use the Body Coil only) (inspiration)

Cardiac Imaging

- Localisers as normal
- Cines - VLA, HLA, LVOT
- Candy Cane
- Cine asc/desc Aorta at level of Right PA

Perfusion

- *Done in 3 blocks. For each perfusion block, give a **small** injection of Ferumoxytol as per dosage chart at 1ml/sec. 100 measurements per perfusion sequence, inject after 4*

measurements.

- **Perfusion block 1**
  - Molli SA (Systole)
  - Perfusion – 1 x SA (copied to position of Molli), 1 x HLA, 1 x transverse at level of Right PA (copy from Cine)
  - Molli SA (Systole)
  - **SA Cine – copied to Molli position**

- **Perfusion block 2**
  - Molli SA (Systole)
  - Perfusion – 1 x SA (copied to position of Molli), 1 x HLA, 1 x transverse at level of Right PA (copy from T2 Trufi axial stack)
  - Molli SA (Systole)
  - **Candy Cane cine**

- **Perfusion block 3**
  - Molli SA (Systole)
  - Perfusion – 1 x SA (copied to position of Molli), 1 x HLA, 1 x transverse at level of Right PA (copy from T2 Trufi axial stack)
  - Molli SA (Systole)
  - **Flow Map – transverse at level of Right PA (copy from T2 Trufi axial stack)**

Infusion of remaining Ferumoxytol (see dosage chart)

Angiogram

- FL3D Coronal @ 2 mins post infusion (copy to StarVIBE).
- Molli SA (Systole) – same as in Cardiac section
- FL3D Coronal – repeat as necessary

Images to PACS	• Recon StarVIBE • Iron sequences • Cardiac mass and function & additional cines • First perfusion sequence – MOCO only • ALL FL3D scans
Archiving	• Everything to DVD • Anonymise and send everything to Archive

Glasgow Clinical Research Imaging Facility

FeMRA Fistula/Graft 1st VISIT - GN16RE117

Iron Contrast Angiogram

Radiologist: Giles Roditi (giles.roditi@glasgow.ac.uk)
Clinician: Soktratis Stoumpos (sstoumpos@nhs.net)

Patient Prep	· Confirm patient ID – EP-7 · Check pregnancy status – EP-8 · Safety checklist · Venflon, Gating, Blood pressure cuff, Pulse oximeter · Tourniquet at shoulder level, loosely attached
Equipment	Spine coil and two Body Arrays
IV Contrast	Ferumoxytol: Weight dependent Ferumoxytol/Normal Saline 0.9% – See dosage chart
	Rate: 1ml/sec

Localisers

- Patient positioned supine with body arrays covering chest and shoulders to wrist
    - *Patient will need to be offset to allow good imaging of affected arm, leaning against side of scanner – this can be done at the time of the Angiogram.*
- HASTE localisers to cover whole chest and affected arm – take time to get good localisers
- Trufi localisers of abdomen for Iron sequences

Liver Iron

- T1 Vibe e-dixon to cover whole Liver (inspiration)
- T1 Vibe q-dixon – coverage must match e-dixon. Use e-dixon to place ROI (inspiration)
    - *Red ROI shows up. Click on it and it will disappear, now scroll through images to find a suitable location avoiding vessels and bile ducts. Click again and ROI will reappear.*
- Liver and Spleen – Single Axial slice to include Liver and Spleen – use e-dixon (use the Body Coil only) (inspiration)

Cardiac Imaging

- Localisers as normal
- Cines - VLA, HLA, LVOT
- SA cine (mid ventricle)
- Candy Cane cine

- Cine asc/desc Aorta at level of Right PA
- Flow Map – transverse at level of PA (copy from Cine asc/desc Aorta at level of Right PA)

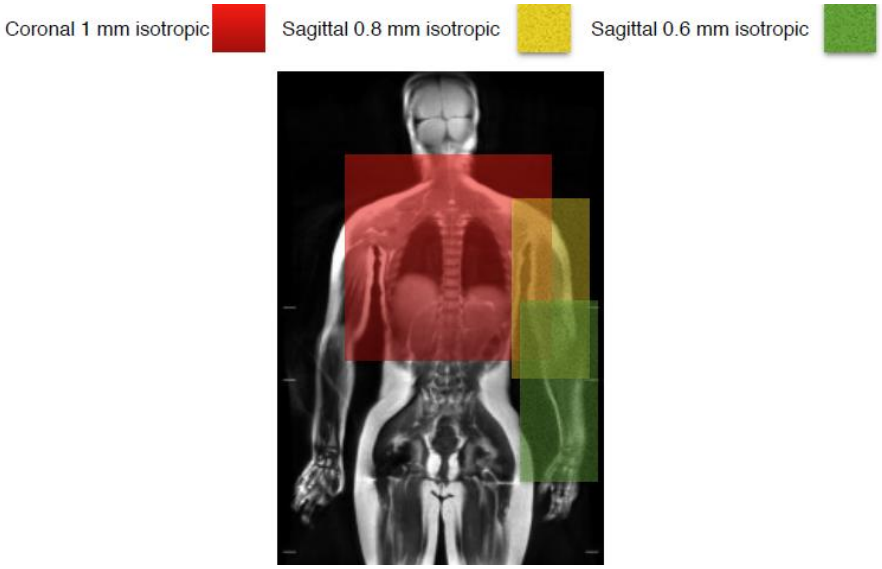
Angiogram

- Infuse Ferumoxytol
- FL3D @ 2mins post contrast:
  - Coronal (1.0mm) to include central veins out to subclavian veins on both sides (BH)

******Sokratis will tighten tourniquet ******

At this point the patient can be repositioned to achieve best arm imaging

  - Additional localisers as required to plan 2x sagittal blocks from shoulder to wrist covering skin2skin: upper arm (0.8mm, free breath) and lower arm (0.6mm, free breath) overlapping around the elbow



Images to PACS	• Iron sequences • Cardiac function & additional cines • ALL FL3D scans
Archiving	• Everything to DVD • Anonymise and send everything to Archive

Glasgow Clinical Research Imaging Facility

FeMRA Fistula/Graft 2nd VISIT - GN16RE117

Iron Contrast Angiogram

Radiologist: Giles Roditi (giles.roditi@glasgow.ac.uk)
Clinician: Soktratis Stoumpos (sstoumpos@nhs.net)

Patient Prep	· Confirm patient ID – EP-7 · Check pregnancy status – EP-8 · Safety checklist · Venflon, Gating, Blood Pressure Cuff, Pulse oximeter · Tourniquet at shoulder level, loosely attached
Equipment	Spine coil and two Body Arrays
IV Contrast	Ferumoxytol: Weight dependent Ferumoxytol/Normal Saline 0.9% – See dosage chart
	Rate: 1ml/sec

Localisers

- Patient positioned supine with body arrays covering chest
- HASTE localisers to cover whole chest
- Trufi localisers of abdomen for Iron sequences

Liver Iron

- T1 Vibe e-dixon to cover whole Liver (inspiration)
- T1 Vibe q-dixon – coverage must match e-dixon. Use e-dixon to place ROI (inspiration)
    - *Red ROI shows up. Click on it and it will disappear, now scroll through images to find a suitable location avoiding vessels and bile ducts. Click again and ROI will reappear.*
- Liver and Spleen – Single Axial slice to include Liver and Spleen – use e-dixon (Use the Body Coil only) (inspiration)

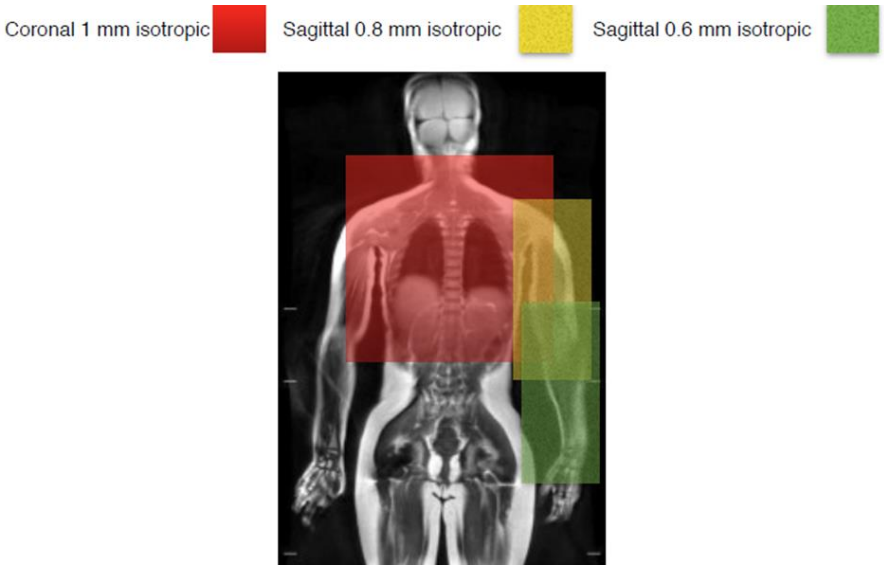
Cardiac Imaging

- Localisers as normal
- Cines - VLA, HLA, LVOT
- SA cine (mid ventricle)
- Candy Cane cine
- Cine asc/desc Aorta at level of Right PA
- Flow Map – transverse at level of PA (copy from Cine asc/desc Aorta at level of Right PA)

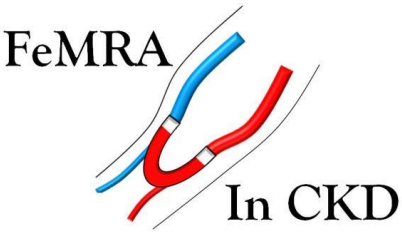
Angiogram

At this point the patient can be repositioned to achieve best arm imaging with additional localisers as required to plan

- **Q-Flow of upper arm brachial artery & veins** - check no aliasing and increase Venc if needed
- **TWIST** to encompass fistula/graft inflow/outflow during infusion, orient for best spatial and temporal resolution, likely sagittal (No BH)
- Use **half of the dose** of Ferumoxytol during infusion for TWIST
- Infuse **remaining dose** of Ferumoxytol
- **FL3D** @ 2mins post contrast:
  - 2 or 3x sagittal blocks from shoulder to wrist covering skin2skin: firstly cover fistula/graft as per TWIST then sagittal upper arm (0.8mm, free breath) and lower arm (0.6 mm, free breath) overlapping around the elbow
- **Q-Flow of upper arm brachial artery & veins** – use appropriate Venc as determined above
  - Coronal (1.0mm) to include central veins out to subclavian veins on both sides - may need repositioned (BH)



Images to PACS	· Iron Sequences · Cardiac function & additional cines · ALL FL3D scans
Archiving	· Everything to DVD · Anonymise and send everything to Archive



FeMRA: GN16RE117

Preparation and Handling Manual

Study title:
Use of Ferumoxytol enhanced Magnetic Resonance Angiography for cardiovascular assessment in late-stage chronic kidney disease

Chief Investigator:
Dr Sokratis Stoumpos

Sponsor:
NHS Greater Glasgow & Clyde

R&D No:
GN16RE117

Version: 2.0 14.11.2017

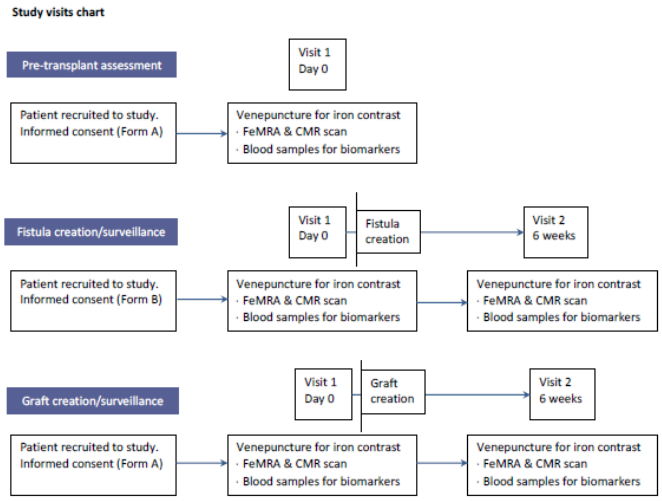
ABBREVIATIONS

CI	Chief Investigator
CRF	Clinical Research Facility
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
NHS GG&C	NHS Greater Glasgow & Clyde
Non-CTIMP	Non-Clinical Trial of an Investigational Medicinal Product
PDC	Pharmacy Distribution Centre
QEUH	Queen Elizabeth University Hospital
SOP	Standard Operating Procedure

Section 1: Study background

1.1 Study summary information

Figure 1: Study visit chart



Section 2: Overview of roles and responsibilities

In this study the CRF pharmacy will be responsible for storage and receipt of the ferumoxytol. The research team will include medically qualified investigators and radiographers who will be responsible for the preparation and administration of the products.

2.1 Research team roles and responsibilities for study products

The research team will be responsible for completion of the following documentation and processes covering the storage and supply of the products:

- requesting supplies prior to each participant visit using the **FeMRA: Ferumoxytol Supply Request Form**
- preparation of each product to the required concentration
- completion of the **FeMRA Preparation & Administration Worksheet**
- Ferumoxytol will be prescribed on SERPR and **Adult Prescription and Administration Chart: For medicines given by syringe or infusion pump** by study trained medical staff
- preparation and administration of ferumoxytol
- destruction of prepared infusions and part used vials immediately after use
- return of any unused vials of ferumoxytol to pharmacy

2.2 Pharmacy roles and responsibilities

The pharmacy team will be responsible for completion of the following documentation and processes covering the storage and supply of the products.

- Ensuring sufficient supplies of ferumoxytol are available for use.
- Correct storage of ferumoxytol prior to use
- Assembling supply for participant visit in response to a completed **FeMRA Ferumoxytol Supply Request Form**
- Completion of **FeMRA Pharmacy Master Accountability Log (GN16RE117).** for traceability purposes and to meet Unlicensed Medicines supply requirements.

Section 3: Ferumoxytol ordering, receipt and management information

3.1 Study products

The medicine used in this study will be Feraheme (ferumoxytol 30mg/ml). The rate of administration for ferumoxytol will be controlled by an MRI compatible infusion pump and is dictated by the study protocol.

3.2 Product quality assessment

Ferumoxytol is an unlicensed medicine in the UK but is available as a licensed medicine in the USA and Canada. Supplies will be procured either via the PDC or via AMAG Pharmaceuticals (contract in place). Where purchased via the PDC, the PDC will be responsible for quality assessment, provision of translations and English language overlabelling if required. Pharmacy clinical trial services will work to the same standards where supply is procured via AMAG Pharmaceuticals.

3.3 Compliance to NHS GG&C Unlicensed Medicine policy (acute division)

The NHS GG&C Unlicensed Medicine Policy is intended to apply to therapeutic use of medicines. As the study will be run to an ethics approved study protocol and subject to governance and oversight via the sponsor there is no requirement for individual unlicensed medicine forms to be completed. Patient identifiable data for traceability purposes (batch numbers, participant name and CHI number) will be collected by pharmacy by completion of study specific documentation. Anonymous information for Good Clinical Practice (GCP) purposes will be collected as part of the individual worksheets.

3.4 Ordering of ferumoxytol

CRF Pharmacy staff will be responsible for ordering and maintaining sufficient supplies of ferumoxytol in liaison with the study team. Supplies ordered via PDC will be charged using the assigned study Ascribe code and costs will be met by the study funds. Supplies via AMAG Pharmaceuticals will be provided free of charge.

3.5 Pharmacy receipt

On receipt of supplies please ensure the following:

- delivery is intact and undamaged
- products listed on the picking ticket or shipment information have been received at site

Ferumoxytol vials should be receipted as per CTU SOP 22.007 with the exception that as licensed medicine in the USA and procured via Pharmacy Distribution Centre, no QP batch certificate is required.

3.6 First supply of products from pharmacy

Pharmacy are permitted to supply products to research staff only once a signed **Authorisation for First Supply of Product to Study Subjects** is provided by R&D pharmacy staff.

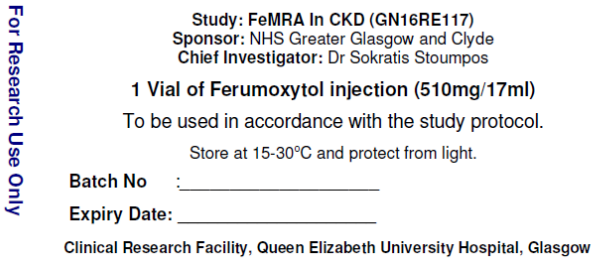
3.7 Pharmacy supply information

A maximum of one ferumoxytol vial will be required for each participant as the dose administered will always be less than the contents of one vial. The only exception to this is where an error in preparation means that a vial has to be discarded and a replacement obtained.

Individual vials must be packed into a skillet in order to protect from light and labelled as per figure 2 below. Each supply must receive a second accuracy check but there is no requirement for a pharmacist clinical/professional check.

A copy of the completed **FeMRA Ferumoxytol Supply Request Form** should be provided with each supply and the original filed in the pharmacy site file.

Figure 2: Ferumoxytol skillet label



3.8 Pharmacy storage of ferumoxytol and temperature deviations

Ferumoxytol should be stored at all times in accordance with the labelled product information. It should be stored in the original package up until the point of supply in order to protect from light and should not be frozen.

In the event of a temperature excursion complete Glasgow CTU SOP form 21.011A and e-mail to R&DIMP@ggc.scot.nhs.uk. Affected stock **must** be physically quarantined until further guidance is given. Please telephone if an urgent response is needed. R&D pharmacy will then onward report temperature deviations for ferumoxytol to the PDC.

An assessment will be made on the suitability for continued use of affected vial and written e-mail confirmation provided from R&D pharmacy. For supplies procured via PDC, the temperature deviation will be reported via PDC processes. Where supplies are procured via AMAG Pharmaceuticals, the defect/complaint will be reported directly to the company. Provided the affected products are suitable for continued use within the study, they may be removed from quarantine. R&D pharmacy will provide further

instructions should any of the products not be suitable for use and approve final destruction. Destruction should be documented using Glasgow CTU SOP 22.011A.

3.9 Product defects, complaints and recall

In the event of a defect or complaint complete Glasgow CTU SOP form 21.011A and e-mail to R&DIMP@ggc.scot.nhs.uk affected stock **must** be physically quarantined until further guidance is given. Please telephone if an urgent response is needed. R&D pharmacy will then onward report defects or complaints for ferumoxytol to the PDC.

An assessment will be made on the suitability for continued use of affected packs and written e-mail confirmation provided from R&D pharmacy. For supplies procured via PDC, the defect/complaint will be reported via PDC processes. Where supplies are procured via AMAG Pharmaceuticals, the defect/complaint will be reported directly to the company. Provided the affected products are suitable for continued use within the study, they may be removed from quarantine. R&D pharmacy will provide further instructions should any of the products not be suitable for use and approve final destruction. Destruction should be documented using Glasgow CTU SOP 22.011A.

Where supplies have been procured via the PDC, any recall will be managed in accordance with PDC procedures. The contract with AMAG Pharmaceuticals requires that AMAG Pharmaceuticals inform the sponsor of any safety issues related to ferumoxytol provided under the contract. Supplies obtained via AMAG Pharmaceuticals would be recalled in accordance with their arrangements with the UK based PCI Services.

3.10 Pharmacy destruction of unused ferumoxytol supplies

It is anticipated there will be minimal destruction required in this study. Destruction of unused products, with the exception of temperature deviation and defects, should be discussed with the research team from a cost perspective. R&D pharmacy will provide final approval for destruction.

Ferumoxytol procured via PDC: Destruction of unused study products must be documented using Glasgow CTU Form 22.011A. Products should be destroyed in accordance with principles of Glasgow CTU SOP 22.011.

Ferumoxytol procured via AMAG Pharmaceuticals: Destruction of unused study products must be documented using Glasgow CTU Form 22.011A. Products should be destroyed in accordance with principles of Glasgow CTU SOP 22.011. A copy must be provided to AMAG Pharmaceuticals.

3.11 Pharmacy product accountability

A record of ferumoxytol movement must be kept for traceability purposes and to fulfil the principles of NHS GG&C ULM procedure. Records should be documented on the **FeMRA Pharmacy Master Accountability Log (GN16RE117)**. Individual patient traceability will be maintained through completion of the **FeMRA Ferumoxytol Supply Request Form.** It is pharmacy's responsibility to ensure the accountability records are kept up-to-date and available for inspection by the sponsor if required.

3.12 Expiry date monitoring

Pharmacy staff will be responsible for expiry date monitoring for the ferumoxytol.

Section 4: Product safe handling information

4.1 Hazard identification and first aid measures

There is not anticipated risk to health in handling intact vials of ferumoxytol. There are no additional handling requirements over and above standard requirements for handling of pharmaceuticals.

4.2 Personal Protective Equipment (PPE):

During preparation of all ferumoxytol infusions, standard PPE of disposable apron and gloves must be used.

4.3 Dealing with breakages and spills

In the event of a spillage follow the procedure below:

- assemble the necessary equipment (spillage kit and clinical waste container)
- open the spillage kit using appropriate personal protective equipment (goggles, disposable gloves and apron
- remove any broken glass/plastic and place immediately in the clinical waste container
- use absorbent material to soak up any spillages and transfer to the clinical waste container using tweezers
- Clean the area with water starting from the outside of the spill area and working inwards with absorbent material; discard the waste in the clinical waste container
- discard all the disposable personal protective equipment in the clinical waste container
- seal the clinical waste container and dispose of as clinical waste.

Safe disposal: Used vials, infusion bags, stock solutions and giving set etc. should be disposed of in a sharps bin, sealed and then disposed of as clinical waste in accordance with the local areas disposal requirements for clinical waste.

Section 5: Product prescribing requirements

5.1 Product prescribing requirements

SERPR: Ferumoxytol must be prescribed on SERPR by an appropriately trained, delegated and qualified member of medical staff and annotated in such a way so that it is clear that ferumoxytol is prescribed as part of the FeMRA study.

Adult prescription and administration chart for medicines given by syringe or infusion pump: Standard NHS GG&C documentation required for administration of infusion of ferumoxytol and 0.9% sodium chloride must be completed. These will then be subsequently filed in the participant's medical records.

Section 6: Preparation of ferumoxytol solutions

6.1 General information

The following are general points to be observed when preparing study products

- Product and volume checks should be performed in accordance with standard NHS GG&C processes
- All infusions must be prepared immediately prior to administration
- A copy of the completed **FeMRA Ferumoxytol Supply Request Form** will be provided with each supply listing batch and expiry dates

6.2 Preparation instructions for ferumoxytol for IV infusion

Setting: Preparation of the final infusion will take place in the radiology department prior to administration by appropriately trained and suitably qualified research staff.

Equipment:

- 1 x 17ml vial containing 510mg (30mg/ml) of ferumoxytol
- 1 x 100ml 0.9% sodium chloride infusion
- 1 x FeMRA: Ferumoxytol Preparation Worksheet
- 1 x syringe suitable for pump
- 1 x clinical trial label
- Needles (for preparation)

Personal protective equipment: standard PPE for preparation of medicines

Dosing information: see current study protocol

Preparation Instructions
Use aseptic technique throughout.

Step 1: Worksheet preparation

1. Complete the following section on the worksheet:
    - Participant Information
    - Accountability information for ferumoxytol
    - Accountability information for 0.9% sodium chloride
    - Ferumoxytol infusion preparation

Step 2: Ferumoxytol solution preparation

1. Withdraw the correct volume of ferumoxytol (30mg/ml) and 0.9% sodium chloride solution and mix thoroughly. Do not shake.
2. Check for foreign matter. The resulting solution should be black to reddish brown.
3. Label as per standard practice and add an additional study specific label as per sample label below.
4. Complete information required on the **FeMRA: Ferumoxytol Preparation Worksheet**.

Additional Study Specific Label:

Study: FeMRA
R&D No: GN16RE117
Sponsor: NHS GG&C
Investigator:
Dr Sokratis Stoumpos
For Research Use Only
Participant No: _____

Section 7: Infusion administration

7.1 Product administration

Ferumoxytol solutions for administration must be prepared in accordance with standard practice at site.

7.2 Post administration

At the end of the ferumoxytol infusion ensure that all sections of the preparation and administration worksheets have been completed. Administration should be recorded on infusion chart. If the total volume required by protocol was not administered the patients Case Report Form and medical notes, should be annotated with the total volume actually administered and reasons for non-administration.

All used vials, infusion bags and giving sets should be destroyed at local site level in a sharps bin in accordance the standard practice.

Section 8: History of Changes

Version 1.0 – Released to sites.

Version 2.0: The following updates were made:

- **Section 3.2 Product quality assessment:** Text amended to reflect that ferumoxytol may be procured via either the PDC or via AMAG Pharmaceuticals (under contract). Where procured via AMAG Pharmaceuticals, Pharmacy Clinical Trial Services will be responsible for the quality assessment.
- **Section 3.4 Ordeing of ferumoxytol:** Text updated to indicate that ferumoxytol supplied via AMAG Pharmaceuticals will be provided free of charge.
- **Section 3.8 Pharmacy storage of products and ferumoxytol and temperature deviations:** Text amended to detail temperature deviation reporting pathway depending on route of supply.
- **Section 3.9: Product defects, complaints and recall:** Text amended to detail defect reporting pathway depending on route of supply. Additional information added on management of recall depending on ferumoxytol source.
- **Section 3.10 Pharmacy destruction of unused ferumoxytol supplies:** Text updated to reflect contractual requirements with AMAG Pharmaceuticals around destruction.
- **Section 7 Product administration:** Text amended to stipulate that ferumoxytol should be prepared in accordance with standard practice at site.
- Amendment of typographical errors

Ferumoxytol Supply Request Form

Study Title: Use of Ferumoxytol enhanced Magnetic Resonance Angiography for cardiovascular assessment in late-stage chronic kidney disease

Sponsor: NHS Greater Glasgow and Clyde

R&D No: GN16RE117 **Investigator:** Dr Sokratis Stoumpos

Study site: Queen Elizabeth University Hospital, Glasgow

Participant information

Attach addressograph label:

Requests must include CHI number

Participant Number: | | | |

Group (Please tick):

- Pre-transplant assessment ☐
- Fistula creation/surveillance ☐
- Graft creation/surveillance ☐

Visit No: Visit 1 ☐, Visit 2 ☐ (**Note:** Visit 2 for Fistula/Graft creation & surveillance groups only)

Supply required: Yes ☐ No ☐
(Note: It is at investigator discretion to determine if a vial supply is required)

Date and time required: _____

Please supply the following

1 x 17 ml vial containing 510mg of ferumoxytol injection (Feraheme® 30mg/ml) ☐

Requested by:

Sign: _____ **Print** :_____ **Date**:_____

Please note that supplies for study GN16RE117 can only be requested by nursing or medical staff delegated appropriate responsibilities on the study delegation log.

For pharmacy use only

Supply required:
If 'Yes' please enter batch, expiry and number of vials supplied below:
If 'No' please enter batch and expiry of vial that will be administered. If required confirm with the research team. Enter the number of vials as '0'.

Batch No:	Expiry date:		No of vials
		/	

Prepared by: Sign: _____ **Print** _____ **Date:** _____

Checked by: Sign: _____ **Print** _____ **Date:** _____

FeMRA: Ferumoxytol Preparation Worksheet

Study Title: Use of Ferumoxytol enhanced Magnetic Resonance Angiography for cardiovascular assessment in late-stage chronic kidney disease
R&D No: GN16RE117
Sponsor: NHS Greater Glasgow & Clyde
Chief Investigator: Dr Sokratis Stoumpos

Starting product, form & strength:
- Each 17ml vial contains 510mg of Ferumoxytol as a solution for infusion
- Each 1ml of solution contains 30mg of ferumoxytol.

Participant information

Participant No:		**Visit Date:**	
Participant Weight	_____ **kg** Round weight down to nearest 1kg.		

Ferumoxytol Prescription

Ferumoxytol for FeMRA study must be prescribed by an investigator delegated responsibility for prescribing on the FeMRA delegation log and in accordance with standard practice using:
- SERPR
- Adult Prescription and Administration Chart: For Medicines Given by Syringe or Infusion Pump

Accountability information for Ferumoxytol

No of vials:	**ONE**	A maximum of one vial/dose is required	
Batch number:		**Expiry Date:**	

Accountability information for 0.9% sodium chloride for infusion:

Batch number:		**Expiry Date:**	

Ferumoxytol infusion preparation: See infusion protocol table in current protocol

Ferumoxytol injection (1ml contains 30mg ferumoxytol) **=** _____ml

Infusion vehicle (0.9% sodium chloride) **=** _____ml

Final infusion volume: = _____ml

Label	Label each prepared syringe with a NHS GG&C additive label as per standard practice and attach the following additional label. **Study:** FeMRA **R&D No:** GN16RE117 **Sponsor:** NHS GG&C **Investigator:** Dr Sokratis Stoumpos **For Research Use Only** **Participant No:** _____
Final check:	Contents of syringe checked for foreign matter. Solution is black to reddish brown and free from particles. A label has been applied.

Prepared by*:		**Date:**	
Checked by*:		**Date:**	

*Staff preparing/administering must be delegated this responsibility on the FeMRA delegation log.

Administration			
Ferumoxytol administration information	**Administered by:**_____ **Volume and duration of infusion:** Infusion 1: _____ ml over _____seconds Infusion 2: _____ ml over _____seconds Infusion 3: _____ ml over _____seconds Infusion 4: _____ ml over _____seconds Infusion 5: _____ ml over _____seconds Total volume infused: _____ ml Administered as per study protocol? Yes ☐ No ☐ Document any exceptions below. If a protocol deviation this should be documented in the participant's medical records.		
Comments:	Please document any discrepancies eg. reason full volume not administered:		
Completed by:		**Date:**	

Contact Information

Local Investigator: _____

Address: _____

_____

_____

Contact telephone number:
(Office hours only)

_____

If you need advice outside of office hours, please contact your GP out-of-hours service or telephone 111 for the NHS 24 hour advice service.

Chief investigator: Dr Sokratis Stoumpos
Queen Elizabeth University Hospital, Glasgow, G51 4TF

Sponsor:
NHS Greater Glasgow and Clyde

Version 1.0 20.09.2016

Patient Alert Card:
FeMRA in CKD Study

FeMRA In CKD

Study title: Use of Ferumoxytol enhanced Magnetic Resonance Angiography for cardiovascular assessment in late-stage Chronic Kidney Disease:

Sponsor protocol no: GN16RE117

Study medicine: Ferumoxytol

I AM CURRENTLY TAKING PART IN A RESEARCH STUDY

This card contains important information and should be carried with you at all times as long as you are participating in the above study. Please show this card to any doctor or other health care professional treating you.

Name: _____

Home Address: _____

Telephone No: _____

Participant No: _____

NHS Greater Glasgow and Clyde

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