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

Sokratis Stoumpos PhD[a,b], Alfred Tan MD[c], Pauline Hall Barrientos PhD[c], Karen Stevenson PhD[a], Peter C Thomson MB ChB[a], Ram Kasthuri MB ChB[c], Aleksandra Radjenovic PhD[b], David B Kingsmore MB ChB[a], Giles Roditi MB ChB[c], Patrick B Mark PhD[a,b]

Abstract

Background: Duplex ultrasound is performed routinely for vascular mapping prior to hemodialysis arteriovenous fistula (AVF) creation but cannot visualize the central vasculature. Ferumoxytol, an iron oxide nanoparticle, provides an alternative to gadolinium contrast for MR angiography for safe use in chronic kidney disease (CKD).

Purpose: To assess the clinical utility of ferumoxytol-enhanced MR angiography for vascular mapping before upper limb AVF creation in CKD compared with Duplex ultrasound.

Materials and Methods: In a prospective comparative study (ClinicalTrials.gov: NCT02997046) from December 2016 and August 2018, participants with CKD underwent ferumoxytol-enhanced MR angiography and Duplex ultrasound. Two independent readers evaluated vessels for diameter, stenosis or occlusion, arterial disease, and central stenosis. Interclass correlation coefficients (ICC) and Bland-Altman plots assessed intra- and inter-reader variability. Based on accepted standards for AVF creation, an algorithm was developed to predict AVF outcome based on imaging findings. Multivariable regression models used AVF success as the dependent variable and age, sex, and Duplex ultrasound or ferumoxytol-enhanced MR angiography findings as the independent variables.

Results: 59 participants with CKD (mean age 59±13 years, 30 women) were evaluated. A total of 51 fistulas were created, of which 24 (47%) were successful. Ferumoxytol-enhanced MR angiography showed excellent inter- and intra-reader repeatability (ICC 0.84-0.99) for all variables assessed. In addition to identifying 15 central vasculature stenoses, ferumoxytol-enhanced MR angiography characterized 88/236 (37%) of the arterial sections examined as unsuitable for AVF creation compared with 61/236 (26%) with Duplex ultrasound (P=0.01). Ferumoxytol-enhanced MR angiography independently predicted AVF success in models including [OR: 6.5 (95% CI 1.7-25); P=0.006] and excluding [OR: 4.6 (95% CI 1.3-17); P=0.02] the central vasculature.

Conclusion: In addition to the identification of central vessel pathology, ferumoxytol-enhanced MR angiography showed peripheral arterial disease not recognized with Duplex ultrasound and predicted the outcome of arteriovenous fistula surgery better than Duplex ultrasound.

Manuscript type: Original Research

Summary statement:

Compared with Duplex ultrasound, ferumoxytol MR angiography had superior detection of central vein stenosis and arterial disease that correlated with outcomes of arteriovenous fistula surgery for hemodialysis.

Key results:

- In 59 participants with chronic kidney disease, ferumoxytol-enhanced MR angiography identified 15 central vessel stenoses and characterized 37% of arterial sections as unsuitable for arteriovenous fistula creation compared with 26% for Duplex ultrasound (P=0.01).
- Ferumoxytol-enhanced MR angiography independently predicted successful fistula outcome for models including [OR: 6.5; P=0.006] and excluding [OR: 4.6; P=0.02] central vasculature.
-Ferumoxytol-enhanced MR angiography showed excellent inter- and intra-reader repeatability (ICC 0.84-0.99).

Abbreviations:

AVF: arteriovenous fistula

CE: contrast-enhanced

CKD: chronic kidney disease

CVS: central vein stenosis

ICC: interclass correlation coefficient

Introduction

Preoperative sonographic mapping of arm vessels is essential for creating permanent hemodialysis access and used for both arterial and venous evaluation to optimize arteriovenous fistula (AVF) placement for avoiding unsuccessful surgery[1-3]. But Duplex ultrasound is limited by an inherent operator-dependence, the inability to provide direct evidence of central stenosis[4] and the lack of image manipulation and reconstruction to inform the surgeon about vascular anatomical course and tortuosity.

Contrast-enhanced MR angiography provides excellent visualization of both central and upper extremity vessels[5,6]. However, the risk of nephrogenic systemic fibrosis in advanced chronic kidney disease (CKD) curtailed its use in arteriovenous access planning [7]. Nonetheless, suspected central stenosis may still require angiography of the central vessels. An alternative option of traditional iodinated contrast-based CT angiography risks nephrotoxicity in patients with residual renal function.

Ferumoxytol has been increasingly used for MR angiography, particularly for patients with CKD[8-10]. Ferumoxytol is an ultra-small paramagnetic iron oxide embedded in a carbohydrate coating[11] originally designed as a contrast agent for

MRI[12]. However, a strategic decision to license the drug as a therapeutic iron supplement eclipsed its use as an MRI contrast agent. A large molecular weight of 750kD[11] 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,[13] ferumoxytol allows enhancement of both the arterial and venous vasculature without the need for bolus timing.

Our study hypothesis was that ferumoxytol-enhanced MR angiography is superior to Duplex ultrasound for AVF planning as a) it can diagnose central stenosis and b) it can precisely assess arm vessels anatomy and identify abnormalities. To test our hypothesis we compared the two modalities using anatomical parameters predictive of fistula outcome in participants with CKD.

Materials and Methods

Study protocol

This was a prospective comparative single center study conducted between December 2016 and August 2018. The study protocol (http://dx.doi.org/10.36399/gla.pubs.215112) was approved by the institutional review board (Research Ethics Committee reference: 16/NS/0099) and registered with the ClinicalTrials.gov (NCT02997046). The study was funded by the Glasgow renal and transplant unit endowment fund and ferumoxytol was supplied by AMAG Pharmaceuticals free of charge. The authors had control of the data and the

information submitted for publication. Written informed consent was obtained from all participants.

Study participants

Participants with CKD (≥18 years of age) requiring vascular mapping before creation of an autogenous upper arm AVF were eligible for enrollment. Consecutive patients with CKD attending the outpatient renal clinics were screened for eligibility. Exclusion criteria were a) frail, elderly or participants with multiple or serious co-morbidities, b) standard contraindications to MRI and c) history of allergic reaction to any intravenous iron product, multidrug allergies, conditions associated with iron overload, and participants with asthma.

Study procedures

All participants underwent ferumoxytol-enhanced MR angiography and Duplex ultrasound on the same day using a standardized protocol (online Supplemental Material). Ultrasound mapping was performed with a Philips iU22 color Duplex scanner (Philips Healthcare, Bothell, WA) (online Supplemental Material).

Ferumoxytol-enhanced MR angiography was performed on a 3.0 T Prisma MRI scanner (Magnetom, Siemens Healthineers, Erlangan; Germany) with phased-array imaging coils. 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 participants 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 minimize image distortion (Movies S1, S2, S3 - online Supplemental Material). For analysis of the vessels, steady state high-spatial-resolution 3D FLASH acquisitions were obtained after administration of the full dose of ferumoxytol. Acquisition parameters for the post-contrast MR angiography included repetition time (TR) of 2.88 msec and echo time (TE) of 1.04 msec (Table S1 – online Supplemental Material). Ferumoxytol (Feraheme®, AMAG Pharmaceuticals, Waltham, MA) was infused intravenously at a dose of 3mg/kg (up to a maximum of 300mg) based on preliminary data from feasibility[14] and dose-finding[15] studies. Ferumoxytol was diluted in sodium chloride 0.9% (1:4 dilution factor) and 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 participants were observed for a minimum of 30 minutes following termination of ferumoxytol infusion.

Image analysis

Two independent readers with more than 3 years of experience in cardiovascular MR imaging (S.S., nephrologist with expertise in hemodialysis vascular access and A.T., interventional radiologist) assessed the ferumoxytol-enhanced MR angiography and one reader (S.S.) the Duplex ultrasound (standard technique). To assess intra-reader agreement for the ferumoxytol-enhanced MR angiography, both readers repeated the analyses within a time interval of >30 days to avoid recall bias. Readers were blinded to all clinical information, Duplex ultrasound results and AVF outcome during analysis.

For comparative analysis arterial and venous cross-sections (4 of each) were selected at specified locations. We analyzed 472 cross-sections for each imaging

technique (8 sections per participant). These circular cross-sections were placed in the radial artery at wrist, mid-forearm and elbow, brachial artery at elbow, cephalic vein at wrist, mid-forearm and elbow, and basilic vein at elbow (Figure 1). 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. 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 arterialized vein after fistula formation[16].

Algorithm to predict AVF outcome

As part of routine clinical practice, most patients in our center have preoperative Duplex ultrasound before AVF creation. The surgeons creating the fistulas had this information available, but were blinded to both the ferumoxytol-enhanced MR angiography and Duplex ultrasound that were performed separately as part of the study.

Based on accepted anatomical criteria for AVF creation[3,17], an algorithm was formulated to predict AVF outcome relying on MR angiography or US findings (Figure 2). 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. Arterial disease was defined as extensive calcification or monophasic flow on Duplex ultrasound, and narrowed arteries with luminal interruptions on ferumoxytol-enhanced MR angiography. 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.

Arteriovenous fistula outcome was defined using US surrogates for maturation and clinical use (online Supplemental Material).

Data analysis

Descriptive statistics are expressed as means ± SD or absolutes and percentages. Interclass correlation coefficient (ICC) with 95% CI using two-way mixed effects models were performed to test intra- and inter-reader consistency of agreement and Bland-Altman plots[18] 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[19]. Three binomial logistic regression models were created with successful AVF outcome as the dependent variable and age, sex, and Duplex ultrasound (model 1), or ferumoxytol-enhanced MR angiography of central and peripheral vessels (model 2) or ferumoxytol-enhanced MR angiography of peripheral vessels (model 3) as the independent variables. To compare our models, the Akaike's Information Criterion (AIC) was used as a measure of the models' fit.

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

Results

Participant Characteristics

Between December 2, 2016, and August 20, 2018, 302 participants were screened and 65 were enrolled (Figure 3). Of the 237 subjects who were excluded, 158 were found to be ineligible for the study. The reasons for exclusion in these 158

subjects are shown in Figure 3 and Table S2 (online Supplemental Material). In total, 59 participants (mean age 59 ± 13 years; 30 women; 27% with diabetic nephropathy) underwent study specific mapping protocols (Table 1). Median follow-up after AVF creation was 22 (interquartile range 18 - 27) months. No adverse events occurred related to ferumoxytol infusions, and there were no systematic changes in blood pressure, heart rate or oxygen saturation following ferumoxytol administration (data not presented).

Repeatability studies

The overall inter-reader agreement for ferumoxytol-enhanced MR angiography 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 S3 – online Supplemental Material). Twenty participants (aged 58 ± 12 years; 11 women; 31% with diabetic nephropathy) were selected at random for intra-reader agreement, interclass coefficients were between 0.91 – 0.99 for all parameters, indicating excellent agreement (Table S3 – online Supplemental Material). 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 4).

Predictors of AVF outcome

We tested three independent variables in each of the binomial logistic regression models used for multivariable analysis: age, sex, and either Duplex ultrasound (model 1), ferumoxytol-enhanced MR angiography of central and

peripheral vessels (model 2), or ferumoxytol-enhanced MR angiography of peripheral vessels (model 3). In univariable analysis for AVF outcome (success vs failure) ferumoxytol-enhanced MR angiography of central and peripheral vessels [odds ratio (OR) 5.1 (95% CI 1.5-17); P=0.008], and ferumoxytol-enhanced MR angiography of peripheral vessels [OR 4.2 (95% CI 1.2-15); P=0.03] predicted a successful outcome. Using multivariable analysis, ferumoxytol-enhanced MR angiography of central and peripheral vessels [OR 6.5 (95% CI 1.7-25); P=0.006], and ferumoxytol-enhanced MR angiography of peripheral vessels [OR 4.6 (95% CI 1.3-17); P=0.02] were independent predictors of successful AVF outcome. There was no significant association between age (P=0.14), sex (P=0.77), or Duplex ultrasound (P=0.14) and outcome (Table 2). The AIC was 72, 66 and 69 for models 1, 2 and 3 respectively, showing that model 2 better predicted AVF outcome.

Ferumoxytol-enhanced MR angiography and Duplex ultrasound equally identified peripheral vein sections unsuitable for fistula creation, but ferumoxytol-enhanced MR angiography classified more arterial sections as unsuitable for fistula attempt predominantly based on diameter criteria (Table 3). Ferumoxytol-enhanced MR angiography detected central vein stenosis (CVS) in 7/59 (12%) participants (Movie S4 - online Supplemental Material). Cephalic arch stenosis was present in 6/59 (10%) and subclavian artery stenosis in 2/59 (3%) participants (Table 3 and Figure 5). Five (71%) of patients with CVS had previous central venous catheterizations for dialysis. Ferumoxytol-enhanced MR angiography better assessed vessel course and tortuosity but both imaging modalities depicted other anatomical characteristics (such as branches or vein depth from skin surface) (Table 3). From the 27 unsuccessful AVF surgeries, 7 (26%) could have been avoided based on the ferumoxytol-enhanced MR angiography findings.

Discussion

Arteriovenous fistula failure is common and invariably associated with preexisting anatomical problems of the inflow and outflow circuit. Ferumoxytol-enhanced MR angiography provided high quality peripheral vascular mapping in participants with CKD referred for arteriovenous fistula creation with accurate depiction of the central vasculature. Compared with Duplex ultrasound, ferumoxytol-enhanced MR angiography better predicted successful fistula outcome (OR 6.5; P=0.006) and identified small arteries unsuitable for fistula creation not recognized with Duplex ultrasound (37% vs 26%; P=0.01). In addition, ferumoxytol safely imaged predialysis patients without concerns for iodine or gadolinium contrast toxicity.

In our study, more than a third of participants had at least one previous central venous catheterization for dialysis, 12% had CVS and another 10% cephalic arch stenosis. Our rates are comparable with other studies, such as Oguzkurt *et al.*, who reported 16% angiographically-proven CVS in dialysis patients with temporary catheters[20] and Wang *et al.*, who reported 9% clinically noticeable CVS in dialysis patients[21]. Central vein stenosis is most commonly related to prior central catheters and can occur due to trauma from catheter insertion, stagnation of blood at the catheter insertion site, and turbulent blood flow during hemodialysis[22]. Our results showed 71% of CVS associated to previous catheters but it was conspicuously seen in participants without prior catheter use, and without the presence of non-dialysis risk factors, 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), ferumoxytol-enhanced MR angiography had a better discriminatory power than Duplex ultrasound, whereas for the distinction between small diameter veins (< vs >2.5 mm), there was no difference in diagnostic performance. Ferumoxytol-enhanced MR angiography has excellent spatial resolution providing a more precise estimate of the vessel lumen, whereas Duplex ultrasound is operator-dependent and susceptible to the presence of calcification. This likely explains why the difference was only noted in the arteries 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, but the effect of these factors (if any) is impossible to quantify.

In the wake of our findings, the adoption of ferumoxytol-enhanced MR angiography in clinical practice could increase the number of successful first-time fistulas and thereby reduce the burden of repeated procedures. Nonetheless, Duplex ultrasound 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. Ferumoxytol-enhanced MR angiography could be reserved for patients with risk factors for venous complications, peripheral arterial disease, previous failed accesses or borderline vessels in Duplex ultrasound. This is highlighted in the recent European Society for Vascular Surgery (ESVS)[2] and Kidney Disease Outcomes Quality Initiative (KDOQI)[23] clinical practice guidelines for vascular access, which recommend various imaging studies to evaluate the suitability of peripheral vessels and central veins for occlusion.

In June 2009, ferumoxytol was approved for parenteral treatment of iron deficiency anemia in patients with CKD[24] 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[25]. Ferumoxytol is less immunogenic compared to other parenteral iron preparations with minimal labile free iron release.[11] But in some patients (1 to 3%) the iron release can cause a constellation of symptoms termed a Fishbane reaction. In 2015, the U.S. Food and Drug Administration (FDA) issued a black-box warning for ferumoxytol[26]. Based on 79 reports of spontaneous adverse events relating to therapeutic use (18 fatal), the FDA warned of rare but serious hypersensitivity reactions including anaphylaxis. New therapeutic prescribing recommendations included dilution, infusion over 15 minutes (in contrast to the originally advocated bolus injection over 17 seconds), and hemodynamic monitoring up to 30 minutes after infusion. While this is applicable for the therapeutic dose of 510mg (approximately 7mg/kg for a 70kg adult), the prorated infusion time for the diagnostic dose of 3mg/kg would be about 6.5 minutes, while still staying within the recommended FDA limits. A multicenter safety report on diagnostic use of ferumoxytol in MRI from 11 institutions worldwide (including our center), demonstrated no serious adverse events and few (<2%) minor adverse reactions following 4,240 ferumoxytol injections[27] using various infusion rates.

Ferumoxytol-enhanced MRI has been used in small CKD studies for a plethora of applications: diagnosis of central venous occlusion[28], assessment of kidney transplant vasculature[29,30] and autogenous hemodialysis arteriovenous fistulas[31], vascular mapping for access planning or transplantation[32] and transcatheter aortic valve replacement[33], venography in pediatric[34] and adult patients.[35] Currently, ferumoxytol-enhanced MRI is being tested for detection of coronary artery stenosis (NCT02954510). In all studies, ferumoxytol-enhanced MR angiography had good performance with comparable or superior image quality, along with reduced flow

artifacts and scanning time compared with conventional digital subtraction angiography and non-enhanced or gadolinium-based MR angiography.

Our study has limitations. First, we did not examine internal jugular and subclavian vein waveforms with Duplex ultrasound to indirectly predict the presence of central vein stenosis. However, this is time-consuming and technically difficult. Second, our study 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[17]. Third, the sample size in our study was relatively modest with respect to absolute participant numbers, but many vascular sections (approximately 500) were analyzed. There are also limitations pertaining to translation of our study protocol to clinical practice. For example, ferumoxytol is not as yet licensed as a contrast agent for MRI and it is only used off-label by clinicians and researchers. Emerging issues with trace gadolinium retention in biologic tissues[36,37] have given rise to new controversies about the use of gadolinium-based contrast agents in MRI and have generated calls for new contrast agent classes. To date, a growing number of imaging studies with ferumoxytol are underway.

In conclusion, our results demonstrated that ferumoxytol-enhanced MR angiography is a useful technique for vascular mapping before hemodialysis access creation to minimize unnecessary surgical procedures. Ferumoxytol-enhanced MR angiography is fast, operator-independent, reliable in the detection of central vein stenosis, and more accurate for visualization of the arm vessels compared with Duplex ultrasound. A randomized study of ferumoxytol-enhanced MR angiography vs Duplex ultrasound with appropriate stratification is needed to identify the patients that would benefit most from each technique.

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Table 1. Baseline characteristics of the 59 study participants

Age (y), mean (SD)	59 (13)
Men, n (%)	29 (49)
Race, n (%)	
White	49 (83)
Asian	9 (15)
Black African	1 (2)
Body weight (kg), mean (SD)	74 (17)
Body mass index categories, n (%)	
<18.5	5 (9)
18.5 - 24.9	16 (27)
25 - 30	18 (30)
>30	20 (34)
Cause of end-stage kidney disease, n (%)	
Diabetes	16 (27)
Glomerulonephritis	13 (22)
Renovascular	7 (12)
Polycystic kidney disease	6 (10)
Unknown	7 (12)
Other[a]	10 (17)
Laboratory values at time of MRI	
Hemoglobin (g/L), mean (SD)	107 (17)
Creatinine (mg/dL), mean (SD)[b]	5 (2)
Estimated glomerular filtration rate (mL/min/1.73m^2), mean (SD)[b]	12 (3)
Chronic kidney disease stage, n (%)	
Stage 4	5 (8)
Stage 5 - non-dialysis	33 (56)
Stage 5 - dialysis	21 (36)
Dose of ferumoxytol given (mg), mean (SD)	227 (48)
At least one previous arteriovenous access, n (%)	9 (15)
At least one previous central venous catheterization, n (%)	21 (36)
[a]Obstructive uropathy (n=3), Pyelonephritis (n=2), Tubulointerstitial nephritis (n=2), Cyclosporine toxicity (n=2), Congenital dysplasia (n=1) [b]Excludes participants on dialysis	

Table 2. Univariable and multivariable analyses of factors associated with arteriovenous fistula outcome (success vs failure)

	Univariable analysis		**Multivariable analysis (US mapping)**		**Multivariable analysis (Fe MR angiography peripheral vessels only)**		**Multivariable analysis (Fe MR angiography central plus peripheral vessels)**	
	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	1 (0.9 – 1)	0.28	1 (0.9 – 1)	0.23	1 (0.9 – 1)	0.21	1 (0.9 – 1)	0.14
Sex	1.3 (0.4 – 4)	0.65	1.2 (0.4 – 3.9)	0.77	1.1 (0.3 – 3.8)	0.85	0.9 (0.3 – 3.2)	0.86
US mapping	2.3 (0.7 – 7.4)	0.17	2.5 (0.7 – 8.4)	0.14				
Fe MR angiography (peripheral vessels)	4.2 (1.2 – 15)	0.03			4.6 (1.3 – 17)	0.02		
Fe MR angiography (central plus peripheral vessels)	5.1 (1.5 – 17)	0.008					6.5 (1.7 – 25)	0.006

Fe, ferumoxytol-enhanced

Table 3. Anatomical lesions and variants identified in 236 vascular cross-sections (ferumoxytol-enhanced MR angiography vs Duplex ultrasound)

	Ferumoxytol-enhanced MR angiography	**Duplex ultrasound**
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
Basilic vein ≥2 branches	10	12
High brachial artery bifurcation	4	3

Figure legends

Figure 1. Method for the comparative analysis using arterial and venous vascular cross-sections. Ferumoxytol-enhanced MR angiography high-resolution steady-state (HRSS) coronal and transverse sections of the arm at the wrist, mid-forearm and elbow. Regions of interest were drawn for estimation of arterial and vein diameter and vein depth from skin surface.
BA, brachial artery; BB, brachial vein bundle; BV, basilic vein; C, collateral vein; CV, cephalic vein; RA, radial artery

Figure 2. Algorithm used to predict arteriovenous fistula outcome based on anatomical parameters evaluated with Duplex ultrasound and ferumoxytol-enhanced MR angiography

Figure 3. Flowchart of recruitment and arteriovenous fistula outcomes
Fe, ferumoxytol-enhanced; AVF, arteriovenous fistula; TCVC; tunneled central venous catheter

Figure 4. Bland-Altman plots of inter-reader variability for ferumoxytol-enhanced MR angiography. 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.

Figure 5. Steady-state thick slab maximum intensity projection (MIP) coronal ferumoxytol-enhanced MR angiography 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 (arrow). F. Occluded right brachiocephalic vein (arrow).

IJV, internal jugular vein; SCV, subclavian vein; BCV, brachiocephalic vein; SVC, superior vena cava

Supplementary Material

Vascular mapping protocol

Veins were evaluated for diameter, patency, compressibility (Duplex ultrasound 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 ultrasound only), and anatomic variants. Central arteries and veins were only assessed with ferumoxytol-enhanced MR angiography for the presence of stenosis or occlusion. Stenosis was defined as reduction of the luminal diameter of ≥50% and occlusion as complete absence of any flow signal.

Ultrasound mapping

Duplex ultrasound of bilateral upper extremities was performed in real-time using a Philips iU22 color Duplex scanner (Philips Healthcare, Bothell, WA) with a 5–17 MHz broadband linear-array transducer (Phillips L17-5). The participants 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. 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 Duplex waveforms were recorded and archived. Average Duplex ultrasound duration was 25 minutes for mapping of both arms.

Arteriovenous fistula 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 participants not on dialysis at the end of follow-up, ultrasound criteria for AVF maturation at 6 weeks (600 ml/min blood flow, 6 mm diameter, and <6 mm depth from the skin[1]) were used as a surrogate of maturation.

References

1. Vascular Access 2006 Work Group, Clinical practice guidelines for vascular access. *Am J Kidney Dis.* 2006;48 Suppl 1:S176-247.

Supplementary Table 1. Pulse sequence parameters for the ferumoxytol-enhanced MR angiography T1-weighted high-resolution 3D acquisitions

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

Supplementary Table 2. Reasons for exclusion from the study (N =158)

Contraindications to MRI (N=80)
29 claustrophobia
21 not fitting into the scanner due to obesity
19 metallic objects in the body
11 unable to lie flat (i.e. back pain, dyspnea)
Frail or co-morbidities (N=52)
39 frail
8 active cancer
3 dementia
2 blind
Allergies and other conditions (N=26)
11 multidrug allergies
7 asthma
6 allergic reaction to intravenous iron
2 haemochromatosis

Supplementary Table 3. Interclass correlation coefficients to test consistency of agreement in ferumoxytol-enhanced MR angiography

	ICC (95% CI) values comparing cross-sections measurements	
	Inter-reader	**Intra-reader**
Arterial diameter		
RA (wrist)	0.90 (0.84 – 0.94)	0.95 (0.91 – 0.97)
RA (mid-forearm)	0.90 (0.83 – 0.94)	0.95 (0.91 – 0.97)
RA (elbow)	0.89 (0.85 – 0.93)	0.97 (0.94 – 0.98)
BA (elbow)	0.94 (0.88 – 0.97)	0.97 (0.94 – 0.98)
All arteries	0.90 (0.87 – 0.93)	0.95 (0.93 – 0.96)
Vein diameter		
CV (wrist)	0.95 (0.92 – 0.97)	0.98 (0.96 – 0.99)
CV (mid-forearm)	0.96 (0.94 – 0.98)	0.98 (0.97 – 0.99)
CV (elbow)	0.98 (0.97 – 0.99)	0.99 (0.98 – 1.00)
BV (elbow)	0.96 (0.93 – 0.98)	0.98 (0.96 – 0.99)
All veins	0.84 (0.78 – 0.88)	0.91 (0.88 – 0.93)
Vein depth from skin surface		
CV (wrist)	0.91 (0.85 – 0.95)	0.95 (0.92 – 0.98)
CV (mid-forearm)	0.99 (0.98 – 0.99)	0.99 (0.99 – 1.00)
CV (elbow)	0.99 (0.98 – 1.00)	0.99 (0.99 – 1.00)
BV (elbow)	0.95 (0.91 – 0.98)	0.98 (0.95 – 0.99)
All veins	0.92 (0.89 – 0.94)	0.96 (0.94 – 0.97)
RA, radial artery; BA, brachial artery; CV, cephalic vein; BV, basilic vein		

Supplementary Movie 1

Maximum intensity projection (MIP) coronal ferumoxytol-enhanced MR angiography slices of the thorax showing normal arterial and venous central vasculature. Note the simultaneous arterial and venous enhancement with ferumoxytol-enhanced MR angiography due to the prolonged intravascular half-life of ferumoxytol.

Supplementary Movie 2

Maximum intensity projection (MIP) sagittal ferumoxytol-enhanced MR angiography slices of the forearm showing the anatomy, course, tortuosity, branches and proximity of vascular structures providing additional information to guide surgical decisions.

Supplementary Movie 3

Maximum intensity projection (MIP) transverse ferumoxytol-enhanced MR angiography slices of the mid-arm showing the diameter and course of the cephalic vein, basilic vein, brachial artery and concomitant brachial vein bundle throughout the length of the arm.

Supplementary Movie 4

Maximum intensity projection (MIP) coronal ferumoxytol-enhanced MR angiography slices of the thorax showing stenosis of the left brachiocephalic vein.

Figure 1

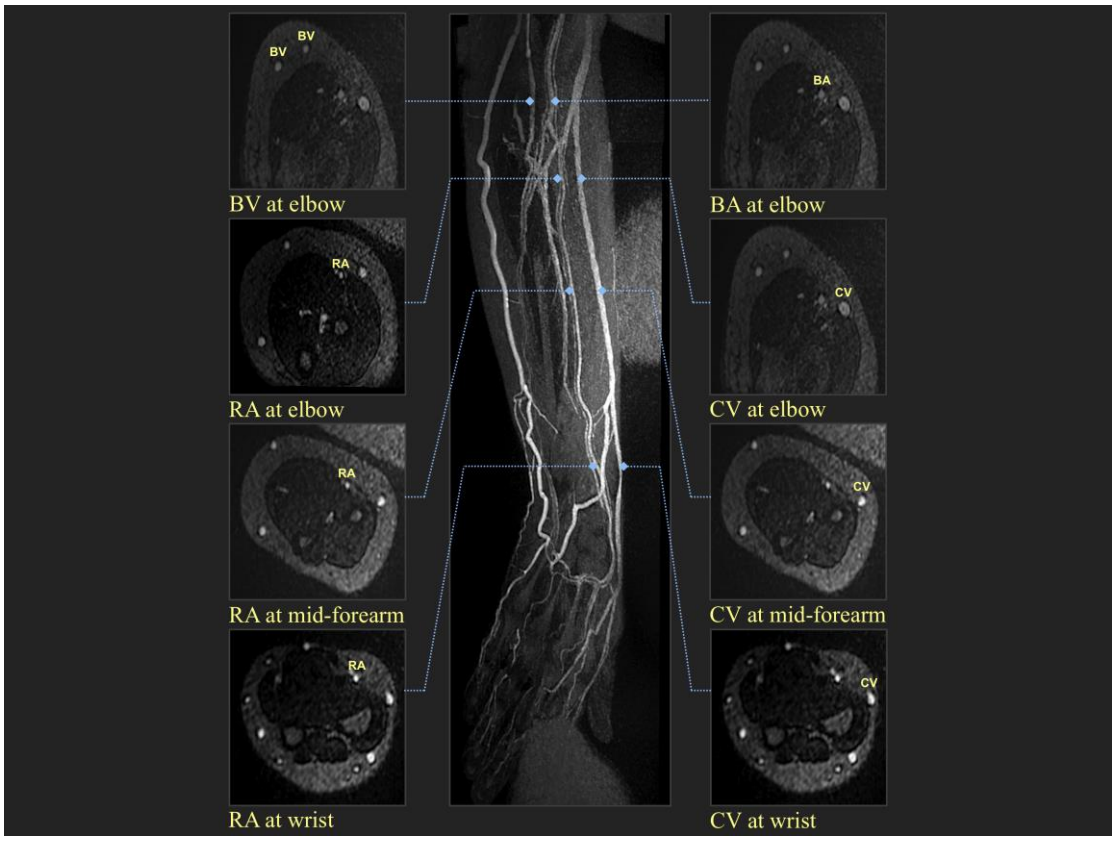
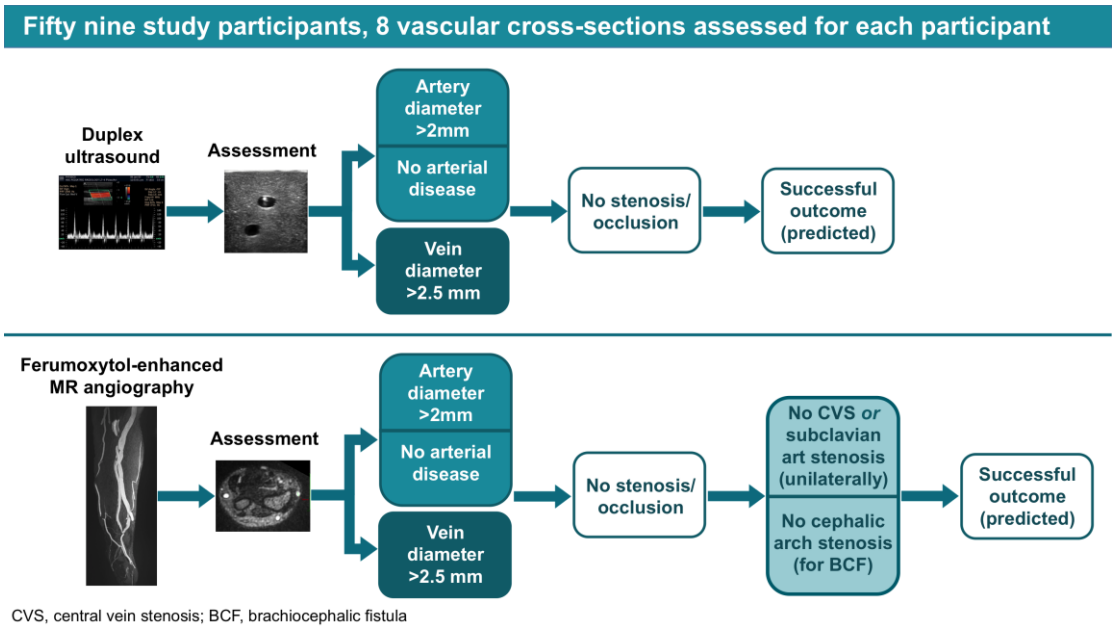

BV
BV
BV at elbow
BA
BA at elbow
RA
RA at elbow
CV
CV at elbow
RA
RA at mid-forearm
CV
CV at mid-forearm
RA
RA at wrist
CV
CV at wrist

Figure 2



CVS, central vein stenosis; BCF, brachiocephalic fistula

Figure 3

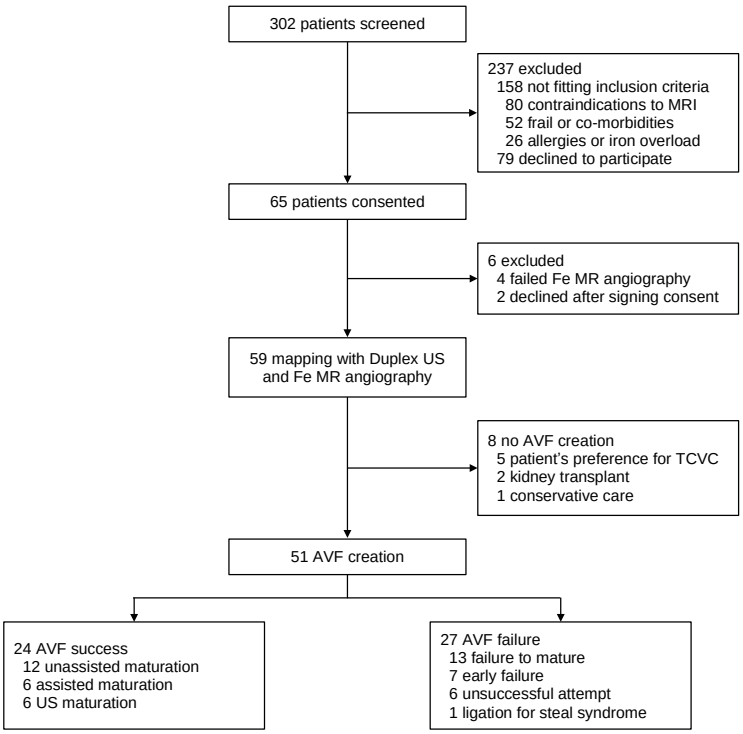

302 patients screened
237 excluded
158 not fitting inclusion criteria
80 contraindications to MRI
52 frail or co-morbidities
26 allergies or iron overload
79 declined to participate
65 patients consented
6 excluded
4 failed Fe MR angiography
2 declined after signing consent
59 mapping with Duplex US and Fe MR angiography
8 no AVF creation
5 patient's preference for TCVC
2 kidney transplant
1 conservative care
51 AVF creation
24 AVF success
12 unassisted maturation
6 assisted maturation
6 US maturation
27 AVF failure
13 failure to mature
7 early failure
6 unsuccessful attempt
1 ligation for steal syndrome

Figure 4

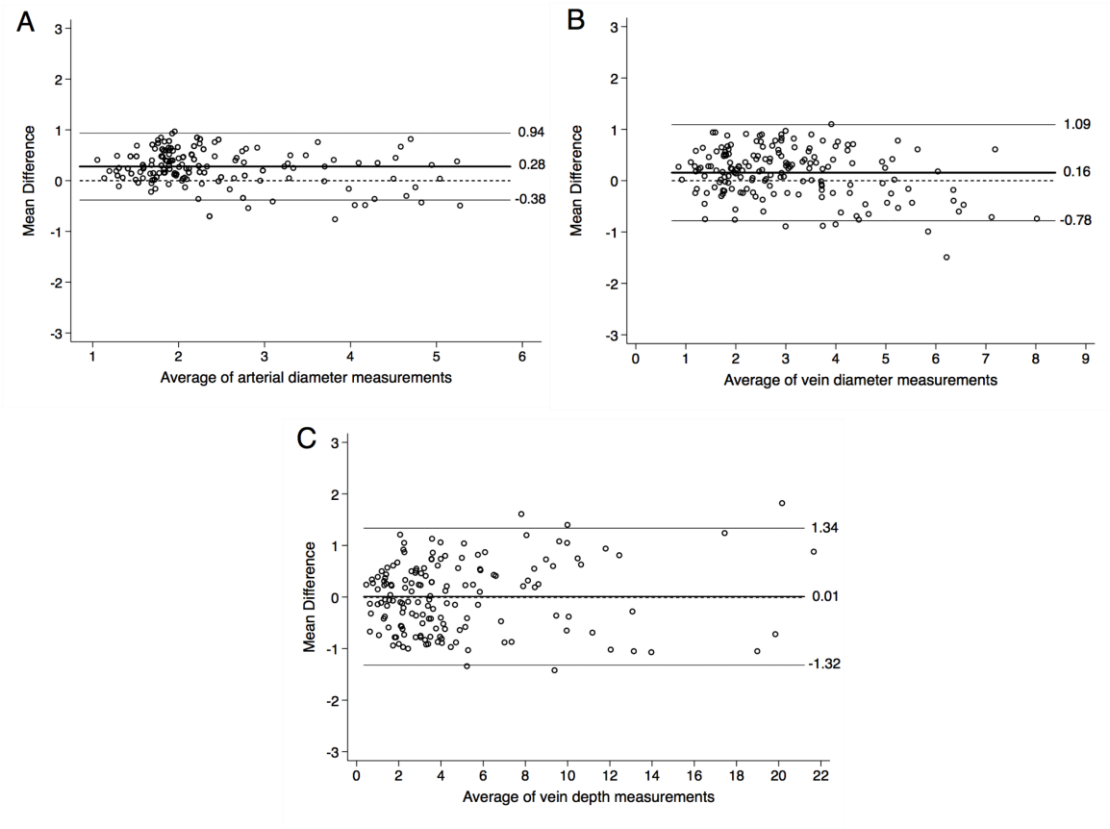

A
Mean Difference
0.94
0.28
-0.38
Average of arterial diameter measurements
B
Mean Difference
1.09
0.16
-0.78
Average of vein diameter measurements
C
Mean Difference
1.34
0.01
-1.32
Average of vein depth measurements

Figure 5