**Protocol and baseline data**

**A multicentre prospective double blinded randomised controlled pilot trial of intravenous iron in Iron deficient but not anemic patients with chronic kidney disease on functional status.**

Short Title: Iron and the Heart Protocol, rationale, trial design, baseline data.

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Abstract

Background: Iron deficiency (ID) is common in patients with chronic kidney disease (CKD) due to inadequate dietary intake of iron, poor absorption from the gut, and increased iron losses. In addition to preventing anemia, iron is important for normal heart function, being involved in processes that generate a necessary continuous energy supply. Treatment with intravenous (IV) iron has been suggested to lead to improvement in heart function and wellbeing in people with ID and CKD.

In the Iron and the Heart Study, we hypothesized that IV iron treatment will primarily improve exercise capacity and may secondarily impact the feeling of wellbeing in comparison to placebo over 3 months in non-anaemic CKD patients who have ID.

Methods: This was a prospective double-blinded explorative randomized, multi-center study designed to compare the effects of IV iron supplementation and placebo in iron deficient but not anemic patients with established CKD stages 3b-5 on functional status, and in addition cardiac structure and function. The study included 54 adults with ferritin (SF)<100mcg/L and/or transferrin saturation (TSAT)<20%, randomized in a 1:1 ratio to 1000mg IV ferric derisomaltose or placebo. Following randomization, participants underwent baseline assessments and then received IV iron or placebo infusion. Each participant was followed up at months 1 and 3. At each visit patients underwent clinical review, measurements of hematinics and hemoglobin (Hb), and assessments of physical function and wellbeing. The primary outcome was exercise capacity using the 6-minute walk test. Secondary objectives included effects on hematinic profiles and Hb concentration, changes in myocardial parameters assessed with speckle tracking echocardiography, and change in patients’ quality of life.

Results: Between October 2016 and April 2018, 55 from 326 individuals from 3 UK centers attended screening and were randomized. The mean (SD) age was 59.6 (11.7) years, 26 (48%) patients were male, the majority were Caucasians (42; 8%), and 32 (59%) were non-smokers. The mean (SD) BMI was 30.3 (6.5); SF was 66.3 (44.1)mcg/L, TS was 20.1 (7.4)% and Hb was 128.7 (10.1)g/L at randomization for the whole group. Mean (SD) serum creatinine was 186.7 (58.6)micromol/L, eGFR was 31.1 (9.6)ml/min/1.73m2 and urinary albumin and protein/creatinine ratios 60.9 (133.3) and 83.8 (128.4)mg/mmol, respectively. The mean (SD) CRP was 5.0 (4.4)mg/L and the mean (SD) 6-minute walk distance at baseline was 401.2 (120.2)m.

Conclusion: The Iron and the Heart Trial will provide important information on the short-term effects of IV iron treatment in CKD patients with ID without anemia on measures of exercise capacity, quality of life, and mechanistic data on myocardial structure and function.

Trial Registration: European Clinical Trials Database (EudraCT) No: 2014-004133-6

REC no: 14/YH/1209

Sponsor ref R1766

Keywords: Anemia, Chronic Kidney Disease (CKD), Intravenous Iron, Iron deficiency, Ferric derisomaltose, Iron isomaltoside, Protocol, Randomized trial,

**Introduction**

Uraemia predisposes to age-adjusted cardiovascular morbidity and mortality. Non-dialysis chronic kidney disease (CKD) G3b or worse is associated with a significant excess mortality (1). The development of cardiovascular disease in patients with CKD is multifaceted. It includes macrovascular structural changes, metabolic abnormalities in calcium and phosphate, hypertension, iron deficiency, anemia and volume overload, which all play their part at increasing the cardiovascular risk. Indeed, mortality rates from conventional cardiac causes like myocardial infarction are more common in patients with CKD and may relate to factors other than conventional coronary artery disease (2). Previously we have shown that in a single centre study of 955 patients with heart failure and CKD, the prevalence of anemia was 32% (3). Furthermore 43% of patients with identified anemia and 15% of those without anemia from the total cohort had iron and/or folate deficiency and survival was worse in deficient patients (3). Hence iron may be an important substrate for optimal cardiac function and reduction in cardiac risk as noted in the recent PIVOTAL study (4).

In addition, iron plays a key role in the cellular uptake of oxygen, transport, storage and metabolism in both skeletal and cardiac muscle (5, 6). The rationale therefore for the current study is based on evidence that myocardial energy production is a crucial aspect of cardiac function. The heart consumes large quantities of energy for myofibril contraction and maintenance of ionic gradients. Abnormalities in myocardial energy metabolism develop in uraemic patients (7, 8). Mitochondria are the main source of energy upon which cardiomyocytes depend for their contraction. In an animal model of stressed hearts with CKD and iron deficiency, Taylor et al showed that there was an increase in stage 4 respiration and uncoupling proteins leading to mitochondrial dysfunction and an increase in transition pore formation leading to impaired contractile function of myocytes (9). Therefore, iron deficiency may lead to mitochondrial dysfunction through possible effects on transition pore opening and subsequent inhibition of the protective pathway and activation of apoptosis. In addition, chronic deficiency of iron may subsequently lead to adaptive structural changes in cardiac myocytes (10). This effect on the cardiac myocytes will undoubtedly lead to reduced exercise capacity and physical performance (11, 12).

In addition, data from Piga *et al* (personal communication, Italy) in Frederich’s ataxia exposed to iron chelation has shown mitochondrial dysfunction which requires iron supplementation to restore function. Correction of this iron deficiency in patients with CKD and either functional or absolute iron deficiency may lead to improved mitochondrial and hence cardiac function. Iron treatment may also correct anemia, has been shown to improve skeletal muscle function (13), and may have other pleotropic effects.

Previously one small cohort study and two larger randomised studies have examined the effects of intravenous (IV) iron in patients with heart failure and demonstrated an increased haemoglobin, better renal function, and lower N-terminal Pro Brain Natriuretic peptide (NT pro BNP) (14-16). This latter study (FAIR-HF) (16) demonstrated benefits in terms of physical capacity (6-minute walking distance- 6MWT), quality-of-life and New York Heart Association (NYHA) functional class. Although the study was not designed for this purpose, there was a trend toward reduced cardiovascular hospitalisation in patients who received IV iron rather than placebo infusions (16). The subsequent CONFIRM-HF study verified these results in a larger RCT (17). Interestingly, this beneficial effect was similar in patients both with and without anemia. Taken together these studies suggest that IV iron may have beneficial effects on the heart which may impact on reduced cardiovascular events, improved functional capacity and reduced symptoms if present. The IRONOUT study which compared high dose oral iron versus placebo over a 16 week period in 225 heart failure patients with iron deficiency found no change in either maximal oxygen uptake or the secondary outcome of 6MWT (change -19m with iron vs +32metres with placebo) (18). The EFFECT-HF trial in 172 patients with systolic heart failure did demonstrate improved functional status and feeling of well-being but also did not show any significant change in maximal oxygen uptake when IV iron was compared to standard care (19). Hence the potential underlying beneficial mechanism, is not clear, nor has this been examined in a specific renal population.

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**Materials and Methods**

**Trial Design**

 would be current enrolledPatients were randomised in a 1:1 ratio after screening into two arms to receive either IV ferric derisomaltose or IV placebo (dummy solution of normal saline) (**Figure 1**). The stage of CKD was determined by calculating the estimated glomerular filtration rate (eGFR) using the CKD- Epidemiology Collaboration (CKD-EPI) equation (20).

**Selection of Participants**

Currently, patients with CKD under the care of a nephrologist are reviewed approximately every 3-4 months in a hospital out-patient clinic. Potential participants were identified either when presenting for routine visits or through searching the renal electronic database for potential patients using the inclusion/exclusion criteria at the three renal centers (**Supp. Fig 1**).

**Eligibility and screening**

Each patient who met all of the inclusion criteria, and no exclusion criteria (**Table 2**), at entry to the trial were recruited by the investigators or any medically qualified member of the local trial teams who had been delegated responsibility for trial recruitment. The patients were given a comprehensive verbal explanation of the trial (explaining both the investigational and standard treatment options and highlighting any possible benefits or risks relating to participation). Time for questions throughout the discussion was given and questions adequately addressed. This included information about the rationale, design and personal implications of the study. Following information provision, the patients had at least 24 hours to consider participation and were given the opportunity to discuss the trial with their family and healthcare professionals before being invited to attend the screening visit.

After consent and following a physical examination, blood samples from willing participants were sent to the hospital’s pathology laboratory for confirmation of eligibility. If the results were considered inaccurate (e.g. hemolyzed sample) by the investigator the samples could be repeated once.

 **Ethics**

This study was carried out in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and received ethical approval from the Northern Regional Ethics Service (NRES) Committee Yorkshire & The Humber - Leeds East, UK), approval reference number REC no: 14/YH/1209. In the event of participants suffering harm due to the study, the trial was covered by NHS Indemnity insurance.

**Randomization Procedure**

After obtaining informed consent, eligible participants were assigned a unique participant's identification number for the Iron and the Heart Trial. Once this number was assigned to participants, the participant’s number was not reused. Participants were randomly allocated in a 1:1 ratio to receive either placebo IV saline fluid or intervention (experimental arm) of IV iron preparation (single 1000 mg dose of ferric derisomaltose) at visit 2 (baseline). The randomization was performed by a computer program (sealedenvelope.com). Labels were consecutively numbered 1-60. These labels were then sealed in non-transparent double sealed envelopes. Access to these envelopes was not available to investigators. Details of the iron therapy were held by pharmacy that matched the choice of interventional iron therapy with the relevant randomization number. Both numbers and iron therapy treatment administered at visit 2 were recorded in the participants’ medical case records. At randomisation, patients were stratified for the presence or absence of diabetes.

**Baseline measurements**

Following randomization, willing and eligible participants were invited to attend a baseline visit, at which baseline investigations were performed (**Supp Table 1**). Data on demographics (date of birth, sex, ethnicity, smoking status, alcohol intake, body mass index (BMI), primary etiology of CKD) was collected and recorded. A detailed disease history including cardiovascular co-morbidity and list of concomitant medications was taken. Vital signs were recorded including blood pressure and a physical examination performed.

Baseline investigations included eGFR and biochemical profile (BCP), Full blood count (FBC), SF, TSAT and C-reactive protein (CRP). Quantification of proteinuria was carried out by measurement of urinary protein:creatinine ratio (uPCR) or if diabetic, urinary albumin:creatinine ratio (uACR) levels in a spot urine sample using standard laboratory techniques.

Two further samples were obtained from participants and placed in EDTA and serum separating tubes (SST). They were centrifuged and the plasma and serum aliquoted into cryovials, ad stored initially locally at -80 °C prior to transfer to the University laboratory in Hull, UK, where they were stored at −80°C until analyzed for inflammatory and oxidative stress biomarkers.

In addition, pulse wave velocity (PWV) was performed using a vicord machine in all three centres.

**Six Minute walk Test (6MWT)**

The six-minute walk test was performed at each visit**.** The 6-minute walk test (6MWT) is a low-cost and valid measure of exercise tolerance. Participants were instructed to walk for 6 minutes up and down a 20-meter-long level corridor as quickly as possible. This test was be carried out in a designated quiet area with chairs placed at various points to allow patients to rest if necessary. Performance was quantified by the total distance walked.

At baseline, participants completed three questionnaires which consisted of the Kidney Disease Quality of Life Short Form Questionnaire (KDQoL-SF-36); The Minnesota Living with Heart Failure Questionnaire (MLHF) and the Restless leg syndrome scale questionnaire (RLSS). The KDQoL-SF is a preference-based measure of health (KD QoL-SF-36) questionnaire, a standardized survey used to assess patient health (21) and two other questionnaires. After all baseline measurements were performed, participants were accompanied to the hospital’s medical day unit where IV iron or placebo was administered as per hospital policy.

A 12-lead electrocardiogram (ECG) and 2-D echocardiography were also performed at each visit, with the latter analysis using speckle tracking soft offline on the images.

**Speckle Tracking Echo (STE)**

A standardized Echo acquisition protocol was used to gather the necessary parameters which were assessed using standardized software on standard echo images for subsequent STE analysis at the main center (**Supp Table 2**).

All studies were performed in accordance with the recommendations of the British Society of Echocardiography using a GE Vivid 5, 7 or 9 echo machines. An adequate frame rate for apical views (between 40 and 80 frame/seconds) was employed with at least 3 cardiac cycles for each acquisition of data. blinded to the physical outcome data and questionnaire results

**Interventions**

Iron replacement was initiated based on a set protocol which is consistent with UK Renal Association and NICE (National Institute of Clinical Excellence) guidelines (22). Participants were randomized to receive an infusion consisting of 1000 mg ferric derisomaltose or 0.9% normal saline which was supplied by hospital pharmacy as per departmental protocol. All preparations were administered by an unblinded nurse not involved in the study via a double curtain so that the patient was also blinded to treatment allocation.

For the intervention (experimental) arm, ferric derisomaltose 1000 mg was dissolved in 100 ml of normal saline 0.9% and given over 30 minutes as a single intravenous infusion.

For the comparator (placebo) arm, 100 ml of normal saline 0.9% was given over 30 minutes as a single intravenous infusion.

Participants were closely monitored throughout the infusion and for an additional 30 minutes for haemodynamic changes or other adverse effects. Any events were recorded in the electronic case report and in the medical notes.

**Follow-up – assessments and monitoring**

Three time points were used to evaluate study outcomes: baseline, one month and three months. This enabled the assessment of physiological effects of iron early after administration via exercise performance and cardiac imaging, and later effects after potential remodelling as a result of iron repletion at a tissue level.

At all visits, the investigators sought information regarding adverse events (serious and non-serious) considered to be related to the intervention therapy. Weight, blood pressure and pulse wave velocity were measured at all visits, and the questionnaire completed at one month and three months visits.

After three months the participants continued to be reviewed as per normal practice every three months but no further data was collected. All information was collected and recorded on a secure encrypted and password protected computer database in the research unit at the NHS Trust.

**Laboratory Tests**

Before starting the trial, the principal investigator at each participating site supplied the Chief Investigator with a list of the normal ranges and units of measurements for the applicable parameters measured in the study. Any changes to these ranges and units were notified to the Chief Investigator. All laboratory parameters were performed and assessed in local laboratories at each site.

Biomarker analysis was carried out at the University of Hull for mechanistic work including inflammatory measures, measures of oxidative stress and endothelial function.

**Monitoring and Governance of Study**

Prior to commencing recruitment, the study staff received training in the study procedures**.** The study was monitored in accordance with Hull University Teaching Hospitals Research and Development Department’s (HUTH R&D) standard operating procedures to ensure compliance with UK Clinical Trial Regulations. Deviations from the protocol or GCP were reported by the investigator to HUTH R&D (as sponsor) on two monthly monitoring report forms. Investigators will take into account all protocol deviations and any serious breaches in the final study analysis and publication.

**Sample size calculation**

This was an explorative pilot study looking for proof of concept and therefore the trial is not large enough to be definitive, but is large enough to provide data on feasibility, desirability and likely size and endpoints to underpin a future definitive randomised controlled trial (RCT). The endpoint measures in the current exploratory pilot study were chosen to provide clinical relevance. Studies of the relationship between patients’ global rating of change in condition and 6MWT indicate that 25 m is the minimum clinically important improvement (23, 24). Calculations from the FAIR-HF study, using a Mann U Whitney test and assuming a mean 6MWT in the control group of 274 m and equal Standard Deviation in each group of 30 m (24), suggested that a study of 90 participants (45 per group) would permit the detection of a 25 m increase in 6MWT between the intervention and control group with 90% power at a 1%, 2-sided significance level (Stata v11.0). This estimate was powered at 90% rather than 80%, and this group have used a significance of 1%, rather than the more conventional 5%. Therefore, using this estimated sample size calculation in a heart failure group, the calculated sample size for the current proposed study assuming a mean 6MWT in the control group of 274 m and equal Standard Deviation in each group of 30 m, a study of 48 participants (24 per group) would permit the detection of a 25 m increase in 6MWT between the intervention and control group with 80% power at a 5%, 2-sided significance level (NQuery V6). This is one sample size calculation for which some data is available to assist us devise a reasonable pilot but is only for guidance. Allowing for trial attrition of approximately 10% we aimed to recruit 54 participants to yield a final evaluable sample of 48 participants (24 per group) for the primary study.

**Statistical Analysis**

All analyses involved comparing outcomes and changes in the different parameters during the scheduled study visits among all participants randomized to receive IV iron or placebo. It was planned to carry out two independent analyses in addition to the functional assessments of the 6MWT and the qualitative assessments using the questionnaires.

Comparisons of continuous outcomes (including the primary outcome) between the treatment and control arms will be performed using ANCOVA adjusted for each patient’s value at baseline. Multiple imputation techniques with such a small study will be of limited value. Therefore, we will analyse all available data without data replacement as these are missing at random rather than related to the trial intervention. Descriptive statistics and graphic approaches will be employed, for the exploratory analysis. Data will be presented as means and standard deviations (SD). Further correlations will be explored.

**Recruitment and baseline results**

Between October 2016 and April 2018, 55 individuals were identified as potential patients at the 3 centres using lists of patients awaiting IV iron therapy as well as using an electronic database of patients with CKD and long-term iron deficiency. 51 patients completed all visits but not necessarily all study tests, two patients missed the final follow-up visit, one patient withdrew before the baseline visit with no reason given (and was therefore not included in the analysis as no data were available), and one withdrew due to side-effects of fatigue and shortness of breath (**Supp Figure 1**). All eligible patients were randomized to intervention or placebo and then followed up at one month and three months after the infusion.

**Baseline characteristics of randomized participants**

A total of 55 individuals out of 327 screened from 3 UK centers were confirmed to meet the eligibility criteria and consented for the study and were randomized 1:1 to either receive IV ferric derisomaltose or IV placebo. One patient had no further data collected subsequently and was excluded leaving 54 patients (Supplementary Figure 1). As shown in **Table 3** for the total population, the mean (SD) age was 59.6 (11.7) years and 26 (49%) patients were male and the majority were white (42; 79%). The mean (SD) SF was 66.3 (44.1) microg/L, TS was 20.1 (7.4) and Hb was 128.7 (10.1) g/L. The mean (SD) serum creatinine was 186.7 (58.6) micromol/L and eGFR was 31.1 (9.6) ml/min/1.73m2. The mean (SD) urinary albumin/creatinine and protein/creatinine ratios were 60.9 (133.3) and 83.8 (128.4) mg/mmol, respectively, and CRP was 5.0 (4.4) mg/L. The mean (SD) 6-minute walk distance was 401.2 (120.2) m. Baseline ECGs, as interpreted by the investigator, were deemed “within normal limits” in 38 cases, “abnormal but not clinically significant” in 13 participants, and “abnormal and clinically significant” in 1 participant (previous changes of cardiac damage),(data for 2 cases was missing). The etiology of the renal disease in the CKD patients is detailed in **Table 3**.

**Discussion**

Evidence of functional improvement in non anaemic iron deficient CKD patients treated with IV iron is lacking, as are head-to-head randomized controlled studies comparing IV iron versus placebo. Explorative studies of cardiac function (Speckle Tracking echo) and oxidative stress markers which are planned to be carried out in this cohort of patients in the present study may also provide important mechanistic data. This randomized double blinded exploratory study may provide valuable information to clinicians to consider in managing non- anemic CKD patients with iron deficiency in order to improve patient reported outcomes. There are several limitations to this study as it included small numbers of patients of which a high percentage were causcasian, and it was of short duration, such that generalisation of the future results may be difficult.

**Conclusions**

The Iron and Heart Trial will provide data to allow evaluation of the use of a single high dose of IV iron, ferric derisomaltose (Monofer®) in non-anemic CKD patients with iron deficiency regarding functional capacity, and will hopefully give insight on its impact on markers of cardiac function, oxidative stress and inflammation. The latter data is likely to be hypothesis generating. In addition, data will be generated on the relative efficacy of IV iron for improving hemoglobin concentrations and hematinic. The future use of the data from this study might provide a rationale to undertake a larger study in non-anemic CKD patients with iron deficiency to further assess IV iron treatment in a clinically meaningful fashion with potential cardiovascular hard endpoints.

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***Competing interests***

AL and VA declare no conflicts of interest. SB, IM and PK have received honoraria for lectures, attended expert opinion committees and received educational funds to attend international Society of Nephrology meetings from Pharmacosmos A/S and Vifor Pharma.

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***Authors' contributions***

VA assessed the statistical plan; SB participated in all aspects of the study, obtained funding for the study and critically revised the manuscript. AL generated and maintained the database. IM and PK contributed to the design of the study and reviewed the drafts of the manuscript and provided editing. The order of authorship has been a joint decision of the co-authors based on substantial contribution to conception and design, execution, analysis and interpretation of data. I (SB) am the senior author.

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**Figure Legends**

**Figure 1**

Iron and Heart Trial Design

**Supplementary Figure 1**

**Consort** Figure of flow of patients through Iron and Heart Trial **detailing disposal of patients screened for the study**