Title page

TITLE:

Impact of Incremental Versus Conventional Initiation of Hemodialysis on Residual Kidney Function: a Multicentre Feasibility Randomized Controlled Trial.

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Running Head

Incremental versus conventional hemodialysis initiation: randomized trial

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Abstract

Twice-weekly hemodialysis(HD), as part of incremental initiation, has reported benefits including preservation of residual kidney function(RKF). This randomized controlled feasibility trial examines these claims. 55 incident HD patients with urea clearance≥3ml/min/1.73m^2 were randomized across 4 UK centres to standard or incremental schedules for 12 months. Incremental HD involved 2x weekly sessions, upwardly adjusting HD dose as RKF was lost maintaining Total(Dialysis+Renal) Std Kt/V>2. Standard HD was 3x weekly for 3.5-4 hours, minimum Dialysis Std Kt/V was 2. Primary outcomes were feasibility parameters and effect size of group differences in rate of loss of RKF at 6 months. Healthcare cost impact and patient-reported outcomes were explored. Around one-third of patients met eligibility criteria. Half agreed to randomization. 26 subjects received standard HD and 29 incremental. At 12 months 21 incremental patients (72%) remained in the study v 12 (46%) in the standard arm. There were no group differences in urea clearance slope. 22/24(92%) incremental patients v 12/16(75%) standard had urea clearance≥2ml/min/1.73m^2 at 6 months(p=0.16). Serious adverse events were less frequent in incremental patients (Incidence Rate Ratio 0.47,CI 0.27-0.81). Serum bicarbonate was significantly lower in incremental patients. There were three deaths in each arm. Blood pressure, extracellular fluid and patient-reported outcomes were similar. Median incremental HD cost was £19,875 compared to £26,125 for standard HD (P<0.001). Incremental HD appears safe and cost-saving in incident patients with adequate RKF, justifying a definitive trial. Bicarbonate supplementation may be required. There was no signal indicating protection of RKF.

Keywords

Hemodialysis, incremental, residual kidney function, adequacy, urea, solute

INTRODUCTION

Incremental dialysis is a method of prescribing dialysis whereby as residual kidney function (RKF) reduces, the amount of dialysis delivered is progressively increased. This is commonly performed in peritoneal dialysis[1] but is unusual in hemodialysis (HD). Safe performance of incremental dialysis requires frequent measurement of RKF and adjustment of dialysis prescription. The concept is to combine clearance by dialysis and RKF into a composite measure and ensuring that this total clearance remains above accepted minimum levels. Incremental HD often involves initiating treatment twice-weekly dialysis and increasing sessional time and frequency as required. Initiation may thus be smoother. With standard approaches to hemodialysis initiation, excess mortality has been reported in the initial months of treatment, perhaps related to associated physical and psychological stresses [2, 3]. Evidence for the safety and effectiveness of incremental HD is limited to observational data [4-6], though a role is recognised in clinical practice guidelines [7].

Retention of RKF is a strong predictor of survival in both HD and peritoneal dialysis. Improved fluid, blood pressure and anaemia control, better nutrition and enhanced middle molecule clearance, may contribute [8-12]. RKF can be lost quickly following initiation of dialysis, though this is by no means inevitable. Many patients retain significant RKF even after several years treatment [8, 13]. Retrospective data suggest that incremental HD may protect RKF which may improve long-term survival [4-6]. Hence dialysis strategies that protect RKF may be beneficial.

Other potential benefits of incremental approaches include reductions in vascular access problems, catheter-related infections, and ultrafiltration-induced myocardial ischaemia [6, 14]. A meta-analysis of incremental HD indicates reduced frequency of vascular access related problems compared to standard haemodialysis[15]. There are potential quality of life benefits,

a reduced incidence of depression and lower treatment burden. In-centre dialysis capacity may be freed up, with less frequent dialysis for some allowing additional patients or enhanced sessional frequency for others. Many units switched patients to twice-weekly treatments during the SARS-CoV-2 pandemic to reduce patient mixing and free capacity [16].

Clinicians may be reticent to prescribe HD twice-weekly due to concerns about potential under-dialysis. However, in a recent US longitudinal study, mortality was not increased in patients who received twice-weekly HD for at least 6 weeks in the first 3 months provided baseline RKF was >3ml/min/1.73m^2 [17]. Rate of loss of RKF was also reduced. An earlier observational US study demonstrated reduced mortality in patients on twice-weekly HD, a benefit attributed to higher levels of RKF[18]. Our recent large retrospective study showed that in incident patients with KRU > 3 ml/min, mortality was reduced and RKF better preserved in those starting twice- rather than thrice-weekly [6]. This suggests the need for randomized controlled trials of incremental initiation. This study was devised to assess the feasibility of conducting such trials.

METHODS

This was a randomized controlled feasibility trial of the impact of incremental versus conventional Initiation of HD on RKF, conducted across four UK Renal Centres: East and North Hertfordshire NHS Trust, Royal Free Hospital, London, Royal Berkshire Hospital and Leicester Renal Network. It was funded by the Kidney Care UK and British Renal Society Joint Grants Programme. Details of ethical approval, funding and governance are included in the trial protocol [19]. Study recruitment was from 28/12/2018 until 3/4/2019 and was ceased when the randomisation target had been reached.

Inclusion/exclusion criteria

Inclusion criteria: age ≥ 18 years; within 3 months of HD initiation; inter-dialytic urea clearance (KRU) ≥3ml/min/1.73m^2; sufficient understanding of study procedures including capacity for explicit agreement to be randomized to standard or incremental regimens.

Exclusion criteria: planned transplant within 3 months; anticipated requirement for high-volume ultrafiltration (UF); blood-borne virus positivity; inability to comply with monthly inter-dialytic urine collection; pregnancy; prognosis <12 months as judged by the Principal Investigator.

Procedures

Screening

Patients were pre-screened by review of medical records. Potentially eligible participants were then approached for informed written consent to be screened by application of inclusion/exclusion criteria and confirmation of KRU ≥3ml/min/1.73m^2.

Randomization

Eligible and consenting patients were randomly assigned on a 1:1 basis to a standard or incremental HD protocol for 12 months. Electronic remote randomization was performed by the University of Hertfordshire.

Dialysis Procedures

All patients received either high-flux HD or haemodiafiltration. Dialysis bicarbonate was not protocol-specified but was 32-35mmol/L plus 3mmol/L acetate for all patients. Clinical, biochemical and haematological parameters, dialysis adequacy and interdialytic urine collections were carried out monthly[19]. KRU and creatinine clearance were calculated as previously described.[19] Glomerular filtration rate(GFR) was calculated from mean urea and creatinine clearance and corrected to 1.73m^2 body surface area (BSA). Dialysis dose adjustment to meet minimum adequacy targets was required in both study arms by standard methods including adjustment of blood flow, dialysis duration, membrane surface area and by optimising vascular access. Details of the method of calculating dialysis dose Standard $Kt/V_{Dialysis}$(Std $Kt/V_{Dialysis}$), RKF expressed as Standard Kt/V_{RKF}(Std Kt/V_{RKF}) and the sum of these, total Standard Kt/V (Std Kt/V_{Total}), have been reported in the study protocol manuscript[19].

For the Standard arm the prescription involved thrice-weekly sessions of 3.5 – 4 hours. Minimum adequacy target was Std $Kt/V_{Dialysis}$ of 2. RKF was not taken into account. Reduction in sessional frequency below thrice weekly was not permitted.

For the incremental arm the prescription involved twice weekly sessions of 3.5-4 hours duration. Minimum adequacy target was Std Kt/V_{Total} of 2. Std Kt/V_{Total} comprised both Std

$Kt/V_{Dialysis}$ and Std Kt/V_{RKF} and was measured monthly. Increase of sessional frequency to thrice-weekly was permitted on the grounds of achieving adequacy targets or on other grounds including prevention or treatment of hyperkalaemia and fluid overload.

Adverse and Serious Adverse Events

Data was collected for Adverse and Serious Adverse Events (SAEs) probably or possibly related to the dialysis regime. These were defined as deaths, Major Adverse Cardiovascular Events (MACE), vascular access events (tunnelled line failures, tunnelled line infections, fistula thrombosis, fistula stenosis, false aneurysm), hyperkalaemic events (potassium >6.5mmol/L), fluid overload events (requiring additional UF), respiratory infections. MACE events were defined as ST segment elevation or non-ST segment elevation myocardial infarction, cerebrovascular accident or transient ischaemic attack. Data was collected on other important medical events and admissions unrelated to dialysis. SAE data was collected continuously during the study and occurrences of Adverse Events data were reviewed at each month time point for the previous month.

Withdrawal from the study

Study withdrawal was for transplantation, patient choice to switch to twice-weekly dialysis, conversion to home-based modality and transfer to another centre

Outcome measures

Primary outcome measures were (i) feasibility criteria: eligibility, recruitability and drop-out rate as defined in Figure 1 (ii) rate of change of RKF in the first 6 months (iii) frequency of hospital admissions with dialysis-related complications (hyperkalaemia, extracellular volume, lower respiratory tract infections, vascular access events).

Secondary outcome measures were proportion of patients with KRU ≥2 or ≥3ml/min/1.73m^2 or having recovered renal function at 6 months, Quality of Life (EuroQol EQ-5D-5L), Depression score (Patient Health Questionnaire, PHQ-9), intrusiveness of medical illness (Illness Intrusiveness Rating Scale, IIRS), cognitive function (Montreal Cognitive Assessment, MoCA), frailty (Clinical Frailty Score, CFS). EQ-5D-5L, PHQ-9, IIRS, MoCA and CFS were measured at baseline, 6 and 12 months. Additional safety secondary outcome measures were mortality and rate of SAEs.

Dialysis quality secondary outcome data was collected monthly as follows: Std Kt/V_{Total}, Std Kt/$V_{Dialysis}$, Std Kt/V_{RKF}, medication use (phosphate binders, antihypertensives, erythropoiesis stimulating agents [ESA]- drug, dose, frequency), biochemistry (serum sodium, potassium, bicarbonate, albumin, corrected calcium, phosphate, haemoglobin), whole body bioimpedance, blood pressure (systolic/diastolic, pre/post dialysis).

Statistical Analysis

Sample size

The sample size of 54 for this feasibility study was determined to provide an estimate of rate of decline in RKF in both study arms at 6 months as published in the protocol manuscript [19].

Residual kidney function analysis

Slope of loss of kidney function over the first 6 month was calculated from an individual linear regression slope over time for each patient. Group slopes were compared using T tests. The proportion of patients retaining KRU ≥2ml/min/1.73m^2 or ≥3ml/min at 6 months was calculated and groups compared using Chi squared test. A linear mixed effects model was used for BSA-corrected GFR. The baseline model used time as a continuous variable and

included fixed effects (study arm, time, their interaction and an intercept) and random effects (time, intercept) with an unstructured covariance matrix. Linear mixed-effect estimation was carried out with use of maximum likelihood method. In other models covariates (baseline BSA-corrected GFR, serum albumin, age, presence of diabetic nephropathy) were included sequentially. The optimum model was determined by comparison against the baseline model for significant reduction in model deviance (-2 log likelihood), tested against the chi-squared distribution.

Other data with repeated measures (biochemistry, bioimpedance data, erythropoietin dose, phosphate binder equivalent dose)

For each of the above parameters, linear mixed effects models were constructed to determine whether study arm was a significant predictor. The optimum model was fitted using repeated measures data with fixed (study arm and timepoint) and random effects (baseline level at screening visit) included in the model with intercepts. Mean phosphate binder equivalent dose (equivalent to mg calcium carbonate) was calculated in each arm at each time point using the described method[20].

Adverse and serious adverse events

Adverse events were compared between study arms using Mann-Whitney U test for days hospitalised and Chi-squared for proportion of patients experiencing ≥1 event. Incidence rates for each event were calculated (events/person years) for each arm and crude Incidence Rate Ratios (IRR) derived. To account for multiple events per person we used Poisson regression for each adverse event category including event count (dependent variable), study arm as a factor and natural log of years in the study as the offset variable. This permitted

reporting of modelled IRR and Wald chi square significance(p) for incremental versus standard arm.

Questionnaire data

For each time point (baseline, 6 and 12 months), scores were compared using T tests or Mann Whitney U Tests. Change in score from baseline to last score (6 or 12 month) was compared between arms with T tests. Analyses compared EQ-5D-5L utility value using region-specific index (1=full health), EQ-5D-5L Visual Analogue Scale (range 0-100), IIRS (score range 13-91), CFS(score range 1-9), MoCA (range 0-30) and PHQ-9 (range 0-27).

Health economic analysis

A within-trial analysis comparing healthcare provider costs out to 12 months was performed, combining HD session, transport, adverse event and urine collection costs based on nationally agreed reference costs. The assumptions made and the sources and references for resource components in the analysis are detailed in Supplementary Materials. As transplantation rates between arms were comparable, costs associated with these transitions were not considered. No urine collection costs were assumed for standard arm. Individuals who withdrew from standard to the incremental regime were assumed to have remained in standard care in a scenario where incremental was not available. Individual cost components are presented as means, with median total costs for the 12 months of the trial censored at transplantation or recovery of renal function with confidence intervals estimated with 1000 bootstraps are presented.

RESULTS

Study recruitment

Of 321 patients within 3 months of starting dialysis, 163 were potentially eligible (CONSORT diagram: Figure 1) and invited for screening and potential study participation. Of these, 53 were excluded due to not meeting eligibility criteria, a further 4 failed eligibility criteria and were re-screened (all failing re-screening), 51 declined to participate and 55 consented to randomization. 26 were randomized to the standard arm and 29 to the incremental arm. There were no group differences at baseline (Table 1). In the standard arm 17 (65%) remained in the study at 6 months versus 25 (86%) incremental patients. At 12 months the numbers were 12 (46%) and 21 (72%) respectively. One subject in the standard and two in the incremental arm recovered RKF to become dialysis independent. The proportion of patients withdrawing for reasons possibly indicating lack of tolerance of in-centre thrice weekly HD (consent withdrawal, request for less frequent therapy, conversion to home HD) was 27% in the standard arm and 0% in the incremental (p=0.01). There were no baseline differences between those withdrawing and those remaining in the study (supplementary materials).

Safety, adverse events and deaths

Adverse events are summarised in Table 2. There were 3 deaths in each arm. Hospitalisation rate was higher in the standard arm [p<0.001, IRR 0.31 (CI 0.17-0.59 events/person/year]. Specific reasons for hospitalisations are detailed in Supplementary Information. Vascular access event rate (IRR 0.49, CI 0.21-1.16) and hyperkalaemia event rate (IRR 0.17, CI 0.02-1.51) were also higher in the standard arm but not significantly. Serious adverse events probably or possibly related to dialysis were less frequent in the incremental arm (IRR 0.47, CI 0.27-0.81, p=0.007), but there were no group differences in the proportion experiencing

one or more of these events (Table 2). Serious adverse events not related to dialysis were also less frequent in the incremental arm (Table 2).

Dialysis adequacy

Standard Kt/V

Though, in the standard arm, only Std $Kt/V_{Dialysis}$ was used to assessment dialysis adequacy (target ≥2.0), Std Kt/V_{Renal} was measured and is shown along with Std Kt/V_{Total} in Figure 2. This illustrates higher overall clearance in the standard HD arm. The fall in Std $Kt/V_{Dialysis}$ in the incremental arm following randomization reflects reduction in sessional frequency to twice-weekly.

Other adequacy indicators

Blood chemistry (at selected timepoints for brevity) is shown in Table 3. Study arm was not a significant predictor, in mixed effect models, of serum sodium, potassium, albumin, calcium, and phosphate, or for erythropoietin resistance index. However immediately following randomization serum bicarbonate fell in the incremental arm ($p = 0.002$) by 3.1 ± 3.2 mmol/L whilst increasing by 0.1 ± 3.2 in the standard arm (Figure 3). In a mixed effects model study arm predicted bicarbonate level ($p=0.02$), which was higher in the standard arm [fixed effect estimate 1.4mmol/L (95% CI 0.28-2.6)]. Phosphate binder equivalent dose was higher in the incremental arm at each time point post-randomisation (Table 3) but this did not reach statistical significance at any time point ($p >0.05$ at each time point)

Blood pressure and volume status

Blood pressure and bioimpedance data at selected timepoints are shown in Table 4. There were no significant group differences in these parameters throughout the study though post-dialysis systolic pressure tended to be higher in the incremental group. Number of anti-

hypertensives (Table 4) in each arm was non-significantly higher pre-randomisation in the incremental HD arm. This difference persisted at each study time point and although the difference did tend to increase over the course of the study, it was not significant at any time point.

Residual kidney function outcome data

There were no significant group differences in RKF at baseline (Table 1 and Figure 4). At 6 months, the proportion of patients with KRU ≥2ml/min/1.73m^2 was 12/16 (75%) in the standard HD arm compared to 22/24 (92%) in the incremental HD arm (p=0.16). Using a ≥3ml/min/1.73m^2 cut-off the proportions were 9/16 (56%) versus 14/25 (56%), (p=0.58). Slope of KRU was -0.05 ± SD 0.40 ml/min/1.73m^2 per month in the standard arm compared to -0.11 ± SD 0.48 in the incremental arm (p=0.51) over the first 6 months. For BSA-corrected GFR, slope was -0.08 ± SD 0.51 ml ml/min/1.73m^2 per month in the standard arm compared to -0.32 ± SD 0.38 in the incremental arm (p=0.07) in the first 6 months.

In the mixed effects models for BSA-corrected GFR, the optimum model for predicting GFR included study arm, time (and interaction) and an intercept as fixed effects and time and an intercept as random effects (Table 5). Baseline BSA-corrected GFR was a significant factor in the model and time was a significant predictor but study arm was not significant [fixed effect 0.15 (95% C.I. -0.53 to 0.56 ml/min/1.73m^2, p=0.95). BSA-corrected GFR decline is shown Figure 5. Inclusion of age, sex and albumin did not improve the model.

Questionnaire data

Data for each timepoint are shown in table 6. There was no significant difference in EQ-5D-5L Index value, EQ-5D-5L visual analogue scale, IIRS, PHQ-9, and CFS between study arms at the baseline, 6m and 12m timepoints (p>0.05 for all comparisons). MoCA was slightly higher in

the incremental group at baseline (p=0.03) but not at other timepoints. Comparing change in score from baseline to last recorded score (6 or 12 months) with T tests, there were no significant differences between groups for any score.

Health economic analysis

The within trial median healthcare provider costs were £26,125 (95% CI £23,025 to £29,224) in the standard care arm and £19,875 (95% CI £17,941 to £21,810) in the incremental arm which benefitted from reduced transport, HD sessions and adverse events costs (Table 7). Figure 6 shows monthly costs in each trial arm according to cost components.

DISCUSSION

The main study aim was to establish the feasibility of conducting a definitive randomized controlled study of incremental versus standard HD in patients with adequate RKF initiating dialysis. We believe this has been broadly demonstrated. Around one-third of incident patients (110/321) were eligible and half of these agreed to be randomized - 17% of the incident patients originally considered. Retention was more of an issue, especially in the standard arm in which only 46% completed 12 months. However, three patients in this group withdrew requesting less frequent therapy, two others withdrew consent for other reasons, and one recovered sufficient kidney function. In a future trial patients withdrawing consent to remain randomised, requesting less frequent dialysis, or recovering renal function might be offered to remain in the study on an intention-to-treat basis. In our trial this would have increased trial follow up by 6 patients in the standard HD arm (18/26 retained instead of 12/26) and 2 in the intervention arm (23/29 instead of 21/29 retained) which would have reduced overall trial dropout rate to 25%. One of the feasibility aims was to establish an effect size for the protective effect of incremental HD on RKF. We did not find such a signal, conflicting with previous observational data [4-6, 17]. This may reflect lack of power but could reflect confounding of patient selection in the observational reports and raises questions about the optimum primary outcome measure for any future trials of incremental versus standard initiation.

Safety data revealed no issues of concern with respect to incremental HD. In fact serious adverse events, judged to be probably or possibly related to dialysis were significantly less

frequent in this group, which is a novel finding. These events included vascular access events, extracellular volume overload and major adverse cardiovascular events. Deaths were similar in the study arms. There was insufficient power to compare event rates in each adverse event subtype but reassuringly many were less frequent in the incremental arm. Serious adverse events felt to be unrelated to dialysis also tended to occur less frequently in the incremental arm. The reasons are unclear.

Patients in the incremental group had lower levels of Std Kt/V_{Total} than the standard arm throughout the study, though levels remained above the minimum target. Potassium and phosphate levels were similar in both groups as was anaemia control. There was a signal of higher post-dialysis systolic blood pressure in the incremental arm though this was not statistically significant, and there were no differences in ECF volume or fat free mass. One striking finding was the fall in bicarbonate levels in the incremental arm following randomization. Levels remained consistently lower than in the standard arm, suggesting bicarbonate supplementation should be considered for patients on twice-weekly regimes. This difference in bicarbonate is likely driven by lower bicarbonate delivery to the patient during dialysis in patients dialysed less frequently in the incremental HD arm.

Overall, we found incremental initiation to be safe, associated with fewer adverse events, hospitalisations, and lower cost than standard treatment. There was no discernible impact on rate of loss of RKF, nor on quality of life, mood, cognitive function and illness intrusiveness. However, this was a small pilot study with insufficient power to draw firm statistical conclusions.

So what have we learned which might inform the design of a definitive trial? The major finding is that the incremental approach appears to be safe. This may reassure clinicians fearful of

underdialysis and its consequences. There are caveats: 1) patients must have an adequate RKF. A threshold of 3 ml/min/1.73m^2 appears safe. 2) regular monitoring of RKF and appropriate adjustment of dialysis dose to maintain Std Kt/V_{Total} above 2.0. Patients in both arms were required to collect monthly interdialytic urine collections. Adherence was good. However it is likely that the uptake of incremental treatments would be facilitated by less onerous collection periods [21] or by the availability of simpler methods to estimate RKF such as those based on blood levels of middle molecules [22-25]. The third proviso is to be aware of the potential need to supplement bicarbonate.

In terms of the feasibility of recruitment and retention into a definitive study, we found that around one third of incident patients met the eligibility criteria and that half of these consented to randomization. The annual incidence rate for kidney replacement therapy in the UK is around 8000 patients and by 90 days 5300 are receiving HD [26]. Assuming a recruitment rate of 17%, this would provide a potential pool of 900 eligible patients per annum. Use of less onerous methods for RKF estimation could potentially boost recruitment, but notwithstanding this possibility, this represents a very limited subject pool, even supposing recruitment across the whole UK

However, the feasibility of this study clearly depends on the primary outcome measure adopted. Our study has not demonstrated a signal of benefit in terms of protection of RKF and Quality of Life score. Broadly, our study demonstrates comparable clinical outcomes in both arms, and benefits in terms of health economics in favour of incremental HD. Hence, this suggests two potential design options for a future trial. Firstly, a non-inferiority study based on patient safety measures but this would most likely necessitate a multi-national study. Secondly, since our data suggest potential benefit in terms of hospitalisation rate and

vascular access event rate, a superiority trial based on these outcome measures could potentially be conducted in a single country. These outcome options would align with recommendations of the SONG HD initiative[27].

Future trials should also assess the health economics benefits of lower intensity dialysis regimes. It is noteworthy that the costs recorded in this study were somewhat lower than those reported elsewhere which may reflect the selective nature of our trial cohort.[28].

There are a number of studies planned and underway investigating the potential benefits of incremental HD. A small US randomized study (n=50, Clinical Trials.gov identifier NCT03874117), is underway which will assess quality of life. A larger Spanish study plans to randomize 152 incident patients 1:1 to incremental or conventional HD with a primary outcome of survival [29]. An Italian study is also planned (n=116 total, NCT04360694) randomizing patients to standard or incremental HD, which will also evaluate survival. Based on our findings larger studies may be required to demonstrate survival or quality of life benefits. The reassuring safety data from our trial, in selected patient with urea clearance>3ml/min/1.73m^2, indicates the need for studies to determine the optimum implementation of incremental dialysis in for routine dialysis care.

In summary, we report the first prospective randomized trial of incremental vs standard HD. Our data are reassuring from the safety perspective, though bicarbonate supplementation may be required in patients on twice weekly regimes. Feasibility data indicate that around 1 in 6 new starters on dialysis screened for a definitive study using this trial inclusion criteria could be randomized which will provide guidance for the design of a definitive study.

DISCLOSURE STATEMENT

None of the authors declare any conflict of interest.

Tables

Table 1: Demographics
Unless otherwise stated, for continuous variable, data show mean ± standard deviation.
IQR denotes Interquartile Range.

	Arm	
	Standard HD	Incremental HD
Number	26	29
Age – years	63.1 ± 12.3	61.4 ± 15.2
Sex – % male / % female	73.1 / 26.9	69.1 / 30.9
Median height (IQR) – cm	169 (166-177)	172 (169-175)
Weight – kg	82.9 ± 16.3	85.3 ± 20.3
Median Total body water, Watson 1980 formula (IQR) – L	39.5 (34.9-43.9)	41.3 (34.3-43.8)
Median Body Mass Index (IQR) – kg/m^2	27.2 (24.6-30.9)	27.2 (23.8-33.0)
Body Surface Area, Dubois equation – m^2	1.94 ± 0.20	1.96 ± 0.23
Ethnicity – %		
Caucasian	84.6	75.9
Black African/Afro-Caribbean	7.7	6.9
Asian	7.7	17.2
Cause of end-stage renal failure – %		
Diabetic nephropathy	26.9	48.3
Renovascular disease	7.7	3.4
Adult polycystic kidney disease	11.5	20.7
Hypertension	7.7	3.4
Chronic glomerulonephritis	7.7	13.8
Tubulointerstitial disease	3.8	0
Other renal disease	34.6	10.3
Vascular access – %		
Catheter	42.3	44.8
Arteriovenous fistula	57.7	55.2
Arteriovenous graft	0	0
Blood pressure – mmHg		
Pre-dialysis systolic	153 ± 18.7	155 ± 22.5
Pre-dialysis diastolic	77.4 ± 12.0	76.3 ± 17.0
Post-dialysis systolic	147.0 ± 21.5	153.5 ± 27.6
Post-dialysis diastolic	73.7 ± 12.1	75.1 ± 12.7
Bioimpedance - L		
Extracellular water	19.3 ± 3.0	19.9 ± 4.1
Intracellular water	20.4 ± 4.4	21.3 ± 4.8
Comorbidities – %		
Diabetes	46.2	55.2
Myocardial infarction	26.9	17.2
Peripheral vascular disease	7.7	3.4
Stroke/TIA	23.1	13.8
Solid tumour	11.5	17.2

Charlson Comorbidity Index	5.9 ± 1.7	6.0 ± 2.7
Haemoglobin – g/dL	97.1 ± 12.2	95.1 ± 13.6
Median Sodium (IQR) – mmol/L	140 (138-141)	139 (137-140)
Potassium – mmol/L	4.7 ± 0.54	4.8 ± 0.79
Pre-dialysis urea – mmol/L	15.9 ± 5.1	16.4 ± 5.2
Median pre-dialysis creatinine (IQR) – µmol/L	534 (475-589)	512 (427-658)
Albumin – g/L	39.7± 3.5	38.1 ± 4.4
Median corrected calcium (IQR) – mmol/L	2.31 (2.20-2.38)	2.25 (2.20-2.35)
Median phosphate (IQR) – mmol/L	1.36 (1.19-1.61)	1.40 (1.14-1.64)
Bicarbonate – mmol/L	23.2 ± 2.7	23.8 ± 2.5
Median urea clearance (IQR) – ml/min	4.89 (4.08-5.73)	5.03 (4.42-5.95)
Median urea clearance (IQR) – ml/min/1.73m^2 BSA	4.21 (3.65-5.17)	4.41 (4.00-5.69)
Median creatinine clearance (IQR) – ml/min	7.59 (6.19-11.31)	9.25 (7.37-12.86)
Median creatinine clearance (IQR) – ml/min/1.73m^2 BSA	7.31 (5.80-8.56)	7.80 (6.39-11.82)
Median GFR (IQR) – ml/min	6.44 (5.09-7.71)	6.98 (5.89-9.41)
Median GFR (IQR) – ml/min/1.73m^2 BSA	6.01 (4.75-6.66)	5.99 (5.22-8.27)

Table 2: Summary of serious adverse events and reportable adverse events
N/A not applicable. †Poisson regression model where the model adjusts for time in study (exposure to risk), § Chi-squared comparison, ¶ Mann-Whitney U Test
**Deaths, major adverse cardiovascular events, vascular access events, hyperkalaemic events, fluid overload events, respiratory infection. Note, modelled Incidence Rate Ratios were very similar to modelled ratios and are not shown for brevity. SAE = Serious Adverse Events

	Standard HD arm	Incremental HD arm	Crude Incidence rate ratio(95% C.I.). Standard HD arm is the comparator	Statistical comparison comparing arms, p
Total patient months in study	204.8	287.0		
Number of hospitalisation events (hospitalisation rate per person years)	32 (1.87)	14 (0.59)	0.31 (0.17 - 0.59)	<0.001 †
Total days hospitalised	311	81		0.22 ¶
Number of deaths (events per person years)	3 (0.18)	3 (0.13)	0.71 (0.14 - 3.54)	0.71 †
Number of adverse events (events per person years)				
Major Adverse Cardiovascular	2 (0.12)	1 (0.04)	0.36 (0.03 - 3.94)	0.36 †
Vascular access	13 (0.76)	9 (0.38)	0.49 (0.21 - 1.16)	0.10 †
Hyperkalaemia	4 (0.23)	1 (0.04)	0.18 (0.02 - 1.60)	0.11 †
Fluid overload	3 (0.18)	2 (0.08)	0.48 (0.08 - 2.85)	0.49 †
Respiratory infection	7 (0.41)	5 (0.21)	0.51 (0.16 - 1.61)	0.25 †
Other important medical events or hospitalisations unrelated to dialysis	15 (0.88)	6 (0.25)	0.29 (0.11 - 0.74)	0.009 †
SAE probably or possibly related to dialysis regime**				
Number of events (events per person years)	32 (1.87)	21 (0.88)	0.47 (0.27 - 0.81)	0.007 †
Proportion of patients experiencing ≥1 event	50%	52%		0.56 §

Table 3: Blood chemistry . Not all timepoints are shown for brevity.

Parameter	Study arm	Timepoint after randomization (months)			
		Screening	1	6	12
		Mean (95% lower and upper CI)	Mean (95% lower and upper CI)	Mean (95% lower and upper CI)	Mean (95% lower and upper CI)
Sodium (mmol/L)	Standard	139.3 (138.0 - 140.6)	138.8 (137.7 - 139.9)	138.6 (136.7 - 140.5)	138.0 (136.4 - 139.6)
	Incremental	138.8 (137.9 - 139.6)	138.5 (137.2 - 139.7)	137.5 (136.2 - 138.9)	138.6 (137.2 - 139.9)
Potassium (mmol/L)	Standard	4.7 (4.4 - 4.9)	4.7 (4.5 - 5.0)	4.9 (4.5 - 5.3)	4.9 (4.4 - 5.4)
	Incremental	4.7 (4.5 - 5.0)	4.9 (4.7 - 5.1)	5.0 (4.7 - 5.3)	5.1 (4.8 - 5.4)
Albumin (g/L)	Standard	39.7 (38.2 - 41.1)	40.4 (38.8 - 42.0)	38.4 (35.5 - 41.2)	39.2 (37.3 - 41.1)
	Incremental	38.1 (36.5 - 39.8)	38.9 (37.0 - 40.7)	38.9 (37.0 - 40.7)	39.9 (38.0 - 41.7)
Corrected_calcium (mmol/L)	Standard	2.31 (2.25 - 2.37)	2.28 (2.22 - 2.33)	2.28 (2.23 - 2.34)	2.31 (2.27 - 2.35)
	Incremental	2.28 (2.23 - 2.33)	2.27 (2.21 - 2.32)	2.28 (2.22 - 2.33)	2.29 (2.22 - 2.35)
Phosphate (mmol/L)	Standard	1.49 (1.32 - 1.67)	1.47 (1.32 - 1.61)	1.63 (1.40 - 1.86)	1.51 (1.32 - 1.70)
	Incremental	1.42 (1.28 - 1.56)	1.67 (1.50 - 1.84)	1.77 (1.49 - 2.06)	1.66 (1.37 - 1.96)
Phosphate binder equivalent dose (equivalent mg calcium carbonate)	Standard	1249 (700-1798)	1191 (592-1789)	1474 (691-2256)	2250 (1049-3451)
	Incremental	1053 (579-1528)	1525 (957-2093)	1571 (980-2161)	2460 (1484-3435)
Bicarbonate (mmol/l)	Standard	23.2 (22.0 - 24.3)	23.5 (22.3 - 24.7)	23.1 (21.7 - 24.4)	24.0 (21.9 - 26.1)
	Incremental	23.8 (22.9 - 24.8)	20.6 (19.6 - 21.6)	21.0 (19.6 - 22.3)	21.7 (20.6 - 22.8)
Haemoglobin(g/L)	Standard	97.1 (92.0 - 102.3)	103.5 (99.3 - 107.6)	109.1 (102.8 - 115.5)	108.3 (100.6 - 116.1)
	Incremental	95.1 (90.0 - 100.3)	97.4 (91.3 - 103.6)	112.5 (107.4 - 117.6)	107.6 (102.8 - 112.3)
Erythropoietin resistance index (epoetin dose per g/dL haemoglobin)	Standard	5.76 (3.44 - 8.07)	6.93 (4.49 - 9.37)	7.97 (4.09 - 11.86)	6.13 (1.66 - 10.61)
	Incremental	4.80 (2.92 - 6.67)	7.56 (5.20 - 9.92)	6.18 (3.93 - 8.42)	6.71 (3.29 - 10.13)

Table 4: Fluid and blood pressure data. Not all timepoints are shown for brevity.

Parameter	Study arm	Timepoint (months after randomization)			
		Screening	1	6	12
		Mean (95% lower and upper CI)	Mean (95% lower and upper CI)	Mean (95% lower and upper CI)	Mean (95% lower and upper CI)
Pre dialysis systolic BP (mmHg)	Standard	153 (146-161)	159 (153-166)	158 (147-169)	160 (143-176)
	Incremental	155 (147-164)	162 (154-170)	165 (154-175)	158 (146-170)
Pre dialysis diastolic BP (mmHg)	Standard	77 (73-82)	79 (73 - 85)	80 (73-86)	80 (71-88)
	Incremental	76 (70-83)	74 (67-82)	80 (74-86)	72 (64-80)
Post systolic BP (mmHg)	Standard	147 (138-156)	145 (137-154)	148 (137-160)	146 (127-165)
	Incremental	153 (143-164)	153 (142-163)	161 (150-172)	159 (146-173)
Post dialysis diastolic BP (mmHg)	Standard	74 (69-79)	74 (68-79)	74 (67-80)	74 (65-84)
	Incremental	72 (65-79)	75 (68-81)	78 (71-84)	71 (65-77)
Bioimpedance extracellular water (L)	Standard	19.3 (18.0-21.0)	19.1 (18.0-20.0)	19.0 (17.0-21.0)	19.9 (18.0-22.0)
	Incremental	19.9 (18.0-22.0)	19.0 (17.0-21.0)	19.5 (18.0-21.0)	20.8 (19.0-23.0)
Bioimpedance intracellular water (L)	Standard	20.4 (19.0-22.0)	20.4 (18.0-23.0)	20.6 (18.0-23.0)	20.8 (18.0-23.0)
	Incremental	21.3 (19.0-23.0)	20.4 (18.0-23.0)	21.3 (19.0-24.0)	22.4 (20.0-25.0)
Bioimpedance fat free mass (kg)	Standard	30.1 (23.0-37.0)	32.6 (24.0-41.0)	27.6 (19.0-36.0)	34.2 (22.0-47.0)
	Incremental	31.9 (26.0-38.0)	29.6 (25.0-35.0)	32.6 (27.0-38.0)	35.0 (28.0-42.0)
Anti-hypertensives (number per patient)	Standard	2.0 (1.4-1.6)	2.0 (1.4-2.5)	2.2 (1.4-3.0)	2.1 (0.9-3.2)
	Incremental	2.2 (1.7-2.7)	2.3 (1.9-2.8)	2.7 (2.1-3.3)	3.1 (2.5-3.8)

Table 5: Mixed effects model for GFR decline.

In the model the dependent variable was body surface area-adjusted GFR.

Fixed effects				
	Regression coefficient	95% C.I.	z	Sig (p)
Intercept	0.81	-0.09 to 1.71	1.77	0.077
Incremental HD arm code (comparator is standard HD arm)	0.02	-0.52 to 0.55	0.06	0.954
Time (months after randomisation)	-0.18	-0.27 to -0.08	-3.69	<0.001
Study arm * time interaction	-0.10	-0.22 to 0.02	-1.58	0.113
Baseline GFR(ml/min/1.73m^2)	0.87	0.73 to 1.00	12.65	<0.001
Random effects				
	Variance and covariance	95% C.I.		
Variance intercept	0.48	0.23 to 0.99		
Variance time(months)	0.03	0.02 to 0.05		
Covariance intercept - time	0.08	0.03 to 0.14		
Residual variance	1.43	1.25 to 1.64		

Table 6: Questionnaire data outcomes

Between arm comparison shows T test comparing change in score from baseline to last score in study available between study arms. Data shows mean(SD) or median (IQR) as appropriate. CFS: Clinical Frailty Scale. IIRS: Illness intrusiveness rating scale. MoCA: Montreal Cognitive Assessment. PHQ9: Patient Health Questionnaire 9.

Questionnaire	Study arm	Timepoint			Between-arm comparison of change in score from baseline to last score (p)
		Baseline	6 months	12 months	
CFS	Standard	2.9 (SD 1.3)	3.1 (SD 1.4)	3.0 (SD 1.4)	0.18
	Incremental	2.9 (SD 1.2)	3.0 (SD 1.0)	2.7 (SD 1.0)	
IIRS	Standard	32.2 (SD 11.8)	35.5 (SD 12.4)	33.8 (SD 12.9)	0.50
	Incremental	33.8 (SD 16.2)	33.0 (SD 15.3)	33.0 (SD 15.3)	
MoCA	Standard	26.0 (IQR 3)	26.5 (IQR 2.0)	26.5 (IQR 6)	0.87
	Incremental	28.0 (IQR 3)	27.0 (IQR 2.0)	27.0 (IQR 3)	
PHQ9	Standard	2.5 (IQR 9)	5.0 (IQR 7)	4.5 (IQR 12)	0.96
	Incremental	2.0 (IQR 4)	2.0 (IQR 3)	2.0 (IQR 3.0)	
EQ-5D-5L utilityvalue	Standard	0.83 (IQR 0.33)	0.74 (IQR 0.32)	0.81 (IQR 0.22)	0.81
	Incremental	0.79 (IQR 0.20)	0.83 (IQR 0.22)	0.81 (IQR 0.24)	
EuroQol Visual analogue scale	Standard	70.0 (IQR 38)	70.0 (IQR 33)	70.0 (IQR 23.0)	0.97
	Incremental	70.0 (IQR 20)	70.0 (IQR 20)	70.0 (IQR 28.0)	

Table 7: Within-trial healthcare provider-born costs (GB pounds). Values reported are the cost incurred during the 12 months of the trial per patient, averaged by treatment arm. Median cost differed between arms (Wilcoxon rank-sum test) with $p<0.001$.

	Incremental Arm (95% CI)	Standard Arm (95% CI)
Transport Costs	441 (84 - 798)	1464 (756 - 2172)
Adverse Event Costs	1185 (552 - 1819)	2497 (1037 - 3957)
Haemodialysis Costs	15195 (12958 - 17432)	20064 (17330 - 22798)
Urine Collection Costs	110 (96 - 124)	0 (0 - 0)
Medication Costs	1591 (1100 - 2081)	1382 (851 - 1913)
Antihypertensives	55 (31 - 80)	37 (18 - 57)
Phosphate Binders	195 (52 - 338)	144 (1 - 287)
Erythrocyte Stimulating Agents	1340 (892 - 1789)	1201 (756 - 1645)
Total Costs (median)	19875 (17941 - 21810)	26125 (23025 - 29224)

List of Figures

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