TITLE:

Initiating haemodialysis twice-weekly as part of an incremental programme may protect residual kidney function

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ABSTRACT:

BACKGROUND:

Initiating twice weekly HD (2XHD), in patients who retain significant RKF, may have benefits. We aimed to determine differences between patients initiated on twice- and thrice-weekly regimes, with respect to loss of kidney function, survival, and other safety parameters.

METHODS:

We conducted a single-centre retrospective study of patients initiating dialysis with a residual urea clearance (KRU) of 3 ml/min or more, over a twenty year period. Patients who had dialysed twice-weekly for 3 months or more during the 12 months following initiation (2XHD) were identified for comparison with those dialysed thrice-weekly (3XHD).

RESULTS:

The 2XHD group consisted of 154 patients, and the 3XHD group 411. 2XHD patients were younger (59 ± 15 vs 62 ± 15: p = 0.014) and weighed less (70 ± 16 vs 80 ± 18: p <0.001). More were female (34% vs 27%: p= 0.004). Fewer had diabetes (25% vs 34%: p = 0.04) and peripheral vascular disease (13% vs 23%: p = 0.008). Baseline KRU was similar (5.3 ± 2.4 vs 5.1 ± 2.8: p = 0.507) but loss KRU slower in the 2XHD group. In a mixed effects model correcting for between group differences in comorbidities and demographics, 3XHD was associated with increased rate of loss of KRU and separation of KRU. In separate mixed effects models, group (2XHD v 3XHD) was not associated with differences in serum potassium or phosphate and the groups did not differ with respect to total standard Kt/V. Survival, adjusted for age, gender, weight, baseline KRU, and comorbidity (prevalence of diabetes, cardiac disease, peripheral vascular disease and malignancy) was greater in the 2XHD group (Hazard ratio 0.755: p = 0.044). In sub-analyses the survival benefit was confined to women, and those of less than median bodyweight.

CONCLUSION:

Twice weekly dialysis initiation as part of an incremental programme with regular monthly monitoring of KRU was safe and associated with a reduced rate of loss of residual kidney function early after dialysis initiation and improved survival. Randomised controlled trials of this approach are indicated.

INTRODUCTION:

Twice weekly haemodialysis (2XHD) was a common modality in the early days of dialysis, usually involving long sessions often exceeding 12 hours [1]. This regime subsequently gave way to adoption of thrice weekly schedules (3XHD) of around four hours per session which is still regarded as standard. Set against this, 2XHD treatments came to be regarded as suboptimal and associated with rationing of resources [2]. Indeed 2XHD treatments remain common in developing countries, conditioned by resource constraints [3-5]. The growing awareness of the importance of residual kidney function (RKF) in dialysis outcomes, has increased interest in incremental dialysis initiation and in 2XHD initiation as part of this [6-9].

Most patients initiating dialysis retain small but significant amounts of RKF which can persist at levels associated with outcome benefits even several years of treatment [6, 7, 10-13]. This preservation of RKF was previously thought to be confined to peritoneal dialysis but it is now apparent that it also extends to the HD setting [14, 15]. Benefits of preserved RKF include improved small and middle molecule clearance, better health- related quality of life, reduced erythropoietin requirements, reduced ultrafiltration requirements, and improved control of blood pressure, nutritional status and phosphate levels [10, 16-19]. Furthermore, RKF improves survival [6, 10, 20, 21]. The presence of levels of renal urea clearance (KRU) as low as 1ml/min/1.73m^2 has been associated with a significantly reduced mortality risk [10]. Dialysis strategies that protect RKF may therefore be beneficial**.** Observational studies have suggested that patients commencing 2XHD may have a slower rate of decline of RKF [22-24]. Incremental dialysis, whereby dialysis dose is individualized according to the prevailing level of RKF [8], might protect against RKF loss by reducing dialysis intensity for patients who retain significant RKF. HD dose is increased successively as RKF declines.

Our centre has practiced incremental dialysis over 25 years with careful and regular monitoring of RKF. In this paper we present our experience of outcomes in patients who started dialysis on 2XHD schedules as part of an incremental HD programme, and compare these to outcomes in

patients with similar levels of kidney function who commenced on 3XHD schedules. The main aim of the study was to determine whether there were differences between patients in the 2XHD and 3XHD groups with respect to rate of loss of RKF and other key indicators of dialysis safety including, anaemia control, potassium control and survival.

METHODS:

Patients

We retrospectively studied patients who initiated HD at the Lister Renal unit with a residual urea clearance (KRU) of 3ml/min or more over the 20 year period between from 1989 (n = 565). All patients had a potential follow up period of at least 5 years following HD initiation. We excluded patients who had HD for <3 months, those transferring from other centres already on dialysis, those transferring from peritoneal dialysis to HD, those returning to dialysis following a failed renal transplant and those who initiated HD in our unit and were transferred out to a different unit.

Definition of groups for comparison

The study population was divided into two groups: those who had initiated HD twice weekly for more than 3 months during the first 12 months of HD (2XHD group) and all other patients who had initiated treatment thrice weekly or received twice weekly treatment for only a brief period of <3 months (3XHD group). Patients in the 2XHD group who subsequently had their dialysis intensity increased to thrice weekly were considered part of the 2XHD group. We excluded from the 2XHD group patients who on review of the case notes had undergone twice-weekly treatment for palliative purposes or during recovery from acute kidney injury.

Haemodialysis Programme

All patients were treated exclusively using high-flux membranes with either high-flux HD or haemodiafiltration. Ultrapure water was used for dialysis and was regularly monitored to ensure tight bacteriological standards. Bicarbonate was used as the buffer. Dialysis fluid microbiological standards were <0.1 cfu/ml and<0.03 EU/ml.

Dialysis adequacy and RKF

HD was delivered using an incremental dialysis regime whereby regardless of dialysis frequency (twice or thrice weekly) patients had the same total target urea clearance. This was achieved by utilizing a total two-pool Kt/V urea target for patients comprised of dialyser clearance ($Kt/V_{dialysis}$) and RKF equivalent clearance (Kt/V_{renal}). Kt/V_{renal} was calculated using the method described by Gotch et al [10] which converts urea clearance to an equivalent per-session Kt/V. This method aims to take into account the higher efficiency of urea removal by RKF compared to that of the dialyser. The approximate equivalent minimum target total two pool Kt/V (Kt/V_{total}) used for both groups, equates to 2.0 per session for 2XHD patients and 1.2 per session for 3XHD.

The following formulae describe the method used to calculate Kt/V_{total}:

$$Kt/V_{total} = Kt/V_{renal} + Kt/V_{dialysis}$$

$$Kt/V_{renal} = (KrU * f)/V$$

where KrU is urea clearance (ml/min)$f = 9500$ for twice weekly HD or $f = 5500$ for thrice weekly and V is Watson volume (ml).

In order to calculate Kt/V_{renal}, the dialysis unit protocol measured RKF monthly using an inter-dialytic urine collection and the mean inter-dialytic urea concentration (the mean of the pre- and post-dialytic serum urea concentrations, with post dialysis urea corrected for rebound). Urine collections were performed over the inter-dialytic period from Monday to Wednesday or Tuesday to Thursday depending on the dialysis schedule for thrice weekly patients and from Friday to Monday or Saturday to Tuesday for twice weekly patients.

The following equation was used to calculate KRU:

$KrU\ (ml/min) = 2(U_{ID} \cdot V_{ID})/t_{ID}\ (C_{post} + C_{pre})$

In this equation, U_{ID} was urinary urea concentration (*mmol/ml*) in the inter-dialytic urine collection; V_{ID} was the urine collection volume (*ml*); t_{ID} was the duration of the inter-dialytic urine collection (*mins*); C_{post} was post-dialysis serum urea (*mmol/l*) and C_{pre} was pre-dialysis serum urea (*mmol/l*).

Patients with urine output <100ml/day for two or more consecutive monthly collections were classified as anuric. All patients passing >100 ml urine/ day were routinely requested to perform monthly inter-dialytic urine collections to calculate Kt/V_{renal}. Patients failing to provide urine collections for ≥3 months were assumed to be anuric to prevent under-dialysis.

Baseline characteristics

Baseline characteristics were collected for all patients which included age, height, pre-dialysis weight at dialysis initiation, sex, cause of underlying renal disease, and routine haematological and biochemical data. Comorbidity data were defined at dialysis initiation including diabetic status, cardiac disease, peripheral vascular disease, and malignancy.

Outcome data

The outcome data were collected at the closest time point ±1 month to 0, 3, 6, 12, 24, 36, 48 and 60 months after dialysis initiation. Parameters including KRU, pre-dialysis weight, frequency of HD, serum potassium levels, serum phosphate levels, haemoglobin levels, serum albumin level, Erythropoiesis-stimulating agent weekly dose, and Erythropoietin resistance index (ERI). Estimates of total standard Kt/V as combined dialysis StdKt/V and renal StdKt/V [25] were also collected at each of these time points. Data were not collected after date of transplantation, transfer to other dialysis modality or transfer to another dialysis centre.

Survival

Patient survival was measured from the date of HD initiation to death.

Statistical analysis

Statistical analysis was performed with IBM ®SPSS®Statistics version 24 and STATA.

To determine if there was a difference in rate of decline of KRU between the 2XHD and 3XHD groups, a mixed effects model was fitted which allowed for within-individual variation in baseline KRU (random intercept). The model was fitted with restricted cubic splines, so that KRU could be modelled flexibly. Knots were placed at 12 and 24 month time points to match the changes in slopes seen in raw data. Group and time were included as fixed factors in the model, and also a group-time interaction parameter was included as a fixed effect. Differences in groups were controlled for by including age, sex, baseline weight and comorbidities as fixed effects.

The following outcome parameters were compared between 2XHD and 3XHD groups also using mixed effect models: potassium, phosphate, haemoglobin, erythropoitetin dose, erythropoietin resistance index, ultrafiltration volume and total Standard Kt/V (residual renal plus dialysis). Mixed model effects were fitted which allowed for within-individual variation in baseline KRU (random intercept), and included group (2XHD or 3XHD) and time as fixed effects and additionally included the interaction of group and time as a fixed effect. A quadratic term for time was assessed as a fixed effect and found to add to the fit of the model for potassium, haemoglobin and erythropoietin resistance index. A random slope was considered, allowing for rate of change of each outcome to vary over time by patient and was found to improve model fit for all models except phosphate.

Survival was compared between the 2XHD and 3XHD groups using Kaplan-Meier univariate analysis. In order to correct for the effect of confounding variables on survival, we used a Cox proportional hazards model comparing survival between the 2XHD and 3XHD groups. Confounding variables included in the model were age, sex, baseline weight, baseline comorbidity (diabetes, cardiac disease, peripheral vascular disease, malignancy), and baseline KRU (the maximum KRU recorded in the first 3 months of treatment). In survival analyses

patients were censored for transplantation, transfer to another dialysis modality or another dialysis centre.

RESULTS:

Baseline characteristics

A total of 583 patients initiated HD with KRU of 3 ml/min. Four hundred and eleven patients initiated three times a week dialysis (3XHD group), and 172 initiated twice a week dialysis. Of these, 18 patients were excluded comprising 6 receiving palliative twice-weekly HD and 12 receiving HD twice-weekly while recovering from acute kidney injury. The 2XHD group therefore comprised 154 patients. Median start year commencing HD was 1998 versus 2001 in 2XHD and 3XHD groups respectively. For patients in the 2XHD group, median duration on twice weekly dialysis was 12 months.

Baseline data for the 2XHD and 3XHD groups are shown in Table 1. Patients in the 3XHD group were significantly older and heavier. Fewer in this group were female. More had diabetes, and peripheral vascular disease. There were no differences between the groups with respect to the level of baseline renal function, baseline haemoglobin levels and the prevalence of malignancy. There were equivocal differences with respect to the prevalence of cardiac disease and the spectrum of primary renal disease between the two groups.

Duration of twice weekly treatment

The median time spent on twice-weekly HD was 9 (IQR 12) months. The time ranged from 3 to 54 months.

Comparison of rate of deterioration of KRU

The decline of KRU over the five years post initiation is shown in Figure 1. Missing KRU data were present in 10.5% of potential datapoints. Though KRU at baseline was similar in each

group, there were significant differences between groups at all other time points up to 60 months (Figure 1).

In the mixed effects model to determine the effect of group (2XHD or 3XHD) on KRU, restricted cubic splines and knots were employed and the optimum model included knots at 12 and 24 months (see Table 2). There was evidence to include time as a random effect in the model (Log Likelihood Ratio test[LLR] 50.86, $p<0.001$) but the resulting standard deviation was small (0.03) indicating that there was little variation over time, therefore this was not included in the model for parsimony. Primary renal disease was not included in the model since it did not contribute significantly to the model (LLR 6.33, $p=0.39$). Year from commencing dialysis also did not contribute significantly to the model. Factors in the model are shown in Table 2 and significant factors predicting KRU included group (2XHD v 3XHD),time, the group-time interaction, sex, weight and presence of heart disease. Use of splines resulted in three time parameters and three group-time interaction parameters.

The modelled effect of a patient being in the 2XHD group (compared to 3XHD group) is shown in Figure 2. There is increasing difference in KRU between groups to 12 months. From 12 to 24 months the difference in KRU between groups decreases as the 3XHD group levels out while the 2XHD groups's KRU continues to decrease. From 36-60 month the difference reduces but with KRU in the 2XHD group remaining around 1ml/min higher than in the 3XHD group. Model performance shown in Figure 3 which shows good agreement between observed and fitted data.

Comparison of haematological, biochemical, dialysis adequacy and volume control parameters

Raw data for haemoblobin, erythropoietin dose and Erythropoietin Resistance Index in 2XHD and 3XHD groups are shown in Figure 4. Raw dialysis adequacy data using Standard Kt/V are shown in Figure 5 which includes Standard Kt/V (Total) plus its components (Standard Kt/V Renal and Standard Kt/V Dialysis). Ultrafiltration volume data are shown in Figure 6.

Summaries of mixed effects models comparing potassium, phosphate, haemoglobin, erythropoietin dose, Erythropoietin Resistance Index, ultrafiltration volume and Total Standard

Kt/V are shown Table 3. All outcomes were affected by time, other than Total Standard Kt/V. There was a significant difference between 2XHD and 3XHD groups for ESA dose, erythropoietin resistance index and ultrafiltration volume (lower in 2XHD groups, see Table 3). He interaction term Group*Time to determine the difference between 2XHD group and 3XHD group over time was significant for erythropoietin dose only, meaning that there was no evidence that the rate of change of the other outcomes differed between groups.

These models with time as a random effect suggest the rate of change of each outcome varies by patient. Erythropoietin dose and ultrafiltration volume had large estimated standard deviations suggesting that the rate of change varies widely across patients, whereas other models showed small differences among patients (see Table 3, Random Effects SD Time) . Similarly, for erythropoietin dose, ultrafiltration volume and haemoglobin the estimated intercept standard deviations were high suggesting a difference in levels of these outcomes across patients at all times. The residual standard deviation for the models represent the residual population standard deviation not explained by the model. This was relatively high for erythropoietin dose and ultrafiltration volume suggesting that other factors are affecting these not accounted for in the model.

Survival

Unadjusted survival was significantly higher for patients in the 2XHD group (median survival 5.6 years vs 4.6 years: p = 0.003). The Cox regression model depicted in Table 4, demonstrates a benefit for twice- vs thrice-weekly dialysis on survival - adjusted for age, sex, baseline body weight, baseline comorbidity (diabetes, peripheral vascular disease and malignancy), and residual kidney function (maximum urea clearance in first 3 months). Twice- weekly treatment was associated with a reduced adjusted mortality risk of 24% (p = 0.044), corresponding to an adjusted median survival of 6.1 vs 5.0 years.

When the analysis was restricted to women it was apparent that the adjusted survival advantage of 2XHD was greater – the reduced mortality risk was 44% (p = 0.038) corresponding

to an adjusted medial survival of 7.8 vs 4.8 years. There was no survival advantage of twice weekly dialysis in men (Table 3). Restricting the analysis to patients with body weight less than the median also showed a benefit for2XHD treatment in this group. Twice-weekly treatment was associated with a reduced adjusted mortality risk of 39% (p = 0.006) corresponding to an adjusted median survival of 6.8 vs 4.3 years. There was no survival advantage for heavier patients (Table 3).

CONCLUSION

We found that the rate of decline of KRU in patients initiating incremental HD with KRU of 3 ml/min or more was significantly slower in patients who received 2XHD compared to 3XHD, with increasing separation of KRU up to 12 months, and after this time KRU remained higher in those on 2XHD even up to 5 years. There were no differences between the groups in a mixed effects model with respect to total standard Kt/V though a greater proportion of the total dose was delivered by RKF in the 2XHD group who correspondingly received less dialysis at all points up to 36 months. 2XHD was associated with lower ultrafiltration volume even after correcting for baseline KRU in a mixed effect model. There were no detrimental effects on anaemia management. Haemoglobin levels similar in both groups, and erythropoietin doses and erythropoietin resistance index were actually lower in the 2XHD. Likewise there were no significant differences between groups in potassium and phosphate levels. Survival was not adversely affected by receiving 2XHD treatment, and in fact we found slightly better unadjusted and adjusted survival in those receiving 2XHD treatments, though in subgroup analysis the effect seemed largely confined to women and those with lower body weight. Overall these data provide reassurance regarding the safety of twice weekly initiation dialysis practiced in the context of an incremental programme, with dialysis duration and frequency subsequently adjusted according to the level of regularly monitored renal function.

There were baseline differences between the groups. There were proportionately more women in the 2XHD group. The group was slightly but significantly younger and had a lower mean body weight. The 2XHD group also had a lower comorbid burden especially with respect to the

prevalence of diabetes and peripheral vascular disease. Though we controlled for these factors in the survival analysis and mixed effects model analyzing decline of KRU, there remains a significant likelihood that other potentially important confounders have not been accounted for in this analysis. In our survival analysis, baseline KRU was not a predictor of survival but this is only because our analysis excluded patients with baseline KRU<3ml/min which will have reduced variance.

The mechanisms underlying the apparent benefits of initiating dialysis on a 2XHD schedule remain to be elucidated. However it is tempting to speculate that reduced exposure to aspects of the dialysis process, including ultrafiltration, probing for dry weight, exposure to the dialysis membrane and extracorporeal circulation, may play a role. Such factors may also be important contributants to some of the other benefits described above. In previous studies preservation of kidney function has also been associated with improved anaemia management, reduced ultrafiltration volumes, and improved survival [6, 10, 16]. There may also be a direct effect of reduced ultrafiltration on limiting dialysis-induced myocardial damage [26]. It is not possible to exclude other factors contributing to these findings such as confounding by selection. Since the frequency of treatment was not randomly allocated it may be that rate of decline of renal function was a factor in decisions to initiate and maintain prescriptions in relation to treatment frequency. In addition as mentioned above, survival may be influenced by other factors which have not been accounted for. The similarity between small solute clearances in the two groups suggest dialysis adequacy was not a factor in the survival findings, though the higher renal clearances in the 2XHD group might suggest that there may have been better middle molecule clearances in this group. Unfortunately, we do not have data to compare blood pressure control between groups.

The survival benefit seemed to be limited to women and patients with lower body weight, suggesting that RKF provides a relatively greater contribution to total clearance of uraemic toxins in women and smaller individuals, and reinforcing the notion that RKF contributes much more to overall wellbeing in dialysis patients than just enhanced small solute clearance. It is

also worthy of comment that this benefit occurs in spite of the relatively higher generation per unit body mass of metabolic waste products in women and smaller individuals [27, 28].

There are some limitations to our study. The study was retrospective and observational. Dialysis frequency was not assigned randomly. There was certainly selection bias evidenced by the baseline differences between 2XHD and 3XHD groups with reference to age, gender distribution, body weight and comorbidity. We attempted to mitigate the effects of the differences on survival but cannot exclude the potential role of other, unaccounted for, confounders. For instance we were unable to control for late referral. Lead-time bias is often a problem in such studies. The similarity between levels of RKF in the two groups suggests that this may not be a major factor in this study. However it is possible that the trajectory of RKF decline was different in the two groups in the pre-dialysis setting and that this has influenced dialysis prescription. Perhaps an argument against this is the lack of major difference between the groups with respect to primary renal disease. We used European Best Practice Guidance method of assessing KRU using average of pre- and post-dialysis urea clearance corrected for rebound but this method may introduce some slight bias, though this is unlikely to have had substantial impact on between-group comparisons as we used the same method for all patients[29]. Small bias may also exist due to not performing formal urea kinetic modelling to estimating time average urea concentration for calculating KRU, and this may have caused slightly higher KRU for patients on twice weekly dialysis, though the effect is small[30].

Our findings suggest that twice weekly dialysis initiation as part of an incremental dialysis programme with regular monthly monitoring of residual kidney function is safe and may reduce loss of RKF and improve outcomes for some patients. Evidence is accumulating suggesting that applying a single fixed dialysis regime at initiation, without taking account of RKF, may be potentially harmful for some individuals. This has led to recent calls for randomised controlled trials comparing an incremental approach including twice weekly initiation with conventional thrice-weekly regimes, in patients with adequate RKF [8, 24, 31-33]. This study adds further weight to these calls.

Conflicts of Interest Statement

The results presented in this paper have not been published previously, either in whole or in part, except in abstract format. No authors declare any conflict of interest.

Table 1

Baseline characteristics of twice-weekly (2XHD) and three-times (3XHD) groups. KRU = urea clearance.

	2XHD group	3XHD group	p-value
N	154	411	
Age (years)	59 ± 15	62 ± 15	0.014
Female (%)	34	27	0.004
Baseline pre-dialysis weight (kg)	70 ± 16	80 ± 18	<0.001
KRU (ml/min)	5.3 ± 2.4	5.1 ± 2.8	0.507
Haemoglobin (g/l)	98 ± 16	99 ± 16	0.509
Primary Renal Disease			
Diabetic Nephropathy (%)	19	24	
Chronic Glomerulonephritis (%)	14	13	
Chronic Interstitial Disease (%)	8	4	
Polycystic Kidney Disease (%)	10	5	0.08
Hypertension/Ischaemia (%)	8	13	
Other diseases (%)	20	15	
Unknown (%)	21	25	
Comorbidity at initiation			
Diabetes (%)	25	34	0.04
Cardiac Disease (%)	21	29	0.06
Peripheral Vascular disease (%)	13	23	0.008
Malignancy (%)	10	13	0.293

Table 2

Mixed effects model for prediction of KRU showing parameters included in the model. The model allowed for within-individual variation in baseline KRU (random intercept) and rate of change in KRU allowed to vary over time. Modelling was fitted using restricted cubic splines and knots at the 12 and 24 month time points. Use of splines resulted in three time parameters and three group-time interaction parameters.

Parameter	Estimate	SE	p-value
Intercept	3.2196	0.3881	<0.001
HD group (2XHD)	0.7018	0.1785	<0.001
Time_1	-0.2577	0.0128	<0.001
Time_2	1.1042	0.0946	<0.001
Time_3	-2.2929	0.2241	<0.001
HD group*time_1	0.1588	0.0248	<0.001
HD group*time_2	-1.0675	0.183	<0.001
HD group*time_3	2.3773	0.4333	<0.001
Sex	0.3674	0.1475	0.013
Age	-0.002	0.0043	0.635
Weight	0.0199	0.0034	<0.001
Diabetes	-0.0556	0.1346	0.68
Cardiac disease	-0.3836	0.1466	0.009
PVD	0.0901	0.1612	0.576

Table 3

Mixed effects model summaries for outcome differences comparing 2XHD and 3XHD groups

Outcome		Intercept	2XHD Group	Time	HD Group*Time (interaction)	Time^2	Random Effects		Residual SD
							SD Time	SD Intercept	
Potassium	Coefficient	4.66	0.01	0.02	-0.001	0.000	0.01	0.44	0.589
	p-value	<0.001	0.925	<0.001	0.676	<0.001			
Phosphate	Coefficient	1.82	-0.03	-0.002	0.001	-	-	0.246	0.503
	p-value	<0.001	0.372	0.007	0.471	-			
Haemoglobin	Coefficient	101.90	-0.55	0.70	0.02	-0.01	0.22	10.00	12.94
	p-value	<0.001	0.647	<0.001	0.586	<0.001			
Erythropoietin dose	Coefficient	7230	-1435	99	-45	-	126	2974	3478
	p-value	<0.001	<0.001	<0.001	0.018	-			
Erythropoietin Resistance Index	Coefficient	0.573	-0.194	0.029	-0.002	0.000	0.016	0.387	0.526
	p-value	<0.001	<0.001	<0.001	0.359	<0.001			
Ultrafiltration volue	Coefficient	1478	-568	9	4	-	21	1118	788
	p-value	<0.001	<0.001	<0.001	0.182	-			
Total Standard Kt/V	Coefficient	2.345	0.011	-0.001	-0.002	-	0.026	0.358	0.574
	p-value	<0.001	0.851	0.525	0.676	-			

Table 4. Cox proportional hazards models for mortality associated with twice-weekly versus thrice weekly treatments (Full model). The model was then applied separately for men and for women, and for those whose body weight was less than and greater than the median. Baseline KRU = best estimate of residual urea clearance in the three months following dialysis initiation

	B	SE	Wald	P-value.	Hazard Ratio	95.0% CI for Hazard Ratio
Full model						
Age at Baseline (years)	.034	.005	44.551	.000	1.035	1.024 - 1.045
Female gender	-.162	.132	1.497	.221	.851	0.657 - 1.102
Weight at baseline (kg)	-.006	.004	2.322	.128	.995	0.987 - 1.002
Diabetes	.297	.117	6.480	.011	1.346	1.071 - 1.692
Cardiac Disease	-.042	.121	.119	.730	.959	0.757 - 1.215
Peripheral Vascular Disease	.379	.128	8.740	.003	1.461	1.136 - 1.879
Malignancy	.665	.153	18.948	.000	1.944	1.441 - 2.622
Baseline KRU (ml/min)*	-.008	.030	.068	.794	.992	0.935 - 1.053
Twice- weekly HD	-.281	.139	4.073	.044	.755	0.574 - 0.992
Gender restricted analyses – same covariates						
In women: Twice-weekly HD	-.580	.280	4.295	0.038	.560	0.323 - 0.969
In men: Twice-weekly HD	-.148	.163	.828	0.363	.862	0.627 – 1.186
Weight restricted analyses –same covariates						
Weight < median: Twice-weekly HD	-.494	.179	7.600	0.006	.610	0.430 – 0.867
Weight > median: Twice-weekly HD	-.137	.232	.349	0.555	1.147	0.723 – 1.806

List of Figures

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