Hemodialysis patients receiving a greater Kt dose than recommended have reduced mortality and hospitalization risk

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Achieving an adequate dialysis dose is one of the key goals for dialysis treatments. Here we assessed whether patients receiving the current cleared plasma volume (Kt), individualized for body surface area per recommendations, had improved survival and reduced hospitalizations at 2 years of follow-up. Additionally, we assessed whether patients receiving a greater dose gained more benefit. This prospective, observational, multicenter study included 6129 patients in 65 Fresenius Medical Care Spanish facilities. Patients were classified monthly into 1 of 10 risk groups based on the difference between achieved and target Kt. Patient groups with a more negative relationship were significantly older with a higher percentage of diabetes mellitus and catheter access. Treatment dialysis time, effective blood flow, and percentage of on-line hemodiafiltration were significantly higher in groups with a higher dose. The mortality risk profile showed a progressive increase when achieved minus target Kt became more negative but was significantly lower in the group with 1 to 3 L clearance above target Kt and in groups with greater increases above target Kt. Additionally, hospitalization risk appeared significantly reduced in groups receiving 9 L or more above the minimum target. Thus, prescribing an additional 3 L or more above the minimum Kt dose could potentially reduce mortality risk, and 9 L or more reduce hospitalization risk. As such, future prospective studies are required to confirm these dose effect findings.

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Adequate dialysis dose is one of the most important goals in hemodialysis (HD) treatment and should be appropriately prescribed. Achieving a minimum dialysis dose is the responsibility of nephrologists and represents an area open to improvement. Because age, gender, and comorbidity cannot be changed, dialysis parameters should be adjusted to ensure that the patient receives the optimal treatment.

Several clinical practice guidelines[1–5] have recommended a minimum Kt/V or urea reduction ratio (URR) as methods for monitoring dialysis dose. Because the urea kinetic method requires pre- and post-dialysis urea determinations, monitoring is performed monthly, bimonthly, or quarterly, and the result of this 3% to 7% of total sessions is extrapolated to the totality of the treatments. Given the relevance of dialysis dose to survival and that multiple factors can influence dialytic efficacy in each session, it seems reasonable to incorporate biosensors to quantify the dose in each session and in real time. Most monitors have incorporated ionic dialysance (ID), which allows calculation of dialysis dose in all sessions, without involving any additional workload, analytical determinations, or cost.[6] Consequently, many dialysis units have already abandoned urea determinations.

In 1999, Lowrie *et al.*[7] proposed Kt as a method of monitoring dialysis dose and mortality. These authors observed a J-shaped survival curve when they distributed the patients into quintiles from the smallest to the highest URR, while the curve descended with Kt for the same patients.[8] In 2005, the minimum Kt dose was individualized according to body surface area (BSA)[9] and validated in a further study.[10] Since 2006, the Guidelines of the Spanish Society of Nephrology[5] have proposed that dialysis centers with dialysis machines that have ionic dialysance use Kt to monitor dialysis dose.

The Optimizing Results in Dialysis research initiative began in 2010 with the aim of improving HD patient outcomes by elucidating patient characteristics and practice of care in Spain.[11] In a previous retrospective study published by this group,[12] monitoring the dialysis dose with Kt instead Kt/V was evaluated. The authors concluded that the advantage of this method is that it identifies 25.8% of patients who did not reach the minimum Kt while achieving Kt/V. This difference

was particularly evident in women, patients with low body weight, and those with a venous central catheter (VCC).

To define and validate the minimum Kt recommendations in the current Spanish dialysis population, therefore, the aim of the Optimizing Results in Dialysis research initiative was to design this prospective, observational, multicenter study. The goal was to assess whether patients receiving the current recommendations for an adequate dialysis dose by Kt individualized for BSA had improved survival and reduced hospitalizations at 2 years compared to those who did not. In addition, we assessed whether patients receiving a greater dose experienced greater benefit.

RESULTS

Baseline patient characteristics

During the recruitment period, 8095 patients were assessed for eligibility in 65 Fresenius Medical Care (FMC) Spanish facilities. Following the inclusion criteria, 6129 patients were subsequently included in this prospective study (Supplementary Table S1). The mean age was 68.9 ± 14 years, 62.3% were male, 65.5% had cardiovascular risk factors, 36.4% had diabetes mellitus, and the mean Charlson index was 5.5 ± 1.9. Vascular access through an autologous arteriovenous fistula (AVF) was present in 67.9% of patients, through a prosthetic arteriovenous fistula in 3.8%, and through VCCs in 28.3%.

Patients were categorized monthly into 1 of 10 risk groups based on the difference between achieved Kt and target Kt ($_{achieved–target}$Kt). The influences of patient characteristics per each dialysis dose group are summarized in Table 1. The patient groups that had a more negative relationship with the $_{achieved–target}$Kt were significantly older and had a higher percentage of diabetes mellitus, higher comorbidity index, and higher percentage of catheters as vascular access. By contrast, the groups were balanced for gender and for the percentage of patients with cardiovascular risk.

HD treatment

The mean effective dialysis duration (Td) was 240.3 ± 14 min, blood flow rate (Q_B) was 413 ± 64 ml/min, dialysate flow rate was 511±10 ml/min, and dry body weight was 69.7 ± 15 kg. Post-dilution online hemodiafiltration (HDF) treatments were performed for a total of 45.3% of the sessions, and the mean substitution volume was 24.2 ± 3.6 L. High-flux nonreusable dialyzers used were FX-50 (0.02%), FX CorDiax 60 (50.9%), FX CorDiax 600 (38.9%), FX CorDiax 80 or 800 (8.8%), FX CorDiax 1000 (0.2%), (Fresenius Medical Care, Bad Homburg, Germany), and Sureflux (Nipro, Osaka, Japan) 19UX or 21L (1.1%).

The mean target Kt was 48.6 ± 3.8 L, and the mean achieved Kt was 55.1 ± 9.3 L. Moreover, the median $_{achieved–target}$Kt was 6.4 (1.7–10.8) L, ranging from –20.1 to +30.5 L. In addition, the minimum target Kt dose was achieved in 80.5% of patients. Nevertheless, significant differences were found for the percentage of women who achieved the target Kt dose compared with men (79.0% vs. 81.5%; $P < 0.001$). Significant differences also were found between the percentage of sessions with the target Kt achieved and performed by VCC or AVF (59.2% vs. 88.9%; $P < 0.001$).

Length of effective treatment dialysis time and Q_B were significantly longer in groups with higher $_{achieved–target}$Kt ($P < 0.001$, both). In contrast, the lower adjusted Kt groups showed significantly lower percentages with the online HDF treatment option ($P < 0.001$) (Figure 1).

Albumin, C-reactive protein, and hemoglobin profiles

The patients included in the project had average albumin levels from 3.6 to 3.9 g/dl. Despite the short range, significant differences were found between groups (Figure 2a). The corresponding *post hoc* Scheffé test revealed significant differences comparing the first $_{achieved–target}$Kt group (lower than –8 L) to the 5 highest groups analyzed (from +3 L and up).

Patients had median C-reactive protein levels of 5.0 (1.8–12.1) mg/l. ANOVA for the logarithmic-transformed variable indicated significant differences for the groups ($P < 0.001$), and the Scheffé test showed that the patients included in the 2 first $_{achieved–target}$Kt groups (the <–8 L group and the –4 to –1 L group) had higher levels of C-reactive protein compared to the last 4 groups (+6 to +9 L group and up) (Figure 2b). This result is consistent with the higher percentage of catheters used in these groups (Table 1).

Table 1 | Patient characteristics and baseline parameters in the 10 groups based on Kt individualized or body surface area

$_{achieved–target}$Kt categories (L)	Number	Age (yr)	Gender (% female)	CV risk (%)	DM (%)	CI	Weight (kg)	VA (%)	Kt/V (median)	Kt/V on target
< –8	203	72.2 (11.8)	36.95	66.50	46.80	6.1 (1.9)	76.4 (19.6)	80.79	1.26 (1.11–1.43)	27.8%
–8 to –4	274	73.0 (11.6)	41.24	64.96	44.16	6.0 (1.7)	73.5 (16.9)	77.37	1.45 (1.32–1.62)	62.0%
–4 to –1	435	71.8 (12.8)	40.46	64.37	42.30	5.9 (1.8)	72.8 (15.0)	71.03	1.57 (1.46–1.71)	84.4%
–1 to +1	437	71.6 (13.4)	40.73	60.87	45.54	5.9 (1.8)	71.9 (15.8)	62.70	1.65 (1.51–1.80)	90.3%
1 to +3	579	70.4 (13.4)	38.69	65.80	41.28	5.7 (1.9)	71.6 (15.4)	54.92	1.71 (1.53–1.89)	91.8%
3 to +6	1000	69.8 (13.5)	35.50	64.60	41.00	5.6 (1.9)	70.9 (14.2)	40.80	1.78 (1.61–1.97)	97.0%
6 to +9	1093	68.6 (14.1)	36.41	67.06	36.14	5.4 (1.9)	69.6 (14.1)	30.10	1.85 (1.68–2.07)	98.2%
9 to +12	918	68.0 (14.8)	38.89	64.60	32.24	5.3 (1.9)	67.7 (14.2)	22.66	1.96 (1.76–2.22)	98.9%
12 to +15	641	66.1 (15.7)	34.48	69.89	28.08	5.2 (2.0)	66.7 (13.9)	17.16	2.06 (1.84–2.31)	99.7%
> +15	549	63.1 (16.9)	38.62	64.85	20.58	4.7 (1.9)	63.2 (14.4)	11.29	2.22 (1.93–2.51)	99.8%
P value		<0.001	0.25	0.21	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Data are presented as mean (SD), percentages (%), or median and interquartile range (25^{th}–75^{th} percentile).
CI, Charlson Index (age adjusted); CV, cardiovascular; DM, diabetes mellitus; VA, venous central catheter.

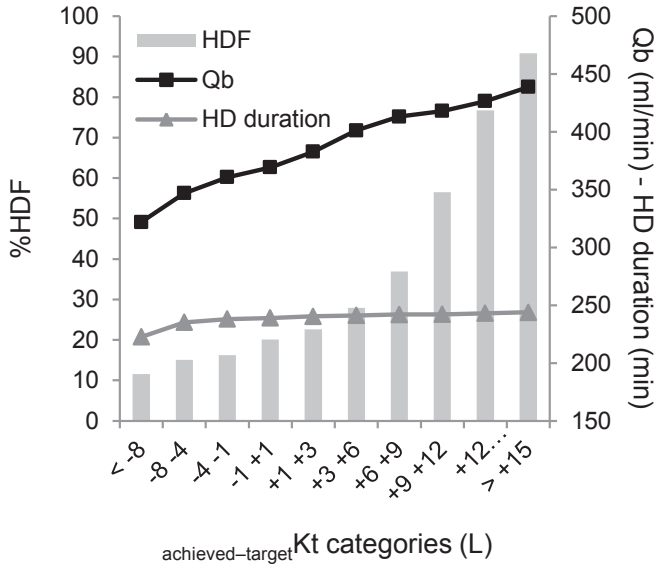

Figure 1 | Influence of hemodialysis treatment parameters for different categories of $_{achieved–target}$Kt. The bars represent the percentage of patients on the HDF treatment option, left axis, for each adjusted Kt category. The squares (■) represent the mean effective blood flow and the triangles (▲) the mean effective treatment time for the patients classified on each adjusted Kt category, right axis.

Finally, the average hemoglobin values for each group ranged from 11.1 to 11.7 g/dl. Again, despite the narrowness of this range, ANOVA revealed significant differences among groups ($P < 0.001$). Of interest, the p*ost hoc* test showed that groups with better outcomes for $_{achieved–target}$Kt had significantly lower levels of hemoglobin compared to the 3 highest groups (Figure 2c).

Factors influencing achievement of target Kt

To identify different predictors that could affect the nonachievement of the target Kt, unadjusted and adjusted generalized linear mixed models were constructed. In every case, these models were built considering repeated measures nested within patients. Moreover, the different Spanish FMC facilities involved in the study were introduced into the different models as a random effect component. The corresponding ORs (odds ratios) and 95% confidence intervals (CIs) are shown in Table 2. After the analysis of a total of 1,076,252 HD sessions, we found that all covariates recorded could affect the outcome. Among nonmodifiable factors, the presence of diabetes mellitus was the covariate associated with a higher risk of not achieving the target Kt, whereas VCC was identified among the modifiable factors. On the other hand, patients treated by HDF had a significantly higher probability of making the target Kt.

Mortality

Patients were monitored for 2 years or until premature termination or death. During the observation period, 790

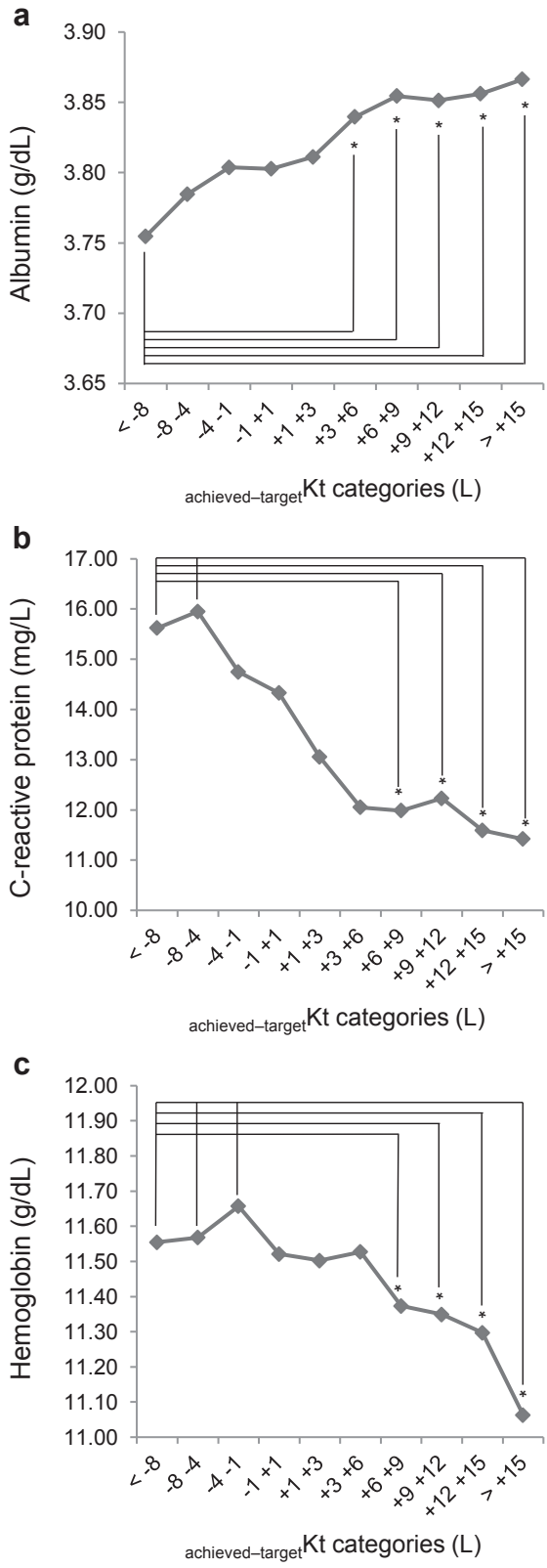

Figure 2 | The analytical profiles for different categories of $_{achieved–target}$Kt. (**a**) Albumin. (**b**) C-reactive protein. (**c**) Hemoglobin. *$P < 0.05$ by *post hoc* Scheffé test.

Table 2 | Generalized Linear Mixed Models to identify fixed effects predictors with a potential negative impact on achieving the Kt individualized for body surface area target

			Univariate				Multivariate			
					95% CI				95% CI	
			P	OR	Lower	Upper	*P*	OR	Lower	Upper
Non–modifiable factors	Vintage (yr)	Ref: <2.00	–	–	–	–	–	–	–	–
		2.00 – 2.99	0.979	1.000	0.985	1.014	0.002	1.027	1.012	1.043
		3.00 – 4.99	0.118	1.010	0.997	1.024	<0.001	1.053	1.039	1.068
		5.00 – 8.00	<0.001	1.026	1.013	1.039	<0.001	1.047	1.033	1.061
		>8.00	<0.001	0.960	0.947	0.972	0.034	1.015	1.001	1.030
	Gender	Ref: female	<0.001	1.055	1.047	1.064	<0.001	1.026	1.012	1.043
	CV risk	Ref: No	0.480	1.003	0.995	1.011	–	–	–	–
	DM	Ref: No	<0.001	1.140	1.131	1.150	<0.001	1.042	1.033	1.052
	Age (yr)	Ref: < 51.00	–	–	–	–	–	–	–	–
		51.00 – 60.00	<0.001	1.086	1.068	1.104	0.086	0.985	0.967	1.002
		61.00 – 70.00	<0.001	1.113	1.096	1.130	0.011	0.979	0.964	0.995
		71.00 – 80.00	<0.001	1.183	1.166	1.200	0.291	0.992	0.977	1.007
		>80.00	<0.001	1.232	1.215	1.250	0.660	0.986	0.970	1.002
Modifiable factors	HDF	Ref: HD	<0.001	0.670	0.665	0.675	<0.001	0.787	0.780	0.794
	VCC	Ref: AVF	<0.001	1.912	1.896	1.929	<0.001	1.332	1.318	1.346
	Weight (kg)	Ref: < 58.00	–	–	–	–	–	–	–	–
		58.00 – 64.00	0.268	0.993	0.980	1.006	<0.001	1.109	1.094	1.124
		65.00 – 72.00	<0.001	1.042	1.029	1.055	<0.001	1.195	1.179	1.211
		73.00 – 81.00	<0.001	1.078	1.064	1.092	<0.001	1.306	1.288	1.325
		>81.00	<0.001	1.190	1.175	1.250	<0.001	1.524	1.503	1.546
	Q_B	(ml/min)	<0.001	0.994	0.994	0.995	<0.001	0.995	0.994	0.995
	Td	(min)	<0.001	0.983	0.982	0.984	<0.001	0.984	0.983	0.984
	Albumin (g/dl)	< 3.50	<0.001	1.163	1.146	1.174	0.011	1.018	1.004	1.031
		3.50 – 4.00	<0.001	1.058	1.049	1.068	0.005	1.014	1.004	1.024
		Ref: >4.00	–	–	–	–	–	–	–	–
	Hb (g/dl)	< 10.00	<0.001	0.939	0.926	0.952	<0.001	0.918	0.905	0.932
		10.00 – 11.00	<0.001	0.965	0.955	0.952	<0.001	0.962	0.952	0.973
		Ref: 11.00 – 12.00	–	–	–	–	–	–	–	–
		12.00 – 13.00	<0.001	1.085	1.073	1.098	<0.001	1.056	1.043	1.069
		>13.00	<0.001	1.295	1.278	1.313	<0.001	1.221	1.203	1.238
	CRP (mg/l)	Ref: < 1.20	–	–	–	–	–	–	–	–
		1.20 – 3.40	0.689	1.003	0.990	1.016	0.770	1.002	0.989	1.015
		3.40 – 7.00	<0.001	1.053	1.040	1.067	0.002	1.021	1.008	1.035
		7.00 – 15.00	<0.001	1.079	1.065	1.093	<0.001	1.036	1.023	1.050
		>15.00	<0.001	1.103	1.089	1.118	<0.001	1.053	1.039	1.068

Generalized Linear Mixed Models considering repeated measures nested within patients; the different Spanish Fresenius Medical Care facilities were introduced in the model as a random effect component; link function: logarithmic.
CRP, C–reactive protein; CV, cardiovascular; DM, diabetes mellitus; Hb, hemoglobin; HDF, hemodiafiltration; Q_B, blood flow; Td, effective treatment time; VCC, venous central catheter.

patients prematurely exited the study because of kidney transplantation (n = 685), change in dialysis unit (n = 62), or other reasons (n = 43). All of these patients were censored at the time of premature termination.

There were 1004 deaths (16.4%) during the follow-up. The main causes of death were cardiovascular diseases (45.6%), infectious diseases (17.9%), sudden death (10.4%), gastrointestinal diseases (6.2%), tumor (5.2%), and other (14.7%).

The independent predictors for all-cause mortality were identified exploring the nonlinear effects of the continuous variables. The corresponding univariate time-dependent Cox model is shown in Table 3. Moreover, the possible center effect on the outcome was identified as a nonsignificant covariate in a univariate analysis (Supplementary Table S2). The independent predictors for all-cause mortality were age, gender, cardiovascular risk, diabetes mellitus, VCC, weight, hemoglobin, albumin, C-reactive protein, and $_{\text{achieved–target}}$Kt.

To assess whether patients receiving an adequate dialysis dose could have a reduced mortality risk, unadjusted and adjusted time-dependent Cox analyses were performed. All covariates that were previously identified as independent predictors for all-cause mortality were introduced into the Cox adjusted model. The reference group selected was the one that incorporated the null value ($_{\text{achieved–target}}$Kt −1 to +1 L/treatment). Results with hazard ratios (HRs) for each group are shown in Figure 3.

The mortality risk profile showed a significant trend ($P < 0.001$) toward a progressive increase in mortality risk with increasingly negative $_{\text{achieved–target}}$Kt. The HR for the lower $_{\text{achieved–target}}$Kt group was associated with significantly higher mortality risk (univariate HR, 1.69; 95% confidence interval [CI], 1.25 to 2.28; $P < 0.001$; multivariate HR, 1.95; 95% CI, 1.41 to 2.71; $P < 0.001$). Of interest, the HR fell as the $_{\text{achieved–target}}$Kt parameter moved into the positive range and became

Table 3 | Univariate and multivariate time dependent Cox regression analysis for all–cause mortality with variables grouped as nonmodifiable or modifiable factors

			Univariate				Multivariate			
					95% CI				95% CI	
Time dependent Cox model			*P*	HR	Lower	Upper	*P*	HR	Lower	Upper
Non–modifiable factors	Gender	Ref: female	0.01	1.407	1.083	1.828	0.003	1.240	1.078	1.425
	CV Risk	Ref: No	0.04	1.120	1.102	1.278	0.888	1.010	.879	1.161
	DM	Ref: No	<0.001	1.322	1.166	1.498	0.004	1.214	1.063	1.386
	Age (yr)	Ref: < 51.0	–	–	–	–	–	–	–	–
		51.0 – 60.0	0.025	1.694	1.068	2.686	0.345	1.257	0.782	2.019
		61.0 – 70.0	<0.001	3.250	2.175	4.858	<0.001	2.267	1.507	3.412
		71.0 – 80.0	<0.001	4.531	3.079	6.668	<0.001	2.859	1.929	4.236
		>81.0	<0.001	6.364	4.344	9.323	<0.001	3.520	2.379	5.208
Modifiable factors	$_{achieved–target}$Kt	(L)	<0.001	0.950	0.942	0.958	<0.001	0.945	0.933	0.957
	HDF	Ref: HD	0.01	0.845	0.742	0.961	0.110	0.883	0.758	1.029
	VCC	Ref: AVF	<0.001	1.499	1.324	1.697	0.036	1.173	1.011	1.362
	Weight (kg)	Ref: < 58.0	–	–	–	–	–	–	–	–
		58.0 – 64.0	<0.001	0.721	0.605	0.860	0.003	0.757	0.630	0.910
		65.0 – 72.0	<0.001	0.640	0.538	0.762	<0.001	0.604	0.500	0.729
		73.0 – 81.0	<0.001	0.507	0.416	0.618	<0.001	0.484	0.390	0.602
		>81.0	<0.001	0.416	0.339	0.511	<0.001	0.415	0.328	0.527
	Td	(min)	<0.001	0.983	0.979	0.987	0.305	1.003	0.998	1.008
	Albumin (g/dl)	< 3.5	<0.001	4.905	4.091	5.881	<0.001	2.383	1.939	2.930
		3.5 – 4.0	<0.001	1.775	1.501	2.098	0.005	1.293	1.080	1.547
		Ref: >4.0	–	–	–	–	–	–	–	–
	Hb (g/dl)	< 10.0	<0.001	6.127	4.970	7.553	<0.001	5.188	4.151	6.485
		10.0 – 11.0	<0.001	1.672	1.437	1.945	<0.001	1.642	1.406	1.918
		Ref: 11.0 – 12.0	–	–	–	–	–	–	–	–
		12.0 – 13.0	<0.001	1.424	1.172	1.732	<0.001	1.436	1.166	1.769
		>13.0	0.032	1.329	1.024	1.726	0.084	1.277	0.967	1.686
	CRP (mg/l)	Ref: < 1.2	–	–	–	–	–	–	–	–
		1.2 – 3.4	0.381	1.168	0.825	1.653	0.728	1.064	0.750	1.510
		3.4 – 7.0	0.034	1.426	1.027	1.979	0.378	1.161	0.833	1.619
		7.0 – 15.0	0.002	1.622	1.186	2.219	0.350	1.164	0.846	1.603
		>15.0	<0.001	3.596	2.672	4.841	<0.001	2.032	1.493	2.766

The plausible center effect was identified as a nonsignificant variable in a univariate analysis.
CRP, C-reactive protein; CV, cardiovascular risk; DM, diabetes mellitus; Hb, hemoglobin; HDF, hemodiafiltration; Td, effective treatment time; VCC, venous central catheter.

significantly lower at the +1 to +3 L group and up for both univariate and adjusted models. From +9 L and up, the mortality risk profile remained flattened and significantly lower than the reference group (Figure 3).

Further Cox models were used for the analysis of different causes of death that were identified as represented in >10% of cases. We found significant differences for these outcomes (Table 4). The risk appeared to be lower as the $_{achieved–target}$Kt parameter moved into the positive range for cardiovascular, sudden death, and infection-related mortality, from +6 to +9 L and up.

Sensitivity analysis for the main outcome: Mortality and target Kt

Reviewing the demographic features of the study groups (Table 1), it would be expected that the more elderly and frail groups and those with catheter access would fail to achieve target Kt (Table 2) and therefore have greater mortality rates. Thus, although the previous adjusted Cox models included all of the independent mortality predictors collected for this study, we cannot exclude a reverse-causality phenomenon. To address this problem, we decided to use a propensity score matching approach. We combined the 10 study categories into 2 population groups according to baseline HD dose: equal to or less than the reference dose group ($_{achieved–target}$Kt –1 to +1 L) and greater than the group with reduced mortality according to our predictive models (+1 to +3 L). We tried to balance these 2 resulting populations for every covariate described as predictors with an impact on achieving the target Kt (Table 2). The resulting balanced population was properly assessed (Supplementary Table S3), and the adjusted cohort was used to estimate the corresponding mortality risk. The Cox model indicated that having an HD dose defined as $_{achieved–target}$Kt above +1 L was associated with a 25% reduction in risk for all-cause mortality compared to the lower HD group (< +1 L) (HR, 0.753; 95% CI, 0.578–0.979; $P = 0.034$).

Hospital admission

There were 6939 hospital admissions for 3042 of the total included patients (49.6%) during the follow-up. The main causes of hospital admissions were vascular access (15.3%), cardiovascular diseases (16.5%), infectious diseases (19.2%), digestive diseases (10.6%), respiratory diseases (6.0%), and other (32.4%).

Again, a negative trend ($P < 0.001$) in hospitalization risk with the progressive increases in dialysis dose was identified (Figure 4). In both models, the HR increased progressively as

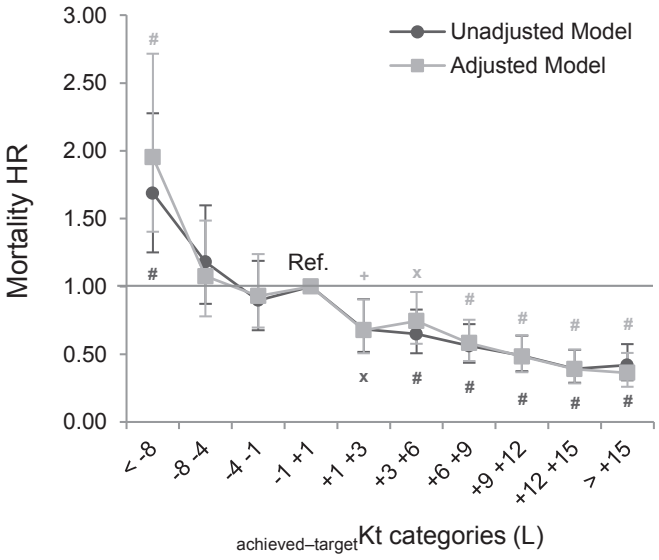

Figure 3 | Death risk profiles for $_{achieved–target}$Kt. Unadjusted (●) and adjusted (■) analyses are shown. The HRs are compared with a common reference category (Ref.) for each analysis. The probability that each ratio is not different from its reference value is shown by a symbol near the ratio: # $P < 0.001$; × $P < 0.01$; + $P < 0.05$; no symbol means no significant differences. Bars = 95% confidence intervals.

the $_{achieved–target}$Kt groups became more negative. On the other hand, as occurred in the mortality risk models, the hospitalization risk appeared to decrease until the last $_{achieved–target}$Kt group, becoming significant with the +6 to +9 L group in the univariate model and with the +9 to +12 L group in the multivariate model.

DISCUSSION

In this study, the current recommendations for monitoring dialysis dose with Kt individualized for BSA were validated in the current Spanish dialysis population and found to be suitable. A dose higher or lower than the recommended minimum is predictably associated with lower or higher death and hospitalization risk. To our knowledge, this is the first prospective trial showing that prescribing more than 1 to 3 L of the current Kt individualized for BSA recommendations reduces mortality risk and more than 9 L reduces hospitalization risk. Thus, both adjusted and unadjusted risk profile results indicated that an adequate dialysis dose as measured by Kt individualized for BSA improved the morbidity–mortality rate in HD patients.

Traditionally, dialysis dose recommendations are based on analytical pre- and post-dialysis urea determinations. US, European, Canadian, United Kingdom, and Spanish guidelines[1–5] recommend a minimum Kt/V of 1.2 and/or a URR of 65% (or Kt/V of 1.3 and a URR of 70% to ensure that these minimum requirements are reached). If urea measurements are carried out only monthly, bimonthly, or quarterly to calculate the dialysis dose, the results from this 3% to 7% of the total sessions will be extrapolated to everything that occurs in all sessions. Because multiple factors can influence dialytic efficacy in each HD session, control systems have been developed to quantify the dose received by the patient in each session and in real time. Most monitors have incorporated ID, which allows the dialysis dose to be calculated in all sessions, without involving additional workload, analytical determinations, or cost.[6] Consequently, many dialysis units have already abandoned urea determinations. In contrast, the lack of the predialysis and postdialysis serum urea measurements entails unknown information about the urea generation rate and net protein catabolic rate as a protein intake guide.

Various authors who have used ID in HD and expressed ID as Kt/V have concluded that Kt/V readings through ID differ from analytical readings, although the correlation between both procedures is good,[13,14] which demonstrates variability between the methods used. To obtain Kt/V, the V must be introduced, but it is an inaccurate value that can be obtained by anthropometric equations such as Watson's, by calculating the measured Kt divided by the analytical Kt/V, or by bioelectrical impedance.[15] Kt/V determined by ID is normally underestimated compared with pre- to post-dialysis analysis.[13,14,16,17] For these reasons, Kt/V with ID has not been validated yet.

With the incorporation of ID, Kt instead of Kt/V was proposed as a method to monitor dialysis dose[7] because it enables avoidance of the J-shaped survival curve, which occurs when patients are distributed according to the URR or Kt/V.[8] In a previous study, minimum Kt dose was individualized in terms of BSA[9] and validated in 59,644 North American FMC patients in a cross-sectional study (March 2004) as a predictor measure during a 1-year period.[10] In the Spanish population, monitoring the dialysis dose with Kt instead of Kt/V identifies from 25% to 40% of patients who did not reach the minimum Kt while achieving Kt/V,[12,18,19] particularly in women, patients with VCC, and those with a low body weight.[12]

Some authors since have proposed rescaling standard Kt/V to BSA[20,21] or using alternative methods instead of V for scaling the dialysis dose.[22] However, incorporation of these alternatives into clinical practice has not been widely accepted because of the difficulty in making appropriate calculations. In our opinion, the use of Kt is simple because it is provided directly by the monitor and its use has been directly proportional to the incorporation of biosensors with ID.

The real possibility of continuous dialysis dose monitoring has been reflected in the growing interest in quality policies regarding adequate dialysis treatment. In a 2006 study in a US dialysis population,[10] the mean delivered Kt was 51 L and mean $_{achieved–target}$Kt was +0.3 L. In a 2013 study in a Spanish dialysis population,[12] the mean delivered Kt was 52.6 L and the mean $_{achieved–target}$Kt was +3.3 L. In the current study, also in a Spanish dialysis population, the mean delivered Kt was 55.1 L and the mean $_{achieved–target}$Kt was +6.5 L. These results reflect HD adequacy improvement in the last 10 years, with the minimum Kt achieved in 53%, 67%, and 81%, respectively. The present study supports $_{achieved–target}$Kt as an independent mortality risk factor and

Table 4 | Primary outcome: mortality

		Univariate				Multivariate			
				95.0% CI				95.0% CI	
Death cause and number of events	$_{achieved-target}$Kt	*P* value	HR	Lower	Upper	*P* value	HR	Lower	Upper
Death from any cause	< −8	0.001	1.688	1.251	2.277	<0.001	1.954	1.405	2.717
1004	−8 to −4	0.283	1.181	0.872	1.598	0.658	1.076	0.779	1.486
	−4 to −1	0.452	0.898	0.678	1.189	0.619	0.930	0.697	1.240
	−1 to +1	Ref.	–	–	–	Ref.	–	–	–
	+1 to +3	0.008	0.686	0.519	0.906	0.008	0.678	0.508	0.904
	+3 to +6	0.001	0.649	0.507	0.830	0.022	0.745	0.579	0.959
	+6 to +9	<0.001	0.563	0.439	0.721	<0.001	0.583	0.450	0.755
	+9 to +12	<0.001	0.490	0.377	0.637	<0.001	0.485	0.368	0.640
	+12 to +15	<0.001	0.394	0.291	0.533	<0.001	0.391	0.285	0.536
	> +15	<0.001	0.420	0.307	0.574	<0.001	0.364	0.259	0.511
Cardiovascular cause	< −8	0.419	1.225	0.749	2.003	0.219	1.395	0.821	2.372
458 (45.62%)	−8 to −4	0.439	1.194	0.762	1.871	0.490	1.185	0.732	1.917
	−4 to −1	0.570	0.886	0.583	1.346	0.952	0.987	0.641	1.519
	−1 to +1	Ref.	–	–	–	Ref.	–	–	–
	+1 to +3	0.067	0.677	0.447	1.027	0.119	0.711	0.464	1.092
	+3 to +6	0.056	0.704	0.491	1.009	0.172	0.771	0.531	1.119
	+6 to +9	0.001	0.537	0.370	0.779	0.002	0.533	0.360	0.789
	+9 to +12	0.001	0.517	0.352	0.761	<0.001	0.457	0.299	0.697
	+12 to +15	<0.001	0.428	0.276	0.663	<0.001	0.359	0.220	0.584
	> +15	0.001	0.484	0.310	0.755	<0.001	0.346	0.205	0.584
Infection	< −8	0.030	2.046	1.072	3.906	0.031	2.077	1.070	4.032
180 (17.93%)	−8 to −4	0.919	0.962	0.461	2.009	0.324	0.661	0.290	1.504
	−4 to −1	0.233	1.418	0.799	2.517	0.417	1.275	0.709	2.294
	−1 to +1	Ref.	–	–	–	Ref.	–	–	–
	+1 to +3	0.560	0.835	0.456	1.530	0.579	0.840	0.454	1.555
	+3 to +6	0.021	0.497	0.274	0.899	0.095	0.601	0.331	1.093
	+6 to +9	0.016	0.490	0.274	0.878	0.025	0.509	0.282	0.920
	+9 to +12	0.003	0.386	0.204	0.731	0.005	0.396	0.208	0.753
	+12 to +15	<0.001	0.203	0.086	0.480	0.001	0.216	0.091	0.513
	> +15	0.001	0.243	0.103	0.575	0.001	0.210	0.083	0.530
Sudden death	< −8	0.231	1.746	0.702	4.340	0.354	1.607	0.589	4.385
104 (10.36%)	−8 to −4	0.074	2.078	0.931	4.638	0.151	1.849	0.798	4.282
	−4 to −1	0.244	0.554	0.205	1.498	0.189	0.491	0.170	1.419
	−1 to +1	Ref.	–	–	–	Ref.	–	–	–
	+1 to +3	0.389	0.686	0.291	1.616	0.218	0.563	0.226	1.405
	+3 to +6	0.365	0.709	0.338	1.491	0.390	0.717	0.336	1.532
	+6 to +9	0.032	0.409	0.181	0.928	0.020	0.374	0.163	0.857
	+9 to +12	0.124	0.538	0.244	1.186	0.034	0.410	0.180	0.935
	+12 to +15	0.021	0.310	0.115	0.839	0.003	0.207	0.073	0.593
	> +15	0.030	0.309	0.107	0.890	0.002	0.168	0.054	0.528

The variables included in the multivariate analysis were gender, cardiovascular risk, diabetes mellitus, age, treatment option, vascular access, weight, effective treatment time, albumin, hemoglobin, C-reactive protein and Spanish Fresenius Medical Care facilities. Variables not deemed significant were excluded from final analysis.

provides evidence that if minimum target Kt is increased 1 to 3 L or more, the risk of all-cause and cardiovascular mortality could be reduced. Thus, our proposal to improve survival should be an increment in the minimum target Kt of approximately 5% to maintain $_{achieved-target}$Kt from 1 to 3 L or higher (Figure 5).

Several groups have shown that the general Kt/V recommendations could lead to under-dialysis in women.[23–25] In a previous study, we found that achievement of minimum Kt recommendations was lower in women than men (63% vs. 69%, respectively) while in the present study, we observed an improvement in both sexes (79% vs. 81.5%), although a significant difference persisted.

The risk of under-dialysis increased in patients with VCC. In European countries, the use of tunneled VCC has gradually increased as a permanent form of vascular access.[26] Maduell *et al.*[27] suggested that the Td should be lengthened by 30 min if a catheter is used in the normal position and by 60 min if in an inverted position. In the present study, although the percentage of patients with VCC was 1.6% higher than in a study conducted 3 years ago and represented the main factor for not achieving the target Kt, the percentage of patients who reached the target Kt was higher (58%) versus 3 years ago (38%). The causes of this improvement likely were the use of better catheters providing higher Q_B (337 ± 87 vs. 363 ± 65 ml/min) and an increment of Td (234.8 ± 17 vs. 240.4 ± 13 min). Therefore, this study confirms that Td should be increased in patients dialyzed with VCC, specifically by 20 min to achieve the target Kt.

Online HDF always increases dialysis dose and reduces the infra-dialysis risk. The high percentage of patients receiving high-volume online HDF in this work confirms that this

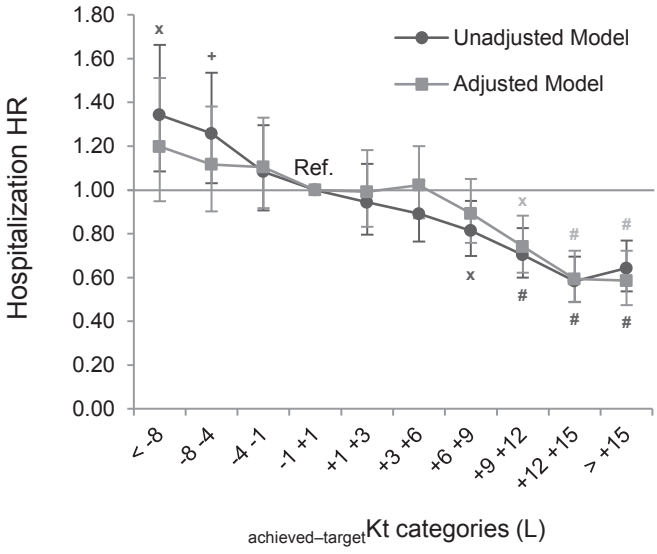

Figure 4 | Hospitalization risk profiles for $_{\text{achieved–target}}$Kt groups. Unadjusted (●) and adjusted (■) analyses are shown. The HRs are compared with a common reference category (Ref.) for each analysis. The probability that each ratio is not different from its reference value is shown by a symbol near the ratio: # $P < 0.001$; × $P < 0.01$; + $P < 0.05$; no symbol means no significant differences. Bars = 95% confidence intervals.

modality of treatment is associated with survival in the univariate analysis, confirming results of the ESHOL study,[28] pooling 4 main randomized clinical trials[29] and meta-analyses.[30] Our results suggest that the mortality benefit provided by online HDF is partly related to a higher dialysis dose; however, the present study was not designed to evaluate the effect of online HDF on mortality, and the sample size and follow-up time are underpowered for such an analysis.

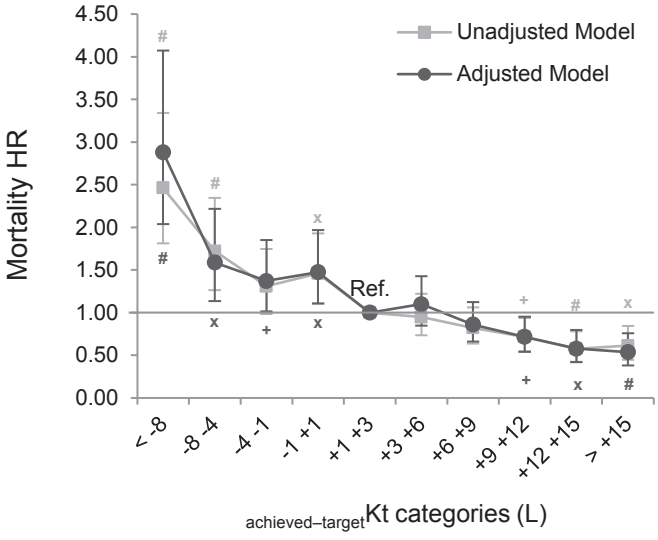

Figure 5 | Proposal to improve survival by increasing the target Kt to +1 to +3 L $_{\text{achieved–target}}$Kt. Unadjusted (●) and adjusted (■) analyses are shown. The HRs are compared with a common reference category (Ref.) for each analysis. The probability that each ratio is not different from its reference value is shown by a symbol near the ratio: # $P < 0.001$; × $P < 0.01$; + $P < 0.05$; no symbol means no significant differences. Bars = 95% confidence intervals.

Cardiovascular, infectious, and sudden deaths represented 74% of mortality causes in our study and were also influenced by dialysis dose received. An increment achieved–targetKt above 6 to 9 L could reduce mortality risk 47%, 60%, and 48%, respectively.

The observational design of this study does not allow for establishing a causal relationship between dialysis dose and mortality. It is important to keep in mind that the HEMO study[31] is the sole randomized clinical trial designed to assess the effect of dialysis dose, and since that trial, clinical guidelines have given Kt/V $\geq$ 1.2 as the minimum recommended dose. Moreover, it is important to consider that the dose-targeting bias was revealed under the controlled conditions of the HEMO study, which emphasizes that caution is necessary when interpreting nonrandomized relationships between dialysis dose and outcome.[32] To address this issue, we have applied propensity score matching in our sample of patients showing that patients receiving a higher dialysis dose have a reduced mortality risk independent of the other comorbidities. The progressive incorporation of ionic dialysance monitors in dialysis units has changed substantially, and to reflect this changing reality for monitoring dose, new randomized trials would be required. Our results suggest that mortality can be further reduced with higher Kt adjusted for BSA dose. In order to test this hypothesis we understand that a prospective, randomized study will be needed, allocating patients with achieved–targetKt from 1 to 3 L (minimum target dose) to maintain this dose or to increase it to higher than 9 L.

This study has some weaknesses but also major strengths. A limitation is that the residual renal function was not monitored, and it has been associated with better survival in HD patients[33] and may confound the dialysis dose–mortality association. The strengths of this study include the large sample size and prospective long follow-up, as well as reflecting current HD treatment, including the high convective mode.

In conclusion, current recommendations for monitoring the dialysis dose with Kt individualized for BSA have been validated in this prospective study in the current Spanish dialysis population, and the dose is predictably associated with death and hospitalization risk. Prescribing an additional 3 L or more of the current Kt individualized for BSA could reduce the risk of mortality, and an additional 9 L or more could reduce the risk of hospitalization.

METHODS

Study design

The clinical trial was designed as a noninterventional, prospective, observational, multicenter study in end-stage renal disease patients undergoing HD performed in all of the Spanish FMC facilities. All included patients signed the appropriate consent form approved by the Hospital Ethics Committee and also for their introduction to the EuCliD database, the Fresenius Medical Care clinical data system.[34] The registered protocol number for this trial is NCT 01932853.

The primary objective was to assess whether patients receiving the current recommendations of an adequate dialysis dose by Kt individualized for BSA have improved survival at 24 months

(October 2013 to September 2015) compared to those who do not get it, as well as to assess whether patients receiving a greater dose obtain more benefit. Therefore, the primary outcome variable was the time to occurrence of death from any cause and its association with the dialysis dose group. A key secondary outcome was to measure the same association with hospitalization risk.

Study population

The inclusion criteria for our study population were adult patients (aged >18 years), receiving thrice weekly standard HD for >6 months at any Spanish FMC center. The patients must have had 5 or more valid measures of Kt during each month. The exclusion criteria were liver cirrhosis or neoplasms. All of these criteria were applied to patients monthly (see Supplementary Table S1 for further details). Given that this was not an interventional study, nephrologists followed current clinical recommendations, and dialysis dose was prescribed according to Spanish FMC guidelines (Kt/V $\geq$ 1.4). Kt measured by ionic dialysance was divided by V, as measured by bioelectrical impedance with the BCM device or calculated using Watson's formula.

Treatment procedures and study variables

The patients were dialyzed with 4008S or 5008 (Fresenius Medical Care) monitors, equipped with OCM sensors. These devices allow automatic noninvasive measurement of the dialysis dose during each dialysis treatment. This system measures the effective *in vivo* urea clearance (K) and calculates the accumulated Kt.[35] The Fresenius machine time setting to adjust the frequency of Kt measurements was 30 minutes in all dialysis units.

The target Kt was calculated monthly for each patient using the following algebraic expression: minimum target Kt in liters = 1/[0.0069 + (0.0237/BSA)], with BSA in m^2 = $weight^{0.425}$ × $height^{0.725}$ × 0.007184, with weight (post-dialysis dry body weight) expressed as kilograms and height measured in centimeters.[9–10] Thus, the adequate dialysis dose was calculated by the difference between achieved Kt and target Kt (achieved Kt – target Kt), referred to as $_{achieved–target}$Kt. As an example, Supplementary Table S4 contains several Kt targets individualized for BSA and used in this study.

Based on $_{achieved–target}$Kt deciles obtained in a previous study,[12] the HD population was assigned monthly to 1 of 10 groups: lower than –8 L, –8 to –4 L, –4 to –1 L, –1 to +1 L (the reference group), +1 to +3 L, +3 to +6 L, +6 to +9 L, +9 to +12 L, +12 to +15 L, or higher than +15 L.

The following parameters were recorded and grouped as nonmodifiable factors: age, gender, cardiovascular risk factors (categorized as yes/no),[36] diabetes mellitus status (categorized as yes/no), Charlson index; or grouped as modifiable factors: treatment technique, HD or post-dilution online HDF dialysis mode, hospitalization/death dates, achieved Kt, target Kt, dialyzer, Td, Q_B, postdialysis body weight, height, and vascular access in use (categorized as AVF or catheter; prosthetic arteriovenous fistula was included in the AVF category). Additionally, the following laboratory data were recorded: albumin, C-reactive protein, and hemoglobin. Residual renal function was not recorded because of missing data.

Statistical analyses

The variables were grouped according to 10 categories of the $_{achieved–target}$Kt. Qualitative variables are shown as percentages and quantitative variables as means accompanied by their corresponding standard deviations or medians and their corresponding 25th and 75th percentiles as appropriate. The chi-square test was used to compare qualitative variables, the Wilcoxon rank-sum test for continuous parameters not normally distributed and ANOVA for continuous normally distributed variables, with logarithmic transformations applied to CRP because of heavy positive skewness. Further *post hoc* multiple range tests (Scheffé) were performed to compare the significant groups in the corresponding ANOVA test.

To identify factors predicting the achievement of the minimum target Kt session by session in the study, generalized linear mixed models analyses were performed, using the GENLINMIXED SPSS module.[37] These mixed-effects logistic regression models were built considering the patients as repeated measures. Moreover, in an effort to incorporate consideration of the different prescribing strategies of treatment modalities in the different centers, Spanish FMC facilities were included in the model as a random effect.

The linear effect of the continuous variables was explored in several univariate models. Only those variables with risk showing a linear effect over the outcome were introduced as continuous variables. The corresponding cutoffs were chosen in a clinically meaningful way in an effort to yield balanced groups. For HD vintage, these cutoffs were <2.00, 2.00 to 2.99, 3.00 to 4.99, 5.00 to 8.00, and >8.00 years. For age, these were <51, 51 to 60, 61 to 70, 71 to 80, and >80 years. For weight, these were <58, 58 to 64, 65 to 72, 73 to 81, and >81 kg. For albumin, these were <3.50, 3.51 to 4.00, and >4.00 g/dl. For hemoglobin, these were <10.00, 10.01 to 11.00, 11.01 to 12.00, 12.01 to 13.00, and >13.00 g/dl. For C-reactive protein, these were <1.20, 1.21 to 3.40, 3.41 to 7.00, 7.01 to 15.00, and >15.00 mg/l.

The primary and secondary outcomes of this trial were to evaluate if the dialysis dose measured by Kt and properly adjusted for BSA improved the morbidity–mortality status of the patients. To examine this possibility, univariate Cox proportional hazard regression models were performed to estimate the corresponding HRs for all of the $_{achieved–target}$Kt groups using a time-dependent variable for the Kt category. Moreover, the corresponding multivariate Cox models were built including all the nonmodifiable and modifiable factors recorded. The nonlinear nature of the relationship between the different covariates and the outcome was considered, as described above. To control for the possible unit effect on mortality, a covariate analysis with the different centers involved in the study was performed. The group containing the null value for the $_{achieved–target}$Kt parameter was selected as reference for these analyses. Trend test and confidence intervals at 95% were calculated for every regression model.

As a sensibility analysis, we used a propensity score matching procedure to deal with the potential reverse causality issue. Then we calculated the propensity score for each patient by modeling the probability of receiving an HD dose equal to or less than ($_{achieved–target}$Kt −1 to +1 L) or more (> +1 to +3 L) than the reference group at baseline. The corresponding logistic regression models were built, introducing into the model all of the predictors with an impact on the nonachievement of the target Kt previously defined (Table 2) and Kt/V. We subsequently used the derived propensity scores to match in a 1:1 ratio both groups using a caliper matching algorithm. We used this type of matching procedure, fixing a caliper parameter equivalent to 0.2 of the pooled standard deviation of the logit of the propensity scores.[38] To evaluate the quality of the propensity score matching, we assessed the balance in covariates by the absolute difference before and after matching between the groups and the proper statistical comparisons.

The statistical analyses in this work were performed using SPSS 23.0 (IBM Armonk, NY). The propensity score matching was

implemented with an SPSS R-menu for propensity score matching[39] using R statistical free software version R3.1.1. A P value < 0.05 was considered statistically significant.

DISCLOSURE

The Optimizing Results in Dialysis group is a scientific advisory board funded by FMC Spain. RR, JV, DM, and JIM are employees of Fresenius Medical Care. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table 1. Study participation inclusion–exclusion process and HD dose classification.

Table 2. Time-dependent Cox analysis of plausible center effect on mortality in study population.

Table 3. Baseline characteristics before and after propensity score matching.

Table 4. Selecting the "target Kt" individualized for each patient for Body Surface Area. Different examples of target Kt calculated by the mathematical expression: Kt = 1 / [0.0069 + (0.0237 / BSA)], expressed in L.

Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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