

Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS

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Hemodiafiltration (HDF) is used sporadically for renal replacement therapy in Europe but not in the US. Characteristics and outcomes were compared for patients receiving HDF versus hemodialysis (HD) in five European countries in the Dialysis Outcomes and Practice Patterns Study. The study followed 2165 patients from 1998 to 2001, stratified into four groups: low- and high-flux HD, and low- and high-efficiency HDF. Patient characteristics including age, sex, 14 comorbid conditions, and time on dialysis were compared between each group using multivariate logistic regression. Cox proportional hazards regression assessed adjusted differences in mortality risk. Prevalence of HDF ranged from 1.8% in Spain to 20.1% in Italy. Compared to low-flux HD, patients receiving low-efficiency HDF had significantly longer average duration of end-stage renal disease (7.0 versus 4.7 years), more history of cancer (15.4 versus 8.7%), and lower phosphorus (5.3 versus 5.6 mg/dl); patients receiving high-efficiency HDF had significantly more lung disease (15.5 versus 10.2%) and received a higher single-pool Kt/V (1.44 versus 1.35). High-efficiency HDF patients had lower crude mortality rates than low-flux HD patients. After adjustment, high-efficiency HDF patients had a significant 35% lower mortality risk than those receiving low-flux HD (relative risk = 0.65, $P = 0.01$). These observational results suggest that HDF may improve patient survival independently of its higher dialysis dose. Owing to possible selection bias, the potential benefits of HDF must be tested by controlled clinical trials before recommendations can be made for clinical practice.

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Despite ongoing technical improvements in both dialysis and overall patient care, the annual mortality rate of patients with end-stage renal disease (ESRD) managed with thrice-weekly hemodialysis (HD) remains high (10–22%).^{1,2} Factors affecting HD patient mortality include advanced age and comorbid conditions at the start of dialysis;³ the efficacy and quality of renal replacement therapy;⁴ and practice pattern variation from region to region.⁵

The clinical condition of patients starting dialysis has been deteriorating over the last decade, as the advanced age and the increased prevalence of comorbid conditions (e.g. diabetes, cardiovascular disease, and malnutrition) among incident ESRD patients expose them to a higher mortality risk than in the past.⁶ However, HD techniques have clearly improved over the last few years. Advanced technical options – such as bicarbonate buffer, ultrafiltration control, sodium and ultrafiltration profiling, and blood volume monitoring – have become routine procedures for reducing intradialytic morbidity, which is particularly important for patients who are older or sicker.

The performance and quality of HD have also improved in relation to efficacy (through enhanced clearances for small and large solutes) and greater biocompatibility (through use of biocompatible membranes and higher quality dialysate).^{7–10} More holistic ESRD patient care has seen greater research and clinical emphasis on the correction of anemia by erythropoietic agents, the control of hypertension by adequate ultrafiltration and antihypertensive drugs, and control of potentially atherogenic dyslipidemia by lipid-lowering agents.^{11,12}

The recently completed hemodialysis (HEMO) Study was a randomized, controlled clinical trial that tested the role of high-flux membranes and high-efficiency dialysis on the

morbidity and mortality of HD patients treated three times per week. The results showed no major overall beneficial effects of an increase in dialysis dose above the currently recommended standard and no improvement in mortality with use of high-flux membranes in 1846 patients followed up to 6.5 years.¹³ Although the effect of dose (small solute clearance) was definitive, convective-based therapies (hemofiltration, hemodiafiltration (HDF)) were not tested, so the role of large solute removal and its effect on patient outcomes requires further testing.¹⁴

In its search for ways to improve dialysis patient outcomes, the nephrology community has suggested that convective-based therapies represent promising modalities.¹⁵ In this context, HDF is appealing. By combining ultrafiltration (convective clearances for removing larger solutes) with diffusion (for removal of small solutes), HDF offers an effective dialysis modality expanding spectrum of uremic toxins to middle-sized and large molecular weight solutes.^{16,17} In addition, the ultrapure dialysis fluid and sterile substitution fluid used for infusion during HDF, combined with high-flux synthetic membranes, results in optimized biocompatibility of the extracorporeal circuit.

Several limited clinical studies have suggested that HDF is associated with superior tolerance and efficacy compared to conventional and high-flux HD. Our study aims to compare the mortality rates of patients receiving HDF to those of patients receiving HD in a large cohort of HD patients followed prospectively in the Dialysis Outcomes and Practice Patterns Study (DOPPS).^{18–22} To minimize the confounding by regional variations in other practice patterns, we selected and analyzed data only from patients in the European cohort of the DOPPS.

RESULTS

Study population

The distribution of dialysis modality for patients at baseline is presented in Table 1. Patients receiving HDF represented 11.7% and those receiving HD represented 88.3%. Among all patients in the study, 7.2% received low-efficiency HDF, 4.5% received high-efficiency HDF, 63.1% received low-flux HD, and 25.2% received high-flux HD.

Patient characteristics, treatment regimens, and intermediate outcomes

Patient characteristics by treatment modalities at baseline are presented in Table 2. As shown in Table 2, patients treated by HDF versus HD tended to be slightly older, have higher body weight, and have longer average time on renal replacement therapy. In addition, patients receiving HDF were more likely to have had lung disease (significantly for high-efficiency HDF versus low-flux HD) and cancer (significantly for low-efficiency HDF versus low-flux HD). It appears that patients were preferentially selected for HDF because of their higher weight and their poor clinical conditions.

Indicators used to evaluate dialysis adequacy in the four dialysis modalities are also presented in Table 2. As shown in

Table 2, dialysis dose (Kt/V) was the only treatment parameter that differed significantly among dialysis modalities. The highest Kt/V values were achieved among patients receiving low- and high-efficiency HDF (averages of 1.37 and 1.44), comparing favorably to the Kt/V values achieved by patients receiving HD (averages of 1.35 for low-flux and 1.33 for high-flux). Most nutritional markers (albumin, cholesterol, triglycerides) of HDF patients did not differ significantly from those of low-flux HD patients. The quality of life scores of HDF patients (both mental and physical component summaries) did not differ significantly from those of low-flux HD patients. Similarly, no difference by modality was found for predialysis blood pressure (systolic or diastolic), acid–base status, or serum levels of potassium or calcium. As shown in Table 2, markers of dialysis efficacy for HDF and HD patients were very similar and within acceptable limits. Such results suggest that most of the ESRD patients in the study received adequate renal replacement therapy.

Adjustments for intermediate outcomes included age, sex, country, time on dialysis, 14 comorbid conditions, catheter use, and weight, as listed in Table 3. Table 3 shows that HDF patients received a higher dialysis dose (+0.06 Kt/V higher) than low- and high-flux HD patients. Additionally, a trend was observed in HDF patients for higher hemoglobin concentration (+0.39 g/dl for low-efficiency HDF ($P=0.01$); +0.34 g/dl for high-efficiency HDF (NS)).

Indicators of inflammation are presented in Table 4. As C-reactive protein measurements were not recorded in DOPPS I, three alternative markers of inflammation were used to assess the consequences of large volume of intravenous replacement fluid during HDF treatment; the markers used were albumin, negative protein of the acute phase; ferritin, positive protein of the acute phase; and transferrin saturation. As shown in Table 4, patients receiving HDF tended to have a greater likelihood of having albumin concentration >4.0 g/dl and a lower likelihood of having ferritin concentration >800 ng/dl, compared with low-flux HD patients. The finding on ferritin persisted after adjusting for transferrin saturation.

Table 1 | Distribution of dialysis modality for prevalent cross-section of patients at baseline

Country	n	Patients (%)			
		Low-efficiency HDF ^a	High-efficiency HDF ^a	Low-flux HD	High-flux HD
France	460	5.4	8.9	45.9	39.8
Germany	440	11.1	4.8	50.5	33.6
Italy	443	14.7	5.4	74.9	5.0
Spain	383	1.8	0.0	61.4	36.8
UK	439	2.3	2.5	83.4	11.8
All	2165	7.2	4.5	63.1	25.2

^aLow-efficiency HDF includes replacements of 5–14.9l, while high-efficiency HDF includes replacement of 15–24.9l.

HD, hemodialysis; HDF, hemodiafiltration.

Table 2 | Crude patient characteristics by dialysis type (mean or %)

Measure	Low-efficiency HDF ^a (n=156)	High-efficiency HDF ^a (n=97)	Low-flux HD (n=1366)	High-flux HD (n=546)
<i>Characteristic</i>				
Age (years)	61.8	63.5	60.4	58.5*
Male (%)	57.1	66.0	55.7	58.0
Time on dialysis (years)	7.0*	5.2	4.7	5.5*
<i>Comorbid conditions (%)</i>				
CAD	35.3	28.8	28.5	30.6
CHF	23.7	25.8	25.9	25.5
Other cardiac disease	51.9	40.2	35.2	36.9
Hypertension	71.1	76.3	71.6	76.0
Cerebrovascular disease	15.4	11.3	13.8	12.5
PVD	25.0	25.8	21.8	22.4
Diabetes	21.8	26.8	18.7	21.3
Lung disease	10.9	15.5*	10.2	11.7
Cancer (excluding skin)	15.4*	8.2	8.7	8.8
HIV/AIDS	0.0	0.0	0.0	0.4
GI bleed	2.6	6.2	4.6	7.2*
Neurological disorder	5.8	4.1	5.7	6.6
Psychiatric disease	28.8	27.8	23.6	24.6
Recurrent cellulitis/gangrene	5.1	7.2	6.7	6.2
Catheter use (%)	3.4	2.2	11.7	5.9*
Weight (kg)	68.6*	70.1*	65.0	67.1*
Hemoglobin (g/dl)	11.0*	10.6	10.7	10.6
Epo dose (U/week) ^b	6428	5334	6386	7083*
Albumin (g/dl)	3.95	3.83	3.91	3.96
nPCR (g/kg/day)	1.13*	1.08	1.09	1.10
Cholesterol (mg/dl)	196	193	191	188*
Triglycerides (mg/dl)	173	176	165	160
Dialysis dose (spKt/V)	1.37	1.44*	1.35	1.33
Treatment time (min)	234*	221*	233	233*
QoL: MCS	43.7	43.2	42.9	43.1
QoL: PCS	34.2	35.5	35.2	36.4
Predialysis systolic BP (mm Hg)	142	145	145	144
Predialysis diastolic BP (mm Hg)	77	77	79	78
Potassium (mEq/l)	5.5	5.3	5.4	5.3
Phosphorus (mg/dl)	5.3*	5.6	5.6	5.9
Calcium (mg/dl)	9.7*	9.4	9.6	9.4
Bicarbonate (mEq/l)	22.1	21.6	22.3	22.4

* $P < 0.05$ versus low-flux HD, adjusts for country and accounts for facility clustering.

^aLow-efficiency HDF includes replacements of 5–14.9l, while high-efficiency HDF includes replacement of 15–24.9l.

^bAmong patients on Epo.

BP, blood pressure; CAD; CHF; Epo, erythropoietin; GI; HD, hemodialysis; HDF, hemodiafiltration; HIV/AIDS, human immunodeficiency virus/acquired immuno deficiency syndrome; nPCR, normalized protein catabolic rate; PCS; PVD; QoL, quality of life.

Crude mortality

Over the period of observation (1998–2001), the crude mortality in this cohort was 35 deaths/278 patient years in the low-flux HD group (12.8 deaths per 100 patient years), 152 deaths among the 1194 patient years in the high-flux HD group (12.7 deaths per 100 patient years). The high-efficiency HDF group had 15 deaths in 169 patient years (8.9 deaths per 100 patient years), and the low-efficiency HDF group had 35 deaths in 278 patient years (12.6 deaths per 100 patient years).

Relative risk of mortality

The relative risk of mortality after adjustments for all variables, including dialysis dose (Kt/V), is presented in Figure 1. The relative risk of mortality was significantly reduced by 35% for patients receiving high-efficiency HDF com-

pared to low-flux HD (relative risk (RR) = 0.65, $P = 0.01$). Patients receiving low-efficiency HDF exhibited a nonsignificant 7% reduction in mortality risk compared to those receiving low-flux HD (RR = 0.93, $P = 0.68$). Since the results for low- and high-flux in the present study were very similar, the HDF results can be compared to all HD combined. In this comparison, the RR for low-efficiency HDF was 0.92 ($P = 0.066$) and for high-efficiency HDF again significantly lower (RR = 0.64, $P = 0.005$). An additional analysis that only adjusted for demographic and comorbid conditions (i.e. not adjusting for the potential benefits of HDF, such as higher Kt/V) yielded similar results: the relative risk of mortality was significantly reduced by 35% for patients receiving high-efficiency HDF (RR = 0.65, $P = 0.008$) and nonsignificantly reduced by 13% for patients receiving low-efficiency HDF (RR = 0.87, $P = 0.46$) (data not shown).

Table 3 | Adjusted^a intermediate outcomes, by dialysis type: direction and extent of difference from low-flux HD group (P-value)

Outcome	Low-efficiency HDF ^b	High-efficiency HDF ^b	High-flux HD
Hemoglobin (g/dl)	+0.39 (0.01)	+0.34 (0.13)	+0.13 (0.12)
Epo dose (U/week) ^c	-13 (0.98)	-551 (0.46)	+541 (0.07)
Epo dose/Hgb (U/week) ^c	-21 (0.70)	-58 (0.47)	+49 (0.13)
Albumin (g/dl)	+0.03 (0.39)	+0.05 (0.40)	+0.03 (0.16)
nPCR (g/kg/day)	+0.02 (0.20)	-0.03 (0.22)	+0.00 (0.81)
Cholesterol (mg/dl)	+0 (0.86)	+0 (0.93)	-4 (0.01)
Triglycerides (mg/dl)	+4 (0.35)	+5 (0.42)	-4 (0.12)
Dialysis dose (spKt/V)	+0.01 (0.57)	+0.06 (0.03)	-0.02 (0.15)
QoL: MCS	+1.6 (0.06)	-0.0 (0.99)	-0.1 (0.89)
QoL: PCS	-0.3 (0.69)	+0.4 (0.66)	+0.3 (0.45)

^aAdjusted for age, sex, country, time on dialysis, 14 comorbid conditions, catheter use, and weight.

^bLow-efficiency HDF includes replacements of 5–14.9l, while high-efficiency HDF includes replacement of 15–24.9l.

^cAmong patients on Epo.

Epo, erythropoietin; HD, hemodialysis; HDF, hemodiafiltration; MCS; nPCR, normalized protein catabolic rate; PCS; QoL, quality of life.

Table 4 | Adjusted intermediate outcomes for surrogate inflammation markers, by dialysis modality

Outcome ^a	OR (P-value)			
	Low-efficiency HDF ^a	High-efficiency HDF ^a	High-flux HD	Low-flux HD
Albumin > 4.0 g/dl	1.44 (0.07)	1.27 (0.58)	1.26 (0.22)	1.00 (ref)
Ferritin > 800 ng/dl	0.59 (0.07)	0.92 (0.86)	0.96 (0.81)	1.00 (ref)
Ferritin > 800 ng/dl, adjusted for TSAT	0.62 (0.09)	0.99 (0.99)	0.97 (0.88)	1.00 (ref)

^aAdjusted for age, sex, country, time on dialysis, 14 comorbid conditions, catheter use, and weight. Accounts for facility clustering.

HD, hemodialysis; HDF, hemodiafiltration; OR, odds ratio; TSAT.

DISCUSSION

This study suggests that high-efficiency HDF has an important positive impact on survival compared to patients treated by HD. This finding supports the hypothesis that convective clearances enhancing the removal of large molecular solutes have a strong impact on survival of dialysis patients.^{23–25} There are several potential explanations for this effect. The benefit may be partly explained by the small solute dialysis dose (Kt/V urea) delivered by HDF, which is higher than that delivered by HD. We found patients receiving HDF to have Kt/V of 1.37 (low efficiency) and 1.44 (high efficiency) versus 1.35 (low-flux HD) and 1.33 (high-flux HD), a difference that confirms the findings of previous studies.^{26,27} However, when the adjustment for Kt/V urea was removed, the results were essentially unchanged. Another potential explanation is the significant increase in larger solute removal achieved by convective clearance.²⁸ This latter explanation is more attractive because the beneficial effects of HDF in terms of reducing mortality risk still persisted after statistical adjustment for dialysis dose (Kt/V). Moreover, relative reduction in mortality risk may be proportional to the intensity of the convective clearance, which itself is linearly related to the amount of fluid exchanged during the sessions. As indicated in Figure 1, the HDF group receiving the higher fluid volume exchange (15–24.9l per session) had a significantly and substantially lowered risk of death (RR = 0.65, P = 0.01).

To our knowledge, this is the first study in a large cohort of patients suggesting that high-efficiency HDF is associated

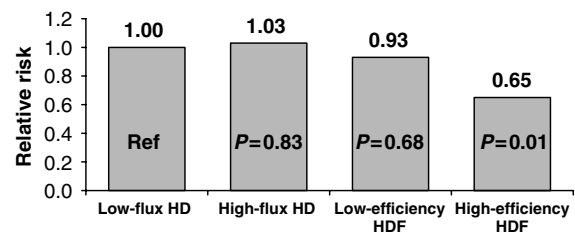


Figure 1 | Relative risk of mortality by dialysis type. (Adjusted for age, sex, time on dialysis, 14 summary comorbid conditions, weight, catheter use, hemoglobin, albumin, normalized protein catabolic rate, cholesterol, triglycerides, Kt/V, erythropoietin, MCS, and PCS.)

with reduced mortality risk compared to both low- and high-flux HD. This potentially beneficial life-saving effect of HDF in dialysis patients still persists after correcting for demographic factors, comorbid conditions, and several potentially confounding therapy-related factors, including previous time spent on dialysis and dialysis dose. It should be noted that HDF patients had more comorbid conditions than HD patients, particularly cardiovascular diseases, underlining the fact this population may have been negatively selected to be treated by HDF.

The superiority of HDF compared to conventional (low- or high flux) HD in potentially improving patient longevity is a quite recent finding.²⁹ This original observation deserves further study and comment. The exact mechanism by which HDF might reduce mortality when compared to HD is not entirely apparent and is beyond the scope of this study.

However, several explanations may be proposed to support this finding. Schematically, HDF's beneficial effects fall into three categories. First, as described above, HDF enhances solute removal of small solutes (urea and creatinine), expands the spectrum of solute removal to include middle-sized and large molecular weight substances.³⁰ Second, on-line HDF enhances intradialytic hemodynamic stability, which facilitates treatment of elderly and high-risk patients. Third, HDF may improve the biocompatibility of the dialysis system, reducing bioactivation and its subsequent inflammation.³¹

The superiority of on-line HDF to HD has been suggested by the results of several studies.^{32–34} Solute removal capacity of uremic toxins is enhanced by high-efficiency on-line HDF.³⁵ Most clinical studies agree that on-line HDF permits a similar reduction rate of small solutes per session as that of HD: 70–80% for urea (60 daltons (da)).³⁶ Using B2M as a solute marker of larger uremic toxins, it has been shown in a controlled study that the reduction ratio of B2M per session was 20–30% higher with on-line HDF than with high-flux HD (72.7 versus 49.7%), and that regular use of on-line HDF significantly reduces circulating levels of predialysis B2M (median value 20 mg/l).²⁰ It has also been shown that HDF can clear larger solutes such as myoglobin (16 kDa) and retinol-binding protein (25 kDa).^{21,37} The capacity to remove middle-sized peptide substances is positively correlated to the convective clearance and the amount of fluid exchanged per session, and it is the enhanced convective clearance achieved by HDF that is the primary mechanism for removing larger uremic solutes.^{38,39} A new aim in dialysis adequacy is to prevent B2M-amyloid occurrence and possibly to reduce patient mortality by using highly permeable and biocompatible membranes.⁴⁰ Very recently, it has been shown that some protein-bound solutes (*p*-cresol) may be more efficiently removed by high-efficiency HDF than by high-flux HD.⁴¹ It has also been shown that on-line HDF reduces the circulating levels of advanced glycation end products that are putatively implied in the dialysis-related complications of long-term dialysis patients.⁴²

A number of studies in the late 1970s and early 1980s demonstrated superior hemodynamic stability with HDF as compared with HD, although these earlier studies involved comparisons with those receiving acetate-buffered dialysate. Although this issue has not been entirely resolved, at least some prospective controlled reports and more recent observational reports also suggest an advantage in comparison to controls treated with bicarbonate-buffered dialysate.^{33,43,44} This unique property of HDF and other convective therapies makes HDF quite useful in treating patients who are elderly, heart-compromised, or prone to hypotension. The precise mechanisms by which HDF maintains the arterial pressure during dialysis sessions are not completely understood. However, several studies tend to favor the hypothesis that hemodynamic stability depends on the increase of the peripheral vascular tone (arterial and venous) and the vascular refilling rate due to the neutral thermal balance.^{45,46}

Several other factors may contribute to this hemodynamic adaptation during HDF, although they remain largely speculative: high sodium concentration of the substitution dialysis fluid, release of vasoconstrictor mediators (e.g. endothelin, renin, angiotensin), clearance of vasodilator mediators, and improvement of sympathetic activity facilitating adaptation of heart rate and vascular resistance.⁴⁷

HDF combines the use of high-flux synthetic membrane with low bioreactive profile and the use of ultrapure dialysis fluid. This combination is recognized as beneficial in reducing the bioactivation (circulating cells and protein systems) induced by blood–hemodialyzer interaction. Longitudinal studies have also shown that the release of proinflammatory mediators (interleukin-1, interleukin-6, tumor necrosis factor) resulting from the patient–hemodialyzer interaction is significantly reduced for patients receiving on-line HDF.⁴⁸ Using well accepted markers of inflammation (albumin, ferritin, and transferrin saturation), our study is in agreement with these findings, showing that despite the administration of large volumes of intravenous replacement fluid, HDF is associated with a lower microinflammatory profile than HD.^{49,50} This effect is of particular importance, as it prevents the induction of microinflammation reaction in HD patients, a state that favors long-term dialysis complications (such as B2M-amyloidosis and atherosclerosis).^{51,52}

In addition to its beneficial effects on ESRD patient mortality, on-line HDF may have been associated with a positive effect on anemia correction. This statistically non-significant finding agrees with prior findings that switching from HD to HDF was associated with a higher hemoglobin level and a reduced weekly consumption of erythropoietin.⁵³ Since this study also agrees with findings from previous comparative HD/HDF studies, further randomized controlled studies should be considered.^{54,55} However, one can speculate that HDF, by enhancing the removal of larger uremic toxins and by reducing the inflammation state of patients, may remove some specific receptor antagonists of erythropoietin and thereby increase the sensitivity of erythroblasts to the drug.

Conclusion

This is the first large observational cohort study with robust adjustments for demographic and comorbid confounding factors to show an association with lower mortality risk for HDF. The modality's beneficial effects on patient outcomes are not related to dialysis dose for small molecules (Kt/V_{urea}), but may be related to factors particular to HDF, which combines enhanced removal of larger molecular weight substances with an improved biocompatible system.

MATERIALS AND METHODS

Data sources

This analysis used a sample of 2165 European HD patients from the DOPPS I, an international, prospective, observational study involving adult HD patients randomly selected from 308 representative dialysis facilities. A total of 101 European facilities (21 in

Germany and 20 each in France, Italy, Spain, and the UK) enrolled patients. In each facility, an algorithm was used to create a sample of 20–40 patients, depending upon facility size. The DOPPS I sampling plan and study methods have been described elsewhere.⁵⁶ Consent to collect anonymous patient information was obtained as needed from the local or national Ethics Committee or Institutional Review Board. Data collection began in 1998 and was gathered at 4-month follow-up intervals through early 2001.

Classification of HD and HDF modalities

HDF operating parameters were reported for each patient by the nurse coordinator at each center; HDF was defined as the patient 'routinely receiving replacement fluid intravenously as part of the treatment.' Data were also captured regarding how much fluid was replaced and this was used to further refine treatment definitions. Patients replacing 15–24.9l of fluid per treatment were classified as receiving high-efficiency HDF, while patients replacing 5–14.9l of fluid per treatment were classified as receiving low-efficiency HDF. HD patients not receiving fluid replacement were classified by the type of dialyzer used (high-flux: KUF >20 ml/h/mm Hg versus low-flux: KUF ≤20 ml/h/mm Hg) independent of the membrane type. KUF, or ultrafiltration coefficient, is a measure of membrane permeability. A total of 253 patients were classified as receiving either low- or high-efficiency HDF.

Statistical methods

The distribution of dialysis type was examined by country in a prevalent cross-section of patients ($n = 2165$). The same sample was used to compare patient demographics (age, sex, time on dialysis), baseline comorbid conditions (listed in Table 2), weight, catheter use for vascular access, hemoglobin, serum albumin, normalized protein catabolic rate, cholesterol, triglycerides, dialysis dose (Kt/V), erythropoietin use and dosage, two summary scales from the SF-36 quality of life questionnaire (MCS and PCS),^{57,58} and HDF status. Linear mixed models and logistic regression models were used to compare both unadjusted and adjusted means and proportions, using the low-flux HD patients as the reference group. All models adjusted for country and accounted for facility clustering. Adjusted models took into account the patient characteristics described above.

Crude mortality rates were calculated for each treatment group and expressed as deaths per 100 patient years. Cox proportional hazards regression models were employed to examine the relationship between mortality and dialysis type, with the adjustments described above. Cox models were stratified by country of residence and a robust variance estimate (the sandwich estimator) was used to account for clustering at the facility level.⁵⁹

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