AJKD
Original Investigation

Hemodiafiltration Versus Hemodialysis and Survival in Patients With ESRD: The French Renal Epidemiology and Information Network (REIN) Registry

*Lucile Mercadal, MD, PhD,[1,2,3,4] Jeanna-Eve Franck, MSc,[2] Marie Metzger, PhD,[2,3,4] Pablo Urena Torres, MD, PhD,[5] François de Cornelissen, MD,[6] Stéphane Edet, MD,[7] Clémence Béchade, MD,[8] Cécile Vigneau, MD,[9] Tilman Drüeke, MD,[2,3,4] Christian Jacquelinet, MD, PhD,[2,3,4,10] and Bénédicte Stengel, MD, PhD[2,3,4] on behalf of the REIN Registry**[*]

Background: Recent randomized trials report that mortality is lower with high-convection-volume hemodiafiltration (HDF) than with hemodialysis (HD).

Study Design: We used data from the French national Renal Epidemiology and Information Network (REIN) registry to investigate trends in HDF use and its relationship with mortality in the total population of incident dialysis patients.

Setting & Participants: The study included those who initiated HD therapy from January 1, 2008, through December 31, 2011, and were dialyzed for more than 3 months; follow-up extended to the end of 2012.

Factor: HDF use at the patient and facility level.

Outcomes: All-cause and cardiovascular mortality, using Cox models to estimate HRs of HDF as time-dependent covariate at the patient level, with age as time scale and fully adjusted for comorbid conditions and laboratory data at baseline, catheter use, and facility type as time-dependent covariates. Analyses completed by Cox models for HRs of the facility-level exposure to HDF updated yearly.

Results: Of 28,407 HD patients, 5,526 used HDF for a median of 1.2 (IQR, 0.9-1.9) years; 2,254 of them used HDF exclusively. HRs for all-cause and cardiovascular mortality associated with HDF use were 0.84 (95% CI, 0.77-0.91) and 0.73 (95% CI, 0.61-0.88), respectively. In patients treated exclusively with HDF, these HRs were 0.77 (95% CI, 0.67-0.87) and 0.66 (95% CI, 0.50-0.86). At the facility level, increasing the percentage of patients using HDF from 0% to 100% was associated with HRs for all-cause and cardiovascular mortality of 0.87 (95% CI, 0.77-0.99) and 0.72 (95% CI, 0.54-0.96), respectively.

Limitations: Observational study.

Conclusions: Whether analyzed as a patient- or facility-level predictor, HDF treatment was associated with better survival.

Am J Kidney Dis. 68(2):247-255.

INDEX WORDS: Hemodialysis (HD); hemodiafiltration (HDF); treatment modality; registry-based study; epidemiology; dialysis; mortality; cardiovascular mortality; survival; end-stage renal disease (ESRD).

Editorial, p. 176

Hemodiafiltration (HDF), which combines diffusion and convection, improves removal of uremic toxins in the middle-molecule range. The first evidence of improved survival with HDF came in the late 2000s, from the observational DOPPS (Dialysis Outcomes and Practice Patterns Study)[1] and from a small randomized controlled study of hemofiltration.[2] At that time, the percentage of hemodialysis (HD) patients treated by HDF was low, ranging from 1.7% in Spain to 20% in Italy. The findings from DOPPS might have been confounded by indication. Three large randomized controlled trials[3-5] and 4 meta-analyses[6-9] followed, reporting different conclusions about the effects of HDF on survival. The most consistent finding was that HDF with a high, but not a

From the [1]Department of Nephrology, Assistance Publique Hôpitaux de Paris, Pitié Salpêtrière University Hospital, Paris; [2]INSERM UMRS-1018, CESP Team 5 (Renal and Cardiovascular Epidemiology), Villejuif; [3]Paris Sud University, Kremlin-Bicêtre; [4]Versailles Saint-Quentin University, Versailles; [5]Clinique du Landy, Saint Ouen; [6]Nephrology Department, Narbonne Polyclinic, Narbonne; [7]Nephrology Department, Dieppe Hospital, Dieppe; [8]Nephrology Department, Caen Hospital, Caen; [9]Nephrology Department, Pontchaillou Rennes University Hospital, Rennes; and [10]Biomedicine Agency, La Plaine Saint-Denis, France.

[*]*The dialysis facilities participating in the REIN Registry are listed in the annual report available at www.agence-biomedecine.fr/Le-programme-REIN.*

Received July 26, 2015. Accepted in revised form November 16, 2015. Originally published online December 24, 2015.

Address correspondence to Lucile Mercadal, MD, PhD, 41-83 bd de l'hôpital, 75013 Paris, France. E-mail: lucile.mercadal@aphp.fr

0272-6386
http://dx.doi.org/10.1053/j.ajkd.2015.11.016

low, convection volume was associated with better survival. However, this observation was based on secondary subgroup analyses. Together with the possible harm to malnourished patients from excessive albumin loss with HDF (a drawback of this technique), as well as its higher cost, this uncertainty currently acts as a barrier to its more widespread adoption. Additional supportive evidence of its superiority to standard HD is clearly required.

To further investigate survival with HDF, we used the French Renal Epidemiology and Information Network (REIN) registry and examined the nationwide incident patient population. The large size of this registry-based population enables analyses of all-cause and cardiovascular mortality. Additional analyses by patient subgroups, defined by sex and various clinical conditions, including serum albumin status, sought to identify patients who might benefit most from HDF. We analyzed HDF as both a patient- and facility-level predictor to take indication bias into account. Finally, because the higher bacteriologic quality of the water used in HDF might explain, at least in part, the benefits found for HDF, we also separately compared outcomes of patients treated with standard HD and online HDF in the dialysis facilities offering both treatment modalities.

METHODS

Population

The REIN registry includes all patients with end-stage renal disease receiving long-term renal replacement therapy in France, either by extracorporeal renal replacement therapy or kidney transplantation. Details of the methods and quality control of the REIN registry have been described elsewhere.[10] Because of the high mortality rate during the first 90 days of dialysis treatment,[11] deaths within the first 3 months of HD were analyzed separately. This study included all incident adult patients who initiated HD therapy from January 1, 2008, through December 31, 2011, and were dialyzed for more than 3 months: 28,407 of a total of 31,850 patients (Fig 1). The REIN registry was approved by the relevant French committees, the Comité consultatif sur le traitement de l'information en matière de recherche (CCTIRS) and the Commission nationale de l'informatique et des libertés (CNIL 903188). For population-based registries requiring exhaustiveness, French regulations require that patients be informed by the clinic that they can choose not to participate (opt out).

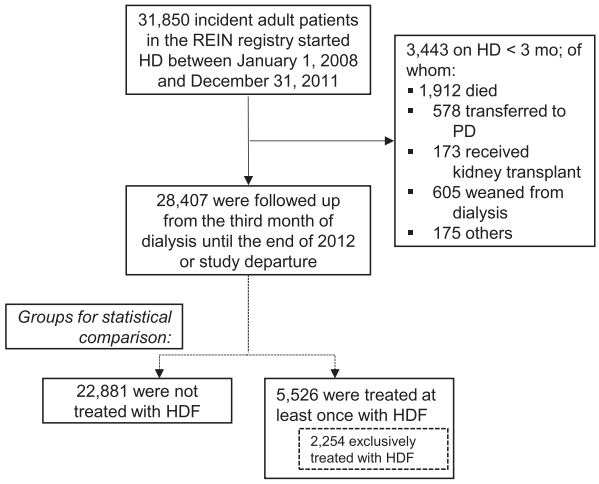

Figure 1. Flow chart of the study. Abbreviations: HD, hemodialysis; HDF, hemodiafiltration; REIN, Renal Epidemiology and Information Network.

Information

Information about patients at initiation included age, sex, primary kidney disease, comorbid conditions, disability status, body mass index, conditions of initial dialysis (including emergency status and catheter use), and laboratory data (serum albumin, creatinine, and blood hemoglobin). Estimated glomerular filtration rate (eGFR) was calculated with the 4-variable MDRD (Modification of Diet in Renal Disease) Study equation. Comorbid conditions included diabetes, heart failure, coronary heart disease, stroke, peripheral vascular disease, chronic respiratory disease, active malignancy, cirrhosis, smoking, and mobility status. Patient-level technical data included use of HDF, frequency and session length of dialysis, facility type (in-center dialysis facility, satellite facility, and self-dialysis), and dialysis facility legal status (for profit vs not for profit). Changes in facility type and legal status, dialysis modality, and vascular access are updated annually as long as the patient remains on dialysis therapy. HDF mode (pre, post, mixed, and mid) is not available from the registry.

Outcomes

Events including kidney transplantation, recovery of kidney function, and death were collected prospectively and reported from the first day of treatment. Study outcomes included overall and cardiovascular mortality. Patients were considered at risk in Cox proportional hazards models from the third month of dialysis until death or study departure due to kidney transplantation, dialysis weaning, loss to follow-up, transfer to peritoneal dialysis therapy, moving out of France, or study end (end of 2012).

Statistical Analyses

Missing data were treated by multiple imputations with a Markov chain Monte Carlo approach. We used a run length of 500 iterations and created 20 imputed data sets (SAS PROC MI; SAS Institute Inc). Variables included in the imputation procedure were age, sex, dialysis facility type and legal status, comorbid conditions and laboratory data as listed above, first dialysis with catheter, and outcome (all-cause death). Results of analyses through the 20 complete imputed data sets were combined, and the final results were averaged across these sets (SAS PROC MIANALYZE). Baseline characteristics at dialysis therapy initiation are shown as estimated mean numbers and percentages, which are compared between patients never treated by HDF and those who were treated by HDF.

Adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for overall mortality were estimated by time-dependent Cox proportional hazards models stratified by region, facility type, and legal status. We used age as the time-scale to better control for the effect of age in this large-scale longitudinal study mainly composed of elderly patients.[12,13] Because of the smaller number of events, cardiovascular mortality models were stratified only by facility type and region and then adjusted for facility legal status. Because some unknown patient characteristics and medical practice patterns may vary by facility, robust variance estimates (sandwich estimators) were used to account for facility-clustering effects.[14,15] The first model was adjusted for sex. Fully adjusted models were further adjusted for baseline comorbid conditions and clinical and laboratory data, specifically diabetes, heart failure, coronary heart disease, peripheral vascular disease, stroke, myocardial infarction, chronic respiratory disease, obesity, cirrhosis, active malignancy, smoking,

mobility, albuminemia, eGFR, and session length. They were also adjusted for facility type, legal status, and catheter use, all treated as time-dependent covariates. Dialysis frequency was not included in the model because it was not significantly associated with mortality. Interactions were tested between HDF and all covariates included in the models. Analyses were repeated for patients treated exclusively by HDF versus patients never treated by HDF. The study of HDF as a time-dependent covariate with multiple entries took into account patient treatment changes and HDF status changes within the dialysis facilities. To explore whether the better bacteriologic quality of the dialysate in facilities using HDF influenced survival, mortality risks were compared for patients dialyzed in facilities without HDF, those on standard HD therapy in facilities also providing HDF, and those on HDF therapy.

To minimize bias from unmeasured confounders, we also conducted analyses using percentage of patients on HDF therapy in each center (facility-level predictor) as the exposure variable, rather than patient HDF exposure (patient-level predictor). This percentage was calculated for each facility and each year. It was then assigned to all patients in the same facility and updated annually or when the patient transferred to another dialysis unit. Cox proportional hazards models evaluated the HRs associated with this facility-level predictor adjusted for individual comorbid conditions and for the updated yearly percentage of patients dialyzed with a catheter per unit, as a facility-level variable. Because of the very low proportion of patients treated by HDF in self-dialysis centers, further facility-level analyses excluded these patients.

Finally, we conducted sensitivity analyses, one to study HRs for overall mortality associated with HDF by subgroups defined by sex and various clinical conditions and the other to study early mortality (<3 months). In all these analyses, the proportional hazards assumption was tested by the Schoenfeld residual method. The log-linearity of continuous covariates was confirmed by the spline method. Two-sided significance tests were used and $P < 0.05$ was considered significant. All statistical analyses were performed with the SAS, version 9.4, and R (R Foundation for Statistical Computing) statistical packages, version 3.2.2.

RESULTS

Trends in HDF Use

The proportion of patients treated by HDF grew substantially during the study period (Fig 2). Similarly to these patient-level results, the percentage of patients treated by HDF at each facility tended to increase over time (Fig 3).

Patient Characteristics According to HDF or HD Use

Among the 28,407 patients analyzed, 22,881 were never treated by HDF, and 5,526 were treated by HDF, 2,254 of them exclusively by HDF (Fig 1). Median follow-up was 1.95 (interquartile range, 1.19-3.00) years for the entire population. Overall median HDF treatment was 1.2 (interquartile range, 0.9-1.9) years, and patients spent 63% of their dialysis vintage on HDF therapy. After excluding those treated exclusively with HDF, patients with both types of treatment spent 45% of their dialysis vintage on HDF.

At dialysis therapy initiation, patients in the HDF group were older, more frequently former smokers, less likely to have polycystic kidney disease, and more likely to have diabetes or vascular or diabetic kidney disease. They more frequently initiated dialysis therapy on an emergency basis, with a catheter, and in a hospital-based facility. They had more cardiovascular comorbid conditions and less mobility (Table 1). Laboratory data at dialysis therapy initiation were similar for both groups, except for a slightly higher eGFR in the HDF group. Patients never treated by HDF had a higher crude kidney transplantation rate (Table 2).

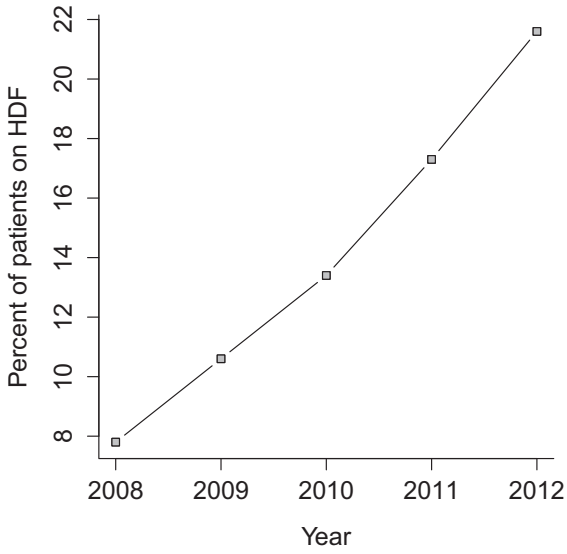

Figure 2. Trends in the percentage of patients treated by hemodiafiltration (HDF) in 2008 to 2012.

Mortality According to HDF Use

Patient-Level Predictor Analyses

In the Cox proportional hazards model analysis adjusted for sex and with age as the time-scale (first model, Table 3), HDF use was associated with a

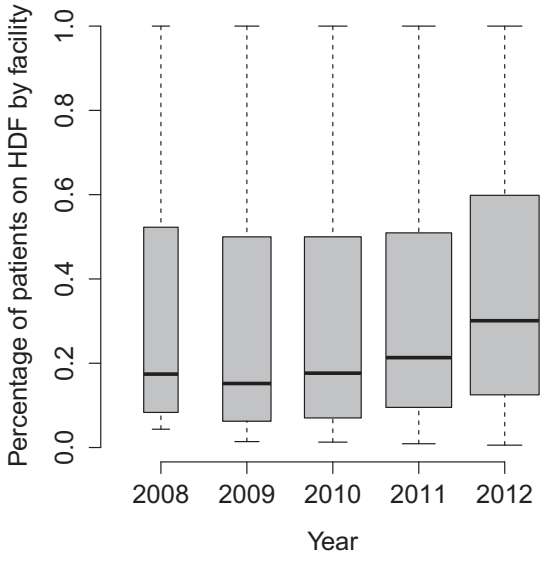

Figure 3. Distribution of the percentage of patients on hemodiafiltration (HDF) therapy by facility in 2008 to 2012.

Table 1. Baseline Characteristics of 28,407 Incident Patients From the REIN Registry, According to HDF Treatment Status

	Never Treated by HDF (n = 22,881)	Treated by HDF (n = 5,526)	*P*	Exclusively Treated by HDF (n = 2,254)	*P*
Age, y	70.6 [58.2-79.1]	71.4 [59.9-79.1]	0.001	73.3 [62.0-80.5]	<0.001
Male sex	14,322 (62.6)	3,465 (62.7)	0.9	1,392 (61.8)	0.4
Comorbid conditions					
Diabetes	9,185 (40.1)	2,608 (47.2)	<0.001	1,051 (46.6)	<0.001
Coronary heart disease	5,196 (22.7)	1,391 (25.2)	<0.001	559 (24.8)	0.03
Peripheral vascular disease	4,856 (21.2)	1,286 (23.3)	0.002	514 (22.8)	0.1
Stroke	2,416 (10.6)	654 (11.8)	0.01	264 (11.7)	0.1
Chronic respiratory disease	2,802 (12.2)	742 (13.4)	0.02	293 (13.0)	0.3
Arrhythmias	4,769 (20.8)	1187 (21.5)	0.3	501 (22.2)	0.1
Heart failure	5,914 (25.8)	1,438 (26.0)	0.8	589 (26.1)	0.8
Myocardial infarction	2,443 (10.7)	644 (11.7)	0.05	257 (11.4)	0.3
Obesity: BMI ≥ 30 kg/m^2	5,110 (22.3)	1,511 (27.3)	<0.001	599 (26.6)	<0.001
Smoking					
Never smoker	13,351 (58.5)	3,065 (55.5)	<0.001	1,275 (56.5)	0.1
Former smoker	5,726 (25.0)	1,604 (29.0)	<0.001	640 (28.4)	0.002
Current smoker	3,805 (16.6)	859 (15.5)	0.08	341 (15.1)	0.1
Cirrhosis	449 (2.0)	127 (2.3)	0.1	58 (2.5)	0.1
Mobility					
Walk without help	18,579 (81.2)	4,452 (80.6)	0.3	1,746 (77.4)	<0.001
Need assistance	3,442 (15.0)	858 (15.5)	0.4	413 (18.3)	<0.001
Totally dependent for transfers	862 (3.8)	218 (3.9)	0.6	97 (4.3)	0.3
Primary kidney disease			<0.001		<0.001
Polycystic kidneys	1,522 (6.7)	225 (4.1)		73 (3.2)	
Hypertension	5,724 (25.0)	1,410 (25.5)		668 (29.6)	
Diabetic nephropathy	5,121 (22.4)	1,528 (27.7)		604 (26.8)	
Glomerulonephritis	2,483 (10.9)	571 (10.3)		203 (9.0)	
Pyelonephritis	965 (4.2)	192 (3.5)		76 (3.4)	
Vascular nephropathy	261 (1.1)	101 (1.8)		50 (2.2)	
Other and unknown	6,805 (29.7)	1,499 (27.1)		580 (25.7)	
Unplanned HD initiation	7,002 (30.6)	1,838 (33.2)	<0.001	787 (34.9)	<0.001
RRT initiation with catheter	11,458 (50.1)	2,919 (52.8)	<0.001	1,217 (54.0)	<0.001
RRT frequency ≥ 3×/wk	21,415 (93.6)	5,123 (92.7)	0.02	2,032 (90.1)	<0.001
RRT session length ≥ 240 min	17,465 (76.3)	4,120 (74.5)	0.006	1,583 (70.2)	<0.001
Facility type			<0.001		<0.001
In-center dialysis facility	20,385 (89.1)	5,238 (94.8)		2,181 (96.8)	
Satellite facility	754 (3.3)	141 (2.6)		21 (0.9)	
Self-dialysis	1,742 (7.6)	147 (2.7)		52 (2.3)	
Laboratory variables					
Albuminemia					
<25 g/L	2,243 (9.8)	512 (9.3)	0.3	203 (9.0)	0.3
25-<30 g/L	4,118 (18.0)	1,000 (18.1)	0.9	425 (18.8)	0.5
30-<35 g/L	6,677 (29.2)	1,674 (30.3)	0.2	687 (30.5)	0.3
≥35 g/L	9,845 (43.0)	2,342 (42.4)	0.5	940 (41.7)	0.3
eGFR					
<10 mL/min/1.73 m^2	15,243 (66.6)	3,427 (62.0)	<0.001	1,296 (57.5)	<0.001
10-<15 mL/min/1.73 m^2	5,284 (23.1)	1,453 (26.3)	<0.001	640 (28.3)	<0.001
≥15 mL/min/1.73 m^2	2,356 (10.3)	647 (11.7)	0.008	320 (14.2)	<0.001
Hemoglobin					
<10 g/dL	9,596 (41.9)	2,289 (41.4)	0.5	866 (38.4)	0.006
10-<11 g/dL	5,323 (23.3)	1,295 (23.4)	0.8	547 (24.2)	0.3
11-<13 g/dL	6,651 (29.1)	1,645 (29.8)	0.3	712 (31.6)	0.03
≥13 g/dL	1,312 (5.7)	299 (5.4)	0.4	130 (5.8)	0.9

Note: Values for categorical variables are given as imputed values, number (percentage); for continuous variables, as median [interquartile range]. There were no missing data for age, sex, dialysis modality, and facility type. Percentages of imputed data ranged from 4% to 8% for diabetes, comorbid conditions, and HD therapy initiation conditions; 21% for eGFR; 25% for hemoglobin level; 31% for BMI; and 49% for serum albumin.

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HDF, hemodiafiltration; REIN, Renal Epidemiology and Information Network; RRT, renal replacement therapy.

Table 2. Number of Person-Years and Events by HDF Exposure Group

	Never Treated by HDF (n = 22,881)	Treated by HDF (n = 5,526)	Exclusively Treated by HDF (n = 2,254)
Person-y treated by HD	41,740.0 (100)	4,566.7 (37)	0 (0)
Person-y treated by HDF	0 (0)	7,659.1 (63)	3,871.4 (100)
Events			
Deaths	6,892 (30.1)	1,292 (23.4)	694 (30.8)
Cardiovascular deaths	1,628 (7.1)	279 (5.0)	135 (6)
Loss to follow-up	223 (1.0)	29 (0.5)	17 (0.8)
Kidney transplantation	3,218 (14.1)	419 (7.6)	183 (8.1)
Dialysis weaning	761 (3.3)	117 (2.1)	77 (3.4)
Transfer to peritoneal dialysis	183 (0.8)	31 (0.6)	20 (0.9)
Crude rates			
Mortality rate, per 100 person-y	16.5	10.6	17.9
Kidney transplantation rate, per 100 person-y	7.7	3.4	4.7

Note: Unless otherwise indicated, values given as number (percentage).
Abbreviations: HD, hemodialysis; HDF, hemodiafiltration.

significant reduction in all-cause and cardiovascular mortality. After full adjustment, the HR for all-cause mortality associated with HDF was 0.84 (95% CI, 0.77-0.91), and for cardiovascular mortality, 0.73 (95% CI, 0.61-0.88). The adjusted HR for non-cardiovascular mortality associated with HDF was 0.89 (95% CI, 0.81-0.97). HRs were constant with age according to Schoenfeld residual testing. HRs for all-cause and cardiovascular mortality of patients treated exclusively by HDF (n = 2,254), compared with those for patients never treated by HDF (n = 22,881), were 0.77 (95% CI, 0.67-0.87) and 0.66 (95% CI, 0.50-0.86), respectively (Table 3).

In addition, patients treated by standard HD in facilities also providing HDF had no survival advantage over patients treated with standard HD in facilities not offering HDF (HR, 1.02; 95% CI, 0.95-1.09). Results were similar (Table 3) when survival was compared for patients on HDF therapy and those dialyzed only in 100% standard HD facilities.

Table S1 shows all factors other than HD modality associated with mortality.

Facility-Level Predictor Analyses

In the overall population, facility-level predictor analyses showed a significant reduction in all-cause

Table 3. HRs of Mortality Associated With HDF Use, Patient- and Facility-Level Predictor Analyses

	All-Cause Mortality[a]	Cardiovascular Mortality[b]	Noncardiovascular Mortality[b]
Patient-level predictor analyses			
Sex-adjusted model, HDF	0.81 (0.74-0.89)	0.71 (0.59-0.86)	0.86 (0.78-0.95)
Fully adjusted model,[c] HDF	0.84 (0.77-0.91)	0.73 (0.61-0.88)	0.89 (0.81-0.97)
Fully adjusted model,[c] HDF exclusive vs never	0.77 (0.67-0.87)	0.66 (0.50-0.86)	0.82 (0.72-0.92)
Facility-level predictor analyses[d]			
Overall population	0.87 (0.77-0.99)	0.72 (0.54-0.96)	0.96 (0.84-1.09)
In-center and satellite facility patients	0.82 (0.72-0.94)	0.68 (0.51-0.93)	0.90 (0.78-1.04)

Note: Associations are given as HR (95% confidence interval). Use of robust variance estimates to account for facility-clustering effects.
Abbreviations: HDF, hemodiafiltration; HR, hazard ratio.
[a]Cox proportional hazards model for all-cause mortality stratified for facility type, region, and facility legal status.
[b]Cox proportional hazards models for cardiovascular and noncardiovascular mortality stratified for facility type and region and adjusted for facility legal status.
[c]HDF as a time-dependent variable, age as the time-scale, Cox model fully adjusted for sex, comorbid conditions, catheter use, session length, and laboratory data. Data used for adjustment were those at baseline, except for facility type, legal status, and catheter use, which were used as time-dependent covariates.
[d]Percentage of patients on HDF therapy per dialysis facility as a time-dependent variable, age as the time-scale; HR for mortality associated with 100% increase in patients on HDF therapy per facility; model adjusted for sex, comorbid conditions, laboratory data, and yearly updated percentage of patients with catheter by facility.

and cardiovascular mortality associated with a higher percentage of patients treated by HDF and a nonsignificant decrease in noncardiovascular mortality (Table 3). Risks for both all-cause and cardiovascular mortality associated with HDF were lower after we excluded self-dialysis patients; this left a population of 21,945 patients, 4,825 of whom were treated by HDF.

Sensitivity Analyses

Analyses of all-cause mortality associated with HDF use by subgroups showed no significant differences in estimated HRs (Fig 4). None of the statistical tests for interaction was significant. HDF treatment was not associated with early mortality (<3 months).

DISCUSSION

Results of this study in a large unselected end-stage renal disease population strongly support earlier reports that HDF therapy, compared to standard HD therapy, is associated with a significant and marked reduction in all-cause and cardiovascular mortality. This association was found after adjustment for several major confounders and analyzing HDF as both an individual- or facility-level predictor. Moreover, the survival benefit was constant over the entire age scale and did not differ by sex or baseline clinical condition.

Our study adds to the body of evidence that HDF improves survival compared to the standard HD technique. A large observational study based on DOPPS data first suggested that patients treated with HDF with high convection volume had better survival rates than those receiving standard HD. Several other observational cohorts reached similar conclusions.[16-22] The favorable outcomes with HDF presented here involve no adjustment for convection volume, which is not

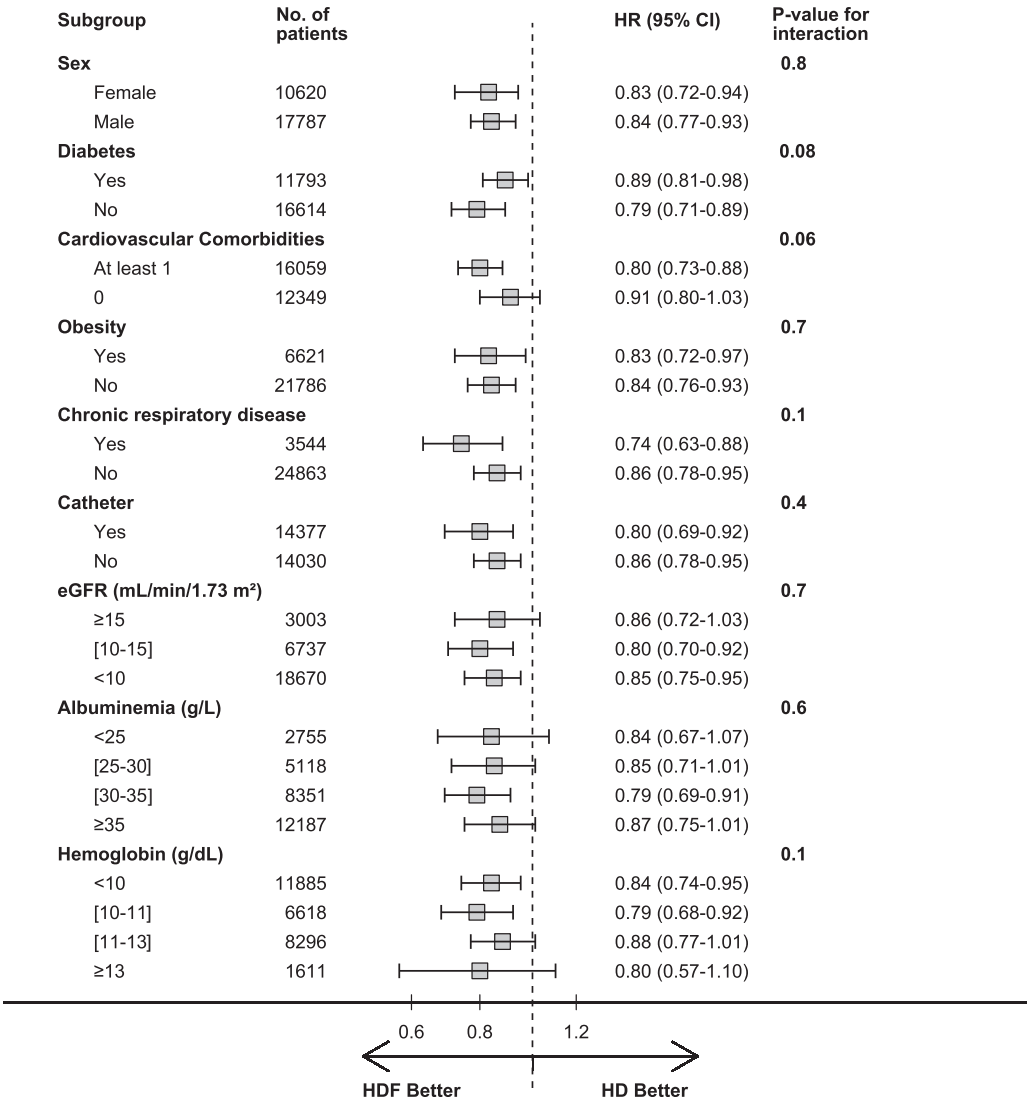

Figure 4. Sensitivity analyses for all-cause mortality risk according to comorbid conditions. Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HDF, hemodiafiltration; HR, hazard ratio.

available in the REIN registry. Nonetheless, the improved survival we observed probably reflects a relatively constant high convection volume with HDF. The relationship of convective volume with mortality has been established, although it remains uncertain whether this result might be due to in part to potential confounders associated with mortality that directly influence the reinfusion volume. Three large randomized trials comparing HD with HDF provided further evidence of better outcomes with high convection volumes.[3-5] Bias nonetheless remains possible in that increased convection volume is associated with confounding factors themselves associated with better survival. Higher convection volume requires a high dialysis blood flow rate, which in turn may be related to a better arteriovenous fistula, better cardiac function, and more favorable vascular conditions, so that the patients selected for HDF begin with better life expectancy. A higher convection volume is also easier to obtain in patients with higher serum albumin levels, an arteriovenous fistula rather than a catheter, longer dialysis session lengths, and lower hematocrits, and all these factors are independently linked to mortality in different ways.[23,24] No randomized trials have been stratified by convection volume: the claim of reduced mortality with higher convection volume is derived solely from subgroup analyses. However, note that the randomized ESHOL (Estudio de Supervivencia de Hemodiafiltración On-Line) trial,[5] which reported 30% lower risk for all-cause mortality with online HDF over standard HD, excluded only 33 of 939 (3%) selected participants for technical conditions and thus substantially reduced the risk of indication bias. In our study, patients exposed to HDF were older and had more comorbid conditions, in particular cardiovascular diseases. In real-life conditions, the criteria that probably motivate nephrologists most to prescribe HDF for any given patient are the combination of the patient's higher probability of a long HD lifetime and lower probability of receiving a kidney transplant. In this case, an indication bias was present, but one that disadvantaged the group treated by HDF.

Four recent meta-analyses have reached somewhat contradictory conclusions, probably because they included different trials.[6-9] The largest of these meta-analyses evaluated the mortality risk reported in 11 randomized controlled trials, with a total of 3,396 participants. It found a nonsignificantly lower HR for all-cause mortality (0.87; 95% CI, 0.7-1.07) and a significantly lower HR for cardiovascular mortality (0.75; 95% CI, 0.58-0.97).[8] All except 3 of the trials examined the effects of online HDF, and the control groups were composed mainly of participants undergoing HD with low-flux membranes. A second meta-analysis included 16 randomized controlled trials reported between 1996 and 2013, with 3,220 participants in all.[6] Ten of these trials compared the mortality risk of HDF with that of HD among 3,011 participants, 4 compared hemofiltration with HD, and 1 compared both HDF and hemofiltration with HD. Nine trials used low-flux membranes, 5 used high-flux membranes, and 2 used both types of dialysis membranes. The results were entirely negative, with no improvement in either all-cause mortality or cardiovascular mortality. The last meta-analysis was still more restricted, examining both 6 recent randomized controlled trials and separately the 3 specifically designed to study mortality as the primary outcome (Turkish OL-HDF study, ESHOL, and CONTRAST [Convective Transport]).[9] The HDF groups had better survival in both sets of trials for both all-cause mortality (HRs of 0.84 [95% CI, 0.73-0.96] with the 6 trials and 0.83 [95% CI, 0.67-0.95] with the 3 trials) and cardiovascular mortality (HR, 0.73; 95% CI, 0.57-0.92).

Interestingly, the HRs for all-cause and cardiovascular mortality found in our analysis of the REIN registry patient population in France are highly consistent with those reported in this latter meta-analysis. Of note, in the most recent randomized controlled trials, the potential bias from incomplete follow-up and participant censoring due to nonfatal events such as kidney transplantation would favor the HDF group because the transplantation rate was higher in the HDF group than in the standard HD patient group. In contrast, in our study, the lower kidney transplantation rate of patients exposed to HDF under real-life conditions would have favored the HD over the HDF group. Another important difference is the median age of participants, which ranged from 42 to 67 years in the 3 most recent trials[6] and was 71 years for the REIN registry patient population treated by HDF.

The better results obtained in the recent trials may be related to progress in HDF techniques. The second-generation software of the 5008 Fresenius dialysis monitor has increased convection volume by 13% over the volume previously obtained.[25] In 4,176 sessions of 366 patients, the Autosub Plus in post-dilution mode reached a convection volume > 21 L during 76% of sessions.[25] In the CONTRAST trial, which used an AK100/200 ultraS (Gambro AB) for HDF, a 5008 ONLINEPlus (Fresenius Medical Care), or aDBB-05 (Nikkiso Co Ltd), all with first-generation automatic software monitoring reinfusion, mean convection volume was 19.7 ± 4.4 L.[23] Because of the better bacteriologic conditions of the dialysate and the significant increase in middle-molecule clearance,[26,27] HDF reduces inflammation[28] and may slow the progression of accelerated atherosclerosis. In our study, HDF patients had significantly lower cardiovascular mortality than HD patients. Finally, hemodynamic tolerance improves in

HDF versus HD,[5] although we have no clear physiologic hypothesis to explain it. This effect could not be linked to the cooler temperature of the reinfusion fluid because in online HDF the reinfusion fluid is warmed to the same extent as the dialysate.

Finally, we also examined whether patients treated with conventional HD in units equipped with water treatment to perform HDF benefited from their exposure to dialysis water of higher bacteriologic quality. Surprisingly, adjusted mortality rates were similar in both settings despite the less stringent water quality requirements in dialysis units not offering HDF therapy. This finding may indicate that ultrapure dialysate is not a major factor in the better survival observed with HDF over standard HD treatment.

The main limitation of our study is its observational design. To reduce this disadvantage, we conducted analyses with HDF use as both a patient- and a facility-level predictor. In the latter, patient allocation to HDF treatment is driven by the instrument (percentage of patients treated by HDF per unit) and not by individual patient characteristics. This analysis attenuates the indication bias intrinsic in the individual analysis. The only precondition to its application is the need for a wide range of exposure in the units, and this condition has been met in recent years due to the widespread expansion of HDF. The self-dialysis units in which younger and healthier patients are treated were secondarily excluded from the facility-level predictor analysis because of consistently very low exposure to HDF there, which made it impossible to evaluate any potential benefit at the unit level. Including these units in the analysis resulted in bias linked to the better outcome of the younger and healthier patients in self-dialysis units, who were treated almost exclusively with HD (Table 3). Additionally, we verified that the benefit of HDF exposure did not vary with adjustment for a facility quality indicator (annual percentage of patients dialyzed with a catheter in the unit). Finally, it is worth noting that the crude mortality rate in patients treated with both HD and HDF was extremely low as a result of survival bias because longer survival increased the likelihood that they would switch to HDF. However, the Cox proportional hazards models took this bias into account by treating HDF as a time-dependent variable.

The strength of the registry is that it offers prospective data collection, includes a large range of comorbid conditions and dialysis techniques, and covers the entire population receiving HD. Therefore, in the absence of evidence of different benefits for any subgroup in the sensitivity analyses, these results can be generalized to the entire population. This scope provided us with a population treated by HDF with more comorbid conditions and a lower transplantation rate than the HD population. Accordingly, no bias due to censoring for transplantation could have favored them. Finally, we did not adjust for the use of acetate-free dialysate, as we did in our last study.[29] Because more dialysis units using HDF also use this type of dialysate, some of the better outcome with HDF observed in this study might therefore be associated with the acetate-free dialysate.

In conclusion, HDF therapy, compared to standard HD, was associated with better patient survival in the French patient population receiving one or the other of these treatment modalities from 2008 through 2012. This benefit appeared to be independent of age and was observed for both all-cause and cardiovascular mortality in all subgroups defined by sex and various clinical conditions. No such benefit was apparent in patients receiving standard HD treatment in facilities that also provided HDF therapy. The benefit was evident in the absence of information for and adjustment or stratification for HDF convection volume, probably because technical progress and guideline adherence have led to relatively constant delivery of large convection volumes. Our observations strongly support recent results about the beneficial effects of HDF on patient outcomes in some, but not all, randomized controlled trials.

ACKNOWLEDGEMENTS

We thank all registry participants, especially the nephrologists and professionals who collected the data and conducted the quality control.

Support: This work was supported by a research grant from the Biomedicine Agency (no. funding: R13180LL). The Biomedicine Agency is responsible for the data collection.

Financial Disclosure: The authors declare that they have no other relevant financial interests.

Contributions: Research idea and study design: LM, BS, CJ; data acquisition: PUT, FdC, SE, CB, CV (contributed data to the REIN registry, which was coordinated by CJ at the Biomedicine Agency); data analysis/interpretation: J-EF, MM, LM, PUT, SE, CB, CV, CJ, TD, BS; statistical analysis: J-EF; supervision or mentorship: LM, BS. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. LM takes responsibility that this study has been reported honestly, accurately, and transparently; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Peer Review: Evaluated by 2 external peer reviewers, a Statistical Editor, a Co-Editor, and the Editor-in-Chief.

SUPPLEMENTARY MATERIAL

Table S1: Multivariate-adjusted HR for all-cause mortality in the patient-level predictor analyses according to patient characteristics and HD modalities.

Note: The supplementary material accompanying this article (http://dx.doi.org/10.1053/j.ajkd.2015.11.016) is available at www.ajkd.org

REFERENCES

1. Canaud B, Bragg-Gresham JL, Marshall MR, et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. *Kidney Int*. 2006;69(11):2087-2093.
2. Santoro A, Mancini E, Bolzani R, et al. The effect of on-line high-flux hemofiltration versus low-flux hemodialysis on mortality in chronic kidney failure: a small randomized controlled trial. *Am J Kidney Dis*. 2008;52(3):507-518.
3. Grooteman MP, van den Dorpel MA, Bots ML, et al; CONTRAST Investigators. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *J Am Soc Nephrol*. 2012;23(6):1087-1096.
4. Ok E, Asci G, Toz H, et al; Turkish Online Haemodiafiltration Study. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. *Nephrol Dial Transplant*. 2013;28(1):192-202.
5. Maduell F, Moreso F, Pons M, et al; ESHOL Study Group. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol*. 2013;24(3):487-497.
6. Wang AY, Ninomiya T, Al-Kahwa A, et al. Effect of hemodiafiltration or hemofiltration compared with hemodialysis on mortality and cardiovascular disease in chronic kidney failure: a systematic review and meta-analysis of randomized trials. *Am J Kidney Dis*. 2014;63(6):968-978.
7. Susantitaphong P, Siribamrungwong M, Jaber BL. Convective therapies versus low-flux hemodialysis for chronic kidney failure: a meta-analysis of randomized controlled trials. *Nephrol Dial Transplant*. 2013;28(11):2859-2874.
8. Nistor I, Palmer SC, Craig JC, et al. Convective versus diffusive dialysis therapies for chronic kidney failure: an updated systematic review of randomized controlled trials. *Am J Kidney Dis*. 2014;63(6):954-967.
9. Mostovaya IM, Blankestijn PJ, Bots ML, et al; EUDIAL1 – an official ERA-EDTA Working Group. Clinical evidence on hemodiafiltration: a systematic review and a meta-analysis. *Semin Dial*. 2014;27(2):119-127.
10. Couchoud C, Stengel B, Landais P, et al. The Renal Epidemiology and Information Network (REIN): a new registry for end-stage renal disease in France. *Nephrol Dial Transplant*. 2006;21:411-418.
11. Robinson BM, Zhang J, Morgenstern H, et al. Worldwide, mortality risk is high soon after initiation of hemodialysis. *Kidney Int*. 2014;85(1):158-165.
12. Lamarca R, Alonso J, Gómez G, Muñoz A. Left-truncated data with age as time scale: an alternative for survival analysis in the elderly population. *J Gerontol A Biol Sci Med*. 1998;53(5):M337-M343.
13. Cologne J, Hsu WL, Abbott RD, et al. Proportional hazards regression in epidemiologic follow-up studies: an intuitive consideration of primary time scale. *Epidemiology*. 2012;23(4):565-573.
14. Glidden DV, Vittinghoff E. Modelling clustered survival data from multicenter clinical trials. *Stat Med*. 2004;3(3):369-388.
15. Therneau TM, Grambsch PM. *Modelling Survival Data: Extending the Cox Model*. Berlin, Germany: Springer-Verlag; 2000.
16. Bosch JP, Lew SQ, Barlee V, Mishkin GJ, von Albertini B. Clinical use of high-efficiency hemodialysis treatments: long-term assessment. *Hemodial Int*. 2006;10(1):73-81.
17. Siriopol D, Canaud B, Stuard S, Mircescu G, Nistor I, Covic A. New insights into the effect of haemodiafiltration on mortality: the Romanian experience. *Nephrol Dial Transplant*. 2015;30(2):294-301.
18. Vilar E, Fry AC, Wellsted D, Tattersall JE, Greenwood RN, Farrington K. Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. *Clin J Am Soc Nephrol*. 2009;4(12):1944-1953.
19. Panichi V, Rizza GM, Paoletti S, et al; RISCAVID Study Group. Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID Study. *Nephrol Dial Transplant*. 2008;23(7):2337-2343.
20. Jirka T, Cesare S, Di Benedetto A, et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis. *Kidney Int*. 2006;70(8):1524-1525.
21. Canaud B, Barbieri C, Marcelli D, et al. Optimal convection volume for improving patient outcomes in an international incident dialysis cohort treated with online hemodiafiltration. *Kidney Int*. 2015;88(5):1108-1116.
22. Davenport A, Peters SA, Bots ML, et al. Higher convection volume exchange with online hemodiafiltration is associated with survival advantage for dialysis patients: the effect of adjustment for body size [published online ahead of print September 9, 2015]. *Kidney Int*. http://dx.doi.org/10.1038/ki.2015.264.
23. Chapdelaine I, Mostovaya IM, Blankestijn PJ, et al; CONTRAST Investigators. Treatment policy rather than patient characteristics determines convection volume in online post-dilution hemodiafiltration. *Blood Purif*. 2014;37(3):229-237.
24. Marcelli D, Scholz C, Ponce P, et al. High-volume post-dilution hemodiafiltration is a feasible option in routine clinical practice. *Artif Organs*. 2015;39(2):142-149.
25. Maduell F, Ojeda R, Rodas L, et al. On-line haemodiafiltration with auto-substitution: assessment of blood flow changes on convective volume and efficiency. *Nefrologia*. 2015;35(1):50-57.
26. Pedrini LA, De Cristofaro V. On-line mixed hemodiafiltration with a feedback for ultrafiltration control: effect on middle-molecule removal. *Kidney Int*. 2003;64(4):1505-1513.
27. Cornelis T, van der Sande FM, Eloot S, et al. Acute hemodynamic response and uremic toxin removal in conventional and extended hemodialysis and hemodiafiltration: a randomized crossover study. *Am J Kidney Dis*. 2014;64(2):247-256.
28. den Hoedt CH, Bots ML, Grooteman MP, et al; CONTRAST Investigators. Online hemodiafiltration reduces systemic inflammation compared to low-flux hemodialysis. *Kidney Int*. 2014;86(2):423-432.
29. Mercadal L, Franck JE, Metzger M, et al. Effect of acetate free dialysis on mortality in the REIN registry. *Nephrol Dial Transplant*. 2015;30(9):1560-1568.