

High-Efficiency Postdilution Online Hemodiafiltration Reduces All-Cause Mortality in Hemodialysis Patients

Francisco Maduell,* Francesc Moreso,[†] Mercedes Pons,[‡] Rosa Ramos,[§] Josep Mora-Macià,^{||} Jordi Carreras,[¶] Jordi Soler,^{**} Ferran Torres,^{††‡‡} Josep M. Campistol,* and Alberto Martinez-Castelao,^{§§} for the ESHOL Study Group

*Nephrology Department, Hospital Clinic, Barcelona, Spain; [†]Nephrology Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [‡]CETIRSA, Barcelona, Spain; [§]Hospital San Antonio Abad, Vilanova i la Geltru, Spain; ^{||}Fresenius Medical Care, Granollers, Spain; [¶]Diaverum Baix Llobregat, L'Hospitalet, Llobregat, Spain; ^{**}Fresenius Medical Care, Reus, Spain; ^{††}Biostatistics Unit, School of Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain; ^{‡‡}Biostatistics and Data Management Platform, IDIBAPS, Hospital Clinic, Barcelona, Spain; and ^{§§}Nephrology Department, Hospital Universitari Bellvitge, L'Hospitalet, Bellvitge, Spain

ABSTRACT

Retrospective studies suggest that online hemodiafiltration (OL-HDF) may reduce the risk of mortality compared with standard hemodialysis in patients with ESRD. We conducted a multicenter, open-label, randomized controlled trial in which we assigned 906 chronic hemodialysis patients either to continue hemodialysis ($n=450$) or to switch to high-efficiency postdilution OL-HDF ($n=456$). The primary outcome was all-cause mortality, and secondary outcomes included cardiovascular mortality, all-cause hospitalization, treatment tolerability, and laboratory data. Compared with patients who continued on hemodialysis, those assigned to OL-HDF had a 30% lower risk of all-cause mortality (hazard ratio [HR], 0.70; 95% confidence interval [95% CI], 0.53–0.92; $P=0.01$), a 33% lower risk of cardiovascular mortality (HR, 0.67; 95% CI, 0.44–1.02; $P=0.06$), and a 55% lower risk of infection-related mortality (HR, 0.45; 95% CI, 0.21–0.96; $P=0.03$). The estimated number needed to treat suggested that switching eight patients from hemodialysis to OL-HDF may prevent one annual death. The incidence rates of dialysis sessions complicated by hypotension and of all-cause hospitalization were lower in patients assigned to OL-HDF. In conclusion, high-efficiency postdilution OL-HDF reduces all-cause mortality compared with conventional hemodialysis.

J Am Soc Nephrol 24: 487–497, 2013. doi: 10.1681/ASN.2012080875

In the last decades, renal replacement therapy with hemodialysis has become a standard of care for patients with ESRD. Despite continuous improvement, annual mortality among these patients ranges between 15% and 25%.^{1,2} Hemodialysis techniques are based on the ability of molecules to diffuse across a semipermeable membrane, which allows adequate clearance of low molecular weight particles. To increase the clearance of middle-to-large molecules, synthetic membranes with high water permeability (high-flux membranes) were introduced years ago. The anticipated benefit of high-flux over low-flux hemodialysis on patient survival was not confirmed in the Hemodialysis (HEMO) study.³ However, the Membrane Permeability Outcome (MPO) study,⁴ as well as a *post hoc* analysis in diabetic patients, showed that high-flux

hemodialysis improved long-term survival in patients with hypoalbuminemia.

Clearance of middle-to-large molecules can be increased by combining diffusive and convective transport through hemodiafiltration. The introduction of online hemodiafiltration (OL-HDF) using ultrapure dialysate as the source of the

Received August 30, 2012. Accepted November 22, 2012.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Francisco Maduell, Department of Nephrology and Renal Transplantation, Hospital Clinic, University of Barcelona, Villarroel, 170 - 08036 Barcelona, Spain. Email: fmaduell@clinic.ub.es

Copyright © 2013 by the American Society of Nephrology

replacement fluid has allowed the convective volume to be increased and has reduced the cost of the procedure.⁵ Randomized studies with limited sample sizes and nonrandomized studies have shown that OL-HDF improves hemodynamic stability and response to erythropoietic-stimulating agents (ESAs) and reduces the incidence of hemodialysis-associated amyloidosis and chronic inflammation.^{6–11} The effect of OL-HDF on patient survival is derived from noncontrolled studies. The European Dialysis Outcomes and Practice Pattern Study was associated with a mortality risk reduction of 35% in patients treated with high-efficiency hemodiafiltration compared with those treated with conventional hemodialysis.¹² These results were confirmed in other noncontrolled studies conducted in several European countries,^{13–15} although two recent, randomized studies failed to show differences in patient survival^{16,17}

In 2007, the Catalan Health Authorities approved a specific additional reimbursement for OL-HDF to dialysis care providers and the Catalan Society of Nephrology promoted this randomized study (On-Line Hemodiafiltration Survival Study, or Estudio de Supervivencia de Hemodiafiltración On-Line [ESHOL]) to compare the effect of OL-HDF over hemodialysis on patient survival.¹⁸

RESULTS

Baseline Patient Characteristics

During the recruitment period, 939 patients were assessed for eligibility in 27 Catalan dialysis units. Thirty-three patients were not included in the randomization, 18 because they did not meet the inclusion criteria, 5 because they refused to provide informed consent, and 10 for other reasons. Finally, 906 patients were included in the randomization (Figure 1). Patient characteristics at enrollment in both groups are summarized in Table 1.

Hemodialysis Treatment

Hemodialysis treatment parameters during follow-up are summarized in Table 2. Length of dialysis time did not differ between the two groups, whereas blood flow (Q_b) and dialysate flow (Q_d) were higher in the OL-HDF group throughout the study. Among patients randomized to hemodialysis, approximately 92% (range, 91.8%–93.6%) were treated with high-flux membranes during the study. The median quarterly replacement volume and convective volume during the study in the OL-HDF group ranged from 20.8 to 21.8 L/session and 22.9–23.9 L/session, respectively.

Primary Outcome

All-Cause Mortality

The mean follow-up was 1.91 ± 1.10 years (median 2.08 years; interquartile range [IQR], 0.86–3.00). During the observation period, 355 patients prematurely finished the study (Figure 1) because of kidney transplantation ($n=180$), change of dialysis

unit ($n=58$), organizational changes ($n=33$), withdrawal of consent ($n=27$), need for a temporary catheter ($n=19$), change of treatment ($n=15$), or because of other, not predefined reasons ($n=23$). All of these patients were censored at the time of premature termination.

There were 207 deaths (22.8%) during the follow-up, with 3-year all-cause mortality rates of 18.6% and 27.1% in the OL-HDF and the hemodialysis groups, respectively, implying a 30% risk reduction (hazard ratio [HR], 0.70; 95% confidence interval [95% CI], 0.53–0.92; $P=0.01$) (Figure 2 and Table 3). The main causes of death were cardiovascular diseases (44.4%) and infectious diseases (15.5%).

Sensitivity analyses were performed on the basis of the following variables, which were found to be independent predictors for all-cause mortality: age, sex, diabetes, the Charlson comorbidity index, and vascular access (Table 4). First, these variables were included in four distinct multivariate analyses to assess the covariate-adjusted risk estimates for the intervention. Second, the treatment risk estimates were also calculated in all subgroups arising from these variables, using the original categories for nominal variables and tertiles for continuous variables. All HRs were consistent for both types of analysis and the statistical tests for interaction were not significant except for the Charlson comorbidity index (Figure 3). The estimated number needed to treat (NNT) for all-cause mortality at 1, 2, and 3 years was 9.75 (5.03–47.41), 7.67 (4.32–33.57), and 7.67 (4.51–31.83), respectively (Table 3).

Secondary Outcomes

Cardiovascular Mortality

The analysis of the distinct causes of cardiovascular mortality (Table 3) showed no significant differences between groups in the number of deaths due to heart failure, ischemic heart disease, mesenteric thrombosis, arrhythmia, or peripheral arteriopathy. However, stroke mortality was significantly lower in the OL-HDF group than in the hemodialysis group ($P=0.03$ by the log-rank test). The Cox proportional hazards model showed that OL-HDF caused a significant 61% risk reduction in mortality from stroke (HR, 0.39; 95% CI, 0.16–0.93).

Other Causes of Mortality

Infection-related mortality was also significantly lower in the OL-HDF group than in the hemodialysis group ($P=0.03$ by the log-rank test; Table 3). The Cox proportional hazards model showed that OL-HDF produced a significant 55% risk reduction in mortality from infection (HR, 0.45; 95% CI, 0.21–0.96). There were no differences in sudden death, cancer, cachexia, or other causes of mortality (Table 3).

Hospitalizations

The rate of all-cause hospital admissions showed a relative risk reduction of 22% favorable to the OL-HDF group (rate ratio, 0.78; 95% CI, 0.67–0.90; $P=0.001$) (Table 5).

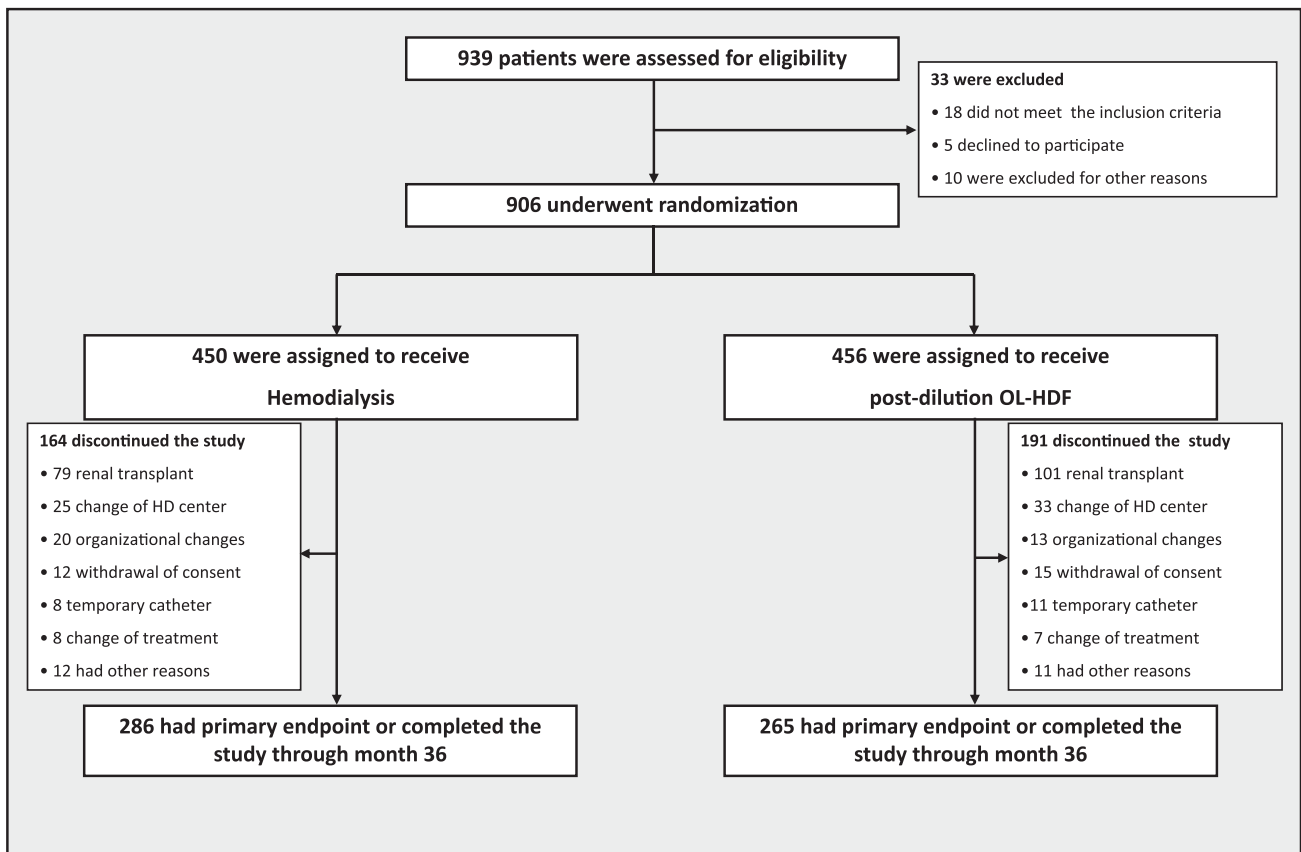


Figure 1. Flow chart of study populations, including the number of patients who were screened, underwent randomization, and completed the study treatment or presented the primary variable. HD, hemodialysis.

Table 1. Demography characteristics and baseline parameters in randomized patients

	All (n=906)	Hemodialysis (n=450)	OL-HDF (n=456)
Age (yr)	65.4±14.4	66.3±14.3	64.5±14.4
Male sex	606 (66.9)	289 (64.2)	317 (69.5)
Diabetes	226 (24.9)	122 (27.1)	104 (22.8)
Charlson comorbidity index	7.0 (5.0–8.0)	7.0 (5.0–8.0)	6.0 (5.0–8.0)
Time on dialysis (mo)	28.0 (12.0–59.0)	27.0 (12.0–58.0)	28.5 (12.0–60.0)
Vascular access			
Fistula	779 (86.0)	372 (82.7)	407 (89.3)
Graft	34 (3.8)	19 (4.2)	15 (3.3)
Catheter	93 (10.3)	59 (13.1)	34 (7.5)

Data are presented as mean ± SD, n (%), or median (IQR).

BP and Intradialysis Tolerance

Neither predialysis nor postdialysis systolic and diastolic BP were significantly modified by treatment, although BP control was improved in both treatment groups during the study (Supplemental Table 1). The percentage of patients requiring antihypertensive drugs did not differ between the groups (Supplemental Table 2).

The incidence of intradialysis symptoms was affected by treatment assignment. There were 679.2 intradialysis hypotension

episodes per 100 patient-years in the OL-HDF group versus 937.7 episodes per 100 patient-years in the hemodialysis group (rate ratio, 0.72; 95% CI, 0.68–0.77; $P<0.001$) (Table 4). The number of intradialysis episodes of arrhythmia and thoracic pain episodes did not differ between the groups (Table 5).

Dialysis Dose and β_2 -Microglobulin

During the study period, the dialysis dose significantly increased in both groups but was higher in patients randomized to OL-HDF than in those randomized to hemodialysis (Supplemental Table 1).

OL-HDF led to a lower accumulation of β_2 -microglobulin than did hemodialysis. β_2 -Microglobulin increased from month 0 to month 36 in both groups but to a lesser extent in the OL-HDF group (Supplemental Table 1).

Nutrition

Dry body weight and albumin changes during follow-up did not differ between treatment groups. However, albumin significantly decreased in both groups throughout the study.

Table 2. Dialysis parameters outcome

	Baseline	Length of Follow-Up						P
		6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	
Dialysis time (min)								
Hemodialysis	234.1 (232.2, 236.1)	235.5 (234.1, 236.9)	235.6 (234.1, 237.1)	235.7 (234.1, 237.4)	236.5 (234.7, 238.3)	238.3 (236.3, 240.2)	237.5 (235.3, 239.6)	0.07 ^a
OL-HDF	235.8 (234.2, 237.3)	234.4 (233.0, 235.9)	234.2 (232.6, 235.7)	234.8 (233.3, 236.4)	235.7 (233.9, 237.5)	235.9 (234.0, 237.8)	236.6 (234.6, 238.7)	0.14 ^b
Time × time	—	0.30	0.18	0.43	0.55	0.09	0.58	0.80 ^c
Qb (ml/min)								
Hemodialysis	380 (374, 387)	367 (363, 371)	371 (366, 375)	375 (370, 380)	370 (365, 376)	378 (372, 384)	380 (374, 387)	<0.001 ^a
OL-HDF	392 (387, 398)	384 (380, 388)	386 (381, 391)	384 (379, 389)	385 (379, 390)	385 (379, 391)	389 (383, 395)	<0.001 ^b
Time × time	—	<0.001	<0.001	0.01	0.001	0.09	0.04	0.54 ^c
Qd (ml/min)								
Hemodialysis	531 (520, 542)	560 (553, 568)	554 (546, 561)	550 (542, 558)	545 (536, 554)	548 (538, 557)	537 (526, 547)	<0.001 ^a
OL-HDF	553 (541, 564)	571 (564, 579)	571 (563, 578)	575 (566, 583)	575 (566, 583)	580 (570, 590)	566 (556, 577)	<0.001 ^b
Time × time	—	0.04	0.002	0.001	0.001	0.001	0.001	0.14 ^c
Replacement volume (L/session)								
Hemodialysis	—	—	—	—	—	—	—	<0.001 ^a
OL-HDF	—	21.8 (21.6, 22.0)	21.5 (21.3, 21.8)	21.1 (20.8, 21.4)	20.8 (20.5, 21.1)	21.2 (20.9, 21.5)	21.7 (21.3, 22.0)	0.01 ^b
Time × time	—	0.001	0.001	0.001	0.001	0.001	0.001	0.01 ^c
Intradialysis weight change (pre–post)								
Hemodialysis	2.1 (2.0, 2.2)	2.1 (2.0, 2.2)	2.1 (2.0, 2.3)	2.1 (1.9, 2.2)	2.3 (2.1, 2.4)	2.0 (1.8, 2.1)	2.1 (1.9, 2.3)	0.91 ^a
OL-HDF	2.1 (2.0, 2.2)	2.1 (1.9, 2.2)	2.3 (2.1, 2.4)	2.1 (2.0, 2.3)	2.1 (1.9, 2.2)	2.1 (2.0, 2.3)	2.1 (1.9, 2.2)	0.12 ^b
Time × time	—	0.77	0.13	0.56	0.08	0.17	0.76	0.56 ^c
Convection volume (L/session)								
Hemodialysis	2.1 (2.0, 2.2)	2.1 (1.8, 2.4)	2.2 (1.9, 2.4)	2.1 (1.7, 2.4)	2.3 (1.9, 2.6)	2.0 (1.6, 2.4)	2.1 (1.7, 2.5)	<0.001 ^a
OL-HDF	2.1 (2.0, 2.2)	23.9 (23.6, 24.2)	23.8 (23.5, 24.1)	23.2 (22.9, 23.5)	22.9 (22.5, 23.2)	23.3 (22.9, 23.7)	23.7 (23.3, 24.1)	0.003 ^b
Time × time	—	0.001	0.001	0.001	0.001	0.001	0.001	0.01 ^c

Data are shown for every 6 months but were collected every 3 months. Data are presented as mean (95% CI) at baseline, and least-squares mean (95% CI) at 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months. Analysis was conducted using a mixed model for repeated measures. Time × time indicates time × time comparisons, which are given as P values.

^aP value of treatment effect.

^bP value of time effect.

^cP value of treatment × time interaction.

The normalized protein catabolic rate was higher in patients randomized to OL-HDF (Supplemental Table 1).

Anemia

Hemoglobin, the transferrin saturation index, and ferritin did not differ between the groups during the study period (Supplemental Table 1). Moreover, there were no differences in the proportion of patients treated with distinct ESA. Intravenous iron supplements and ESA doses did not differ between the groups (Supplemental Table 2).

Phosphate and Other Biochemical Parameters

Serum phosphate (Supplemental Table 1) and the number of phosphate binding tablets (Supplemental Table 2) did not

significantly change during the study and did not differ between the treatment groups. There were no significant changes for predialysis C-reactive protein, creatinine, sodium, potassium, uric acid, calcium, and intact parathyroid hormone (Supplemental Table 3).

Influence of Convection Volume on All-Cause Mortality

In *post hoc* analyses, the association between convective volume per session in comparison with convective volume per square meter of body surface area and convective volume per body mass index was evaluated (Supplemental Table 4). The convective volume per session is the variable that best represents the trend compared with the ratio of the convective volume per session both with the body mass index and with the body surface area. In the group of patients with the highest delivered convection volume, mortality in the intermediate tertile (23.1–25.4 L) and upper tertile (>25.4 L) was considered lower than that in patients randomized to hemodialysis (HR, 0.60; 95% CI, 0.39–0.90; and HR, 0.55; 95% CI, 0.34–0.84, respectively).

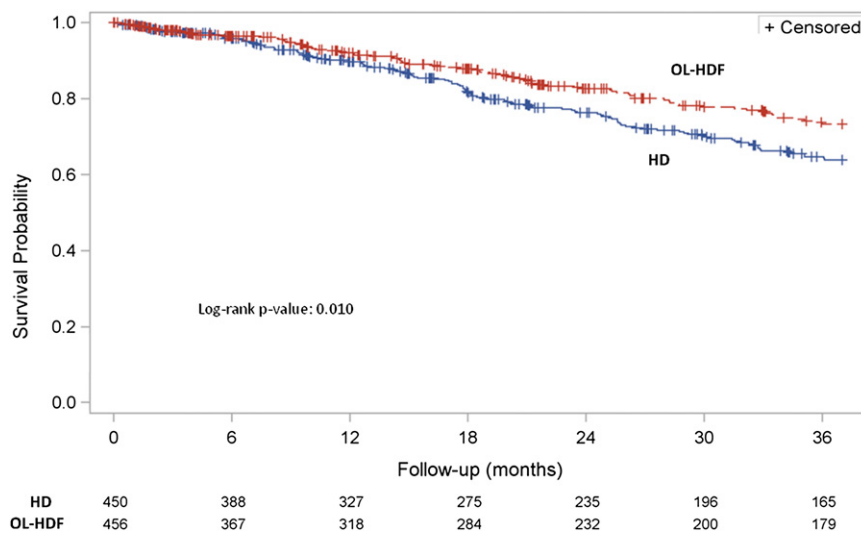


Figure 2. Kaplan–Meier curves for 36-month survival in the intention-to-treat population ($P=0.01$ by the log-rank test). HD, hemodialysis.

DISCUSSION

In this prospective, randomized clinical trial, we found that high-efficiency OL-HDF in patients with ESRD on hemodialysis was associated with a 30% reduction in all-cause mortality compared with conventional high-flux hemodialysis. This mortality reduction was related to a significant risk reduction for stroke and infectious mortality. The estimated NNT showed that

Table 3. Primary outcome: Mortality

	Hemodialysis Group (n=450) (867.3 patient-years at risk)		OL-HDF Group (n=456) (863.1 patient-years at risk)		HR (95% CI)	P^a
	Events	Events/100 Patient-Years	Events	Events/100 Patient-Years		
Death from any cause	122	14.1	85	9.8	0.70 (0.53–0.92)	0.01
Cardiovascular cause	55	6.3	37	4.3	0.67 (0.44–1.02)	0.06
Heart failure	10	1.2	7	0.8	0.69 (0.26–1.82)	0.46
Ischemic heart disease	15	1.7	14	1.6	0.93 (0.45–1.94)	0.86
Mesenteric thrombosis	6	0.7	5	0.6	0.84 (0.26–2.77)	0.78
Stroke	18	2.1	7	0.8	0.39 (0.16–0.93)	0.03
Dysrhythmia	5	0.6	3	0.3	0.59 (0.14–2.47)	0.46
Peripheral arteriopathy	1	0.0	1	0.0	0.97 (0.06–15.48)	0.98
Infection	22	2.5	10	1.2	0.45 (0.21–0.96)	0.03
Tumor	6	0.7	10	1.2	1.67 (0.61–4.59)	0.32
Sudden death	14	1.6	14	1.6	0.99 (0.47–2.08)	0.98
Cachexia	8	0.9	4	0.5	0.51 (0.15–1.70)	0.27
Death from other causes	17	2.0	10	1.2	0.59 (0.27–1.28)	0.18

Data are given as n or NNT (95% CI). NNTs (95% CIs) for all-cause mortality at 1, 2, and 3 years were 9.75 (5.03–47.41), 7.67 (4.32–33.57) and 7.67 (4.51–31.83), respectively.

^a P value by the log-rank test.

Table 4. Univariate cox regression analysis for all-cause mortality

	HR (95% CI)	P
OL-HDF (reference: hemodialysis group)	0.70 (0.53–0.92)	0.01
Age (per 1-yr increment)	1.05 (1.03–1.06)	<0.001
Sex (reference: female)	1.43 (1.05–1.94)	0.02
Diabetes (reference: absence of diabetes)	1.43 (1.07–1.91)	0.02
Charlson comorbidity index (per 1-unit increment) ^a	1.37 (1.28–1.47)	<0.001
Vascular access (reference: fistula)	1.45 (1.20–1.76)	<0.001

^aThe Charlson comorbidity index was calculated excluding diabetes.

to prevent one annual death, eight patients would need to be switched from hemodialysis to OL-HDF. To our knowledge, this is the first prospective, randomized clinical trial showing that high-efficiency postdilution OL-HDF reduces all-cause mortality compared with conventional hemodialysis in the chronic prevalent population. The survival benefit observed in this study has sufficient statistical robustness to support the finding that OL-HDF was the major determinant of survival. Furthermore, the results were consistent in distinct subgroups of patients according to age, sex, diabetes mellitus, the Charlson comorbidity index, and vascular access. Although all patient groups benefitted from OL-HDF, the subgroups obtaining the greatest benefit were older, had no diabetes, were dialyzed through an arteriovenous fistula, and had a higher Charlson comorbidity index.

The ESHOL study was designed to compare high-flux hemodialysis versus postdilution OL-HDF. However, a small proportion of patients on low-flux hemodialysis (6%) were allowed to be included; therefore, this study represents routine clinical practice in Catalonia. In this study, we did not record the number of screened patients, which is a potential limitation to the external validity of the study. However, the patients included in this trial corresponded to >25% of all patients maintained on hemodialysis in Catalonia and the mean age as well as the proportion of patients with diabetes were similar to data reported by the Catalan Registry of Renal Patients.¹ Importantly, as in other trials conducted in hemodialysis patients, a significant number of observations were censored, mainly due to renal transplantation. Indeed, in our trial, 38% of the patients were censored before reaching the end-point of the study or completing 3 years of follow-up, a figure close to those reported in other hemodialysis studies (32% for the HEMO study,³ 37% for the MPO study,⁴ and 33% for the Convective Transport [CONTRAST] study¹⁶).

There is some controversy on the potential benefits of OL-HDF in mortality risk reduction. Retrospective, observational studies suggested that OL-HDF could improve patient survival,^{12–15} although two recent, prospective, randomized studies failed to demonstrate a survival advantage of OL-HDF over hemodialysis.^{16,17} In the CONTRAST study,¹⁶ also conducted in a prevalent population, 714 patients were randomized to low-flux hemodialysis or OL-HDF and no survival difference between the groups was observed at the end of the study with a mean follow-up of 3 years. In the Turkish study, 782 prevalent patients were randomized to high-flux hemodialysis or OL-HDF and,

again, the all-cause outcome was not affected by treatment allocation over 2 years of follow-up.¹⁷ On the basis of the results of the CONTRAST and Turkish studies, the convective volume seems to be an important issue. In the *post hoc* analysis, both studies showed a 39% and 46% mortality risk reduction in patients receiving high convection volumes (>22 and >20 L/session, respectively). Similarly, the *post hoc* analysis in the ESHOL study showed a 40% and 45% mortality

risk reduction in patients receiving convection volumes between 23–25 L/session and >25 L/session, respectively. These results provide evidence of the need to deliver high convection volumes to reduce all-cause mortality. To achieve this goal, high blood flow rates and long dialysis times are required. In this ESHOL study, the mean blood flow rate was higher (387 ml/min) than in the CONTRAST and Turkish studies (300 and 310 ml/min, respectively), whereas the mean length of dialysis was longer (236 minutes) than in the CONTRAST study (226 minutes) and was similar to that of the Turkish study (236 minutes). These factors led to a higher mean delivered convection volume in this study (23.7 L/session) than in the CONTRAST (20.7 L) and Turkish (20.7 L) studies. These results indicate that the treatment modality could modify patient survival when a sufficient convective volume is reached. Therefore, in future studies, the convective volume dose should be defined as a minimum postdilution volume, a minimum infusion flux, a convective volume normalized to body-size, or other factors.

The reduction in all-cause mortality associated with OL-HDF treatment observed in this trial was focused on cardiovascular and infectious diseases. Cardiovascular disease is the most common cause of mortality in chronic hemodialysis patients and the mortality rate is still 10 times higher than in the general population.¹⁹ Cardiovascular disease contributed to 44.4% of mortality in our study and there was a trend toward lower risk in the OL-HDF group. This result links with the finding that convective techniques are associated with a higher removal of several mediators involved in inflammation regulation, cytokine production, and accelerated atherosclerosis.²⁰ Remarkably, stroke risk reduction largely contributed to the reduction of cardiovascular mortality, even though the clinical variables associated with stroke in epidemiologic studies such as BP control²¹ or ESA doses²² did not differ between the groups. The significant reduction of intradialytic symptomatic hypotension episodes with OL-HDF observed in this trial may have contributed to reducing cardiovascular events and especially stroke. This benefit of OL-HDF on intradialytic hypotension episodes has previously been described.^{23,24} In addition, infection-associated mortality was also reduced by OL-HDF. ESRD patients have a significant risk of infectious complications, which represent the first cause of hospitalization and the second cause of death in hemodialysis patients. Hemodiafiltration has been associated with a reduced inflammatory state¹¹ and improved granulocyte function.²⁵ Several granulocyte-inhibitory proteins retained in uremic

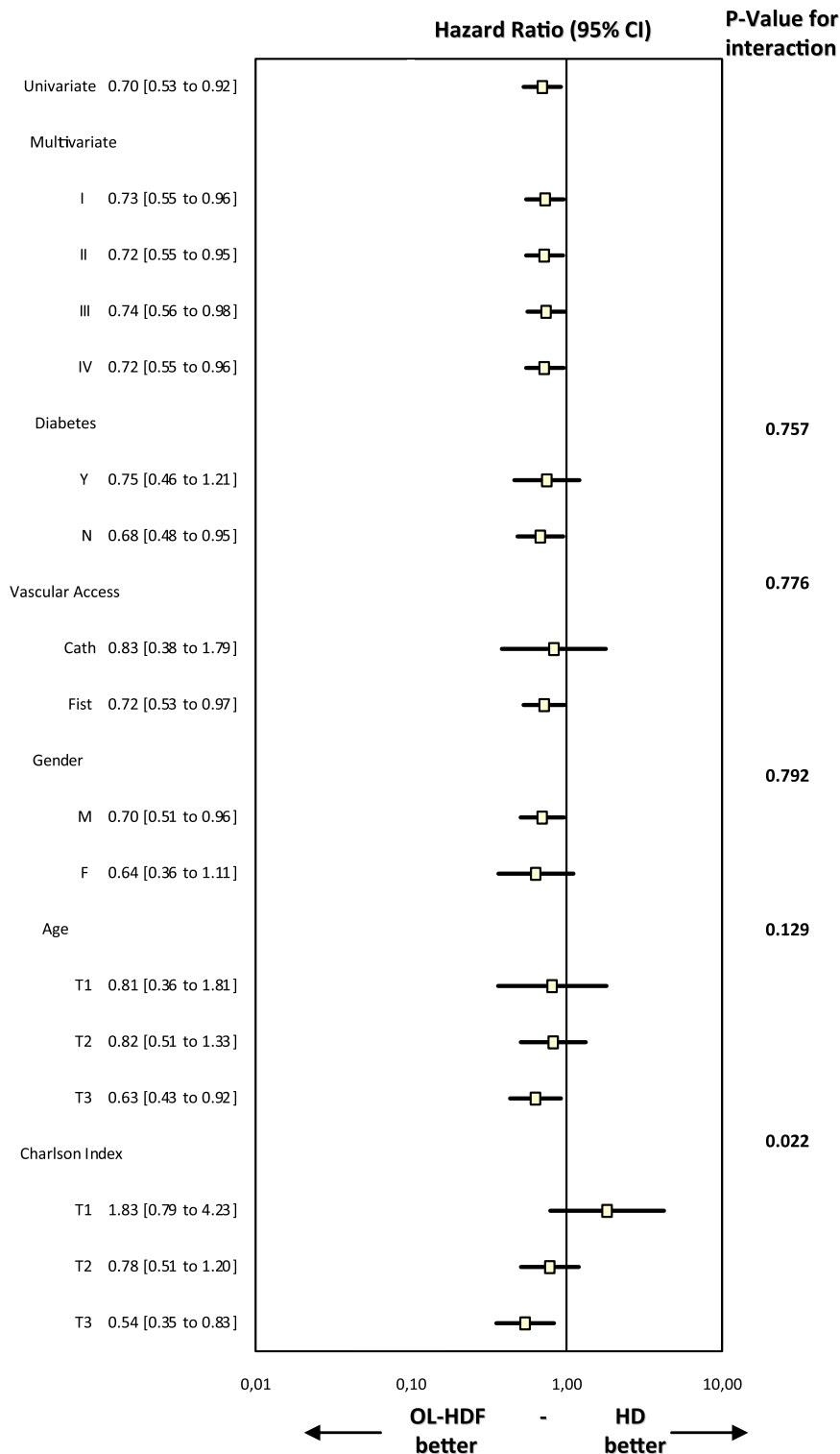


Figure 3. Sensitivity analyses for the main outcome showing HRs (95% CIs) for the intervention based on relevant variables that were found to be independent predictors for all-cause mortality. Multivariate I, age, sex, vascular access, diabetes, and the Charlson comorbidity index (excluding diabetes); multivariate II, age, sex, vascular access, and the Charlson comorbidity index (excluding diabetes); multivariate III, age, sex, vascular access, and diabetes; multivariate IV, age, sex, vascular access, and the Charlson comorbidity index (including diabetes); Y, yes; N, no; Cath, catheter; Fist, fistula; M, male; F, female; T1, T2, and T3, first, second, and third tertiles; HD, hemodialysis.

Table 5. Outcome data: Hospitalizations and intradialysis symptoms

	Hemodialysis Group (n=450) (867.3 Patient-Years at Risk)		OL-HDF Group (n=456) (863.1 Patient-Years at Risk)		Rate Ratio (95% CI)	P ^a
	No. of Events	No. of Events/100 Patient-Years	No. of Events	No. of Events/ 100 Patient-Years		
All-cause hospitalizations	412	47.5	317	36.7	0.78 (0.67–0.90)	0.001
Infections	73	8.4	72	8.3		
Vascular access	98	11.3	56	6.5		
Heart failure	28	3.2	15	1.7		
Ischemic heart disease	25	2.9	16	1.9		
Respiratory disease	26	3.0	28	3.2		
Gastrointestinal bleeding	10	1.2	4	0.5		
Other reasons	152	17.5	126	14.6		
Symptomatic hypotension episodes ^b	8133	937.7	5862	679.2	0.72 (0.68–0.77)	<0.001
Dysrhythmia ^b	444	51.2	477	55.3	1.08 (0.86–1.35)	0.50
Thoracic pain ^b	327	37.7	318	36.8	0.98 (0.75–1.28)	0.87

Data are the number of hospitalizations (hospital admissions per 100 patient-years) and number of complicated dialysis sessions (number of symptoms per 100 patient-years).

^aPenalized quasi-likelihood under restricted maximum likelihood models.

^bPooled data (data were collected 1 month per each 3-month period).

patients—contributing to the high incidence of infections—could be better removed with OL-HDF therapies.²⁶ OL-HDF was also associated with a significant reduction in hospitalization rates, which could reasonably be linked to the decrease in cardiovascular and infectious complications.

Clearance of middle-to-large molecules depends on the type of dialysis membrane and the amount of convection volume and may be increased with OL-HDF treatment. However, the observed increase of β_2 -microglobulin serum levels in both groups during this study was an unexpected finding. Previous data²⁷ showed that there is a positive correlation between infusion volume and the β_2 -microglobulin reduction ratio but this does not mean that predialysis levels were reduced, because β_2 -microglobulin has a low distribution volume.²⁸ Moreover, several studies have shown that predialysis β_2 -microglobulin levels were reduced after patients were switched from high-flux hemodialysis to OL-HDF.^{7,29} Unfortunately, residual renal function, one of the major determinants of β_2 -microglobulin serum levels, was not monitored during the study period. These results suggest that the benefit of OL-HDF to patient survival partly depends on clearance of molecules other than β_2 -microglobulin. OL-HDF can remove other middle-sized molecules or protein-bound uremic toxins more efficiently than hemodialysis, which may influence endothelial function, inflammatory status, or vascular calcification, providing cardioprotective effects and/or improving the immunologic system.

The ESHOL study has some weaknesses but also major strengths. A limitation is that a small proportion of patients (6.3%) were treated with low-flux membranes and, additionally, residual renal function was not monitored. Small differences might be suggested in diabetic patients, grafts, or catheters between the two groups in our study. To address this point, additional multivariate Cox regression sensitivity analyses were conducted, adjusting by age, sex, diabetes, the Charlson comorbidity index, and type of vascular access. The

results from the multivariate analyses were robust and the risk estimates and 95% CIs were very much in line with the main analysis conducted with any baseline adjustments. Because this was a randomized study, the apparent small baseline differences were considered likely to be obtained by chance rather than due to bias, and this statement holds true because of the randomization procedure. The lower number of intradialysis hypotension episodes observed in this study was not apparently due to major differences in sodium removal among treatments, as suggested by the similar pretreatment and post-treatment plasma sodium concentrations, the similar ultrafiltration rate, and the similar dry body weight behavior during the follow-up; however, our measurement was a crude estimation of dialytic sodium removal and therefore the possibility of a negative sodium balance during OL-HDF could not be ruled out.²³ The strengths of this study include the randomized design, the large sample size and long follow-up, as well as the requirement of high convection volumes. Hemodialysis units participating in this clinical trial were trained to utilize high blood flow rates and long dialysis times in order to deliver a mean convective volume close to 24 L/session.

In summary, the results of the ESHOL trial indicate that high-efficiency postdilution OL-HDF reduces all-cause mortality versus conventional hemodialysis in prevalent patients. Furthermore, the main causes of mortality, cardiovascular and infectious diseases, were significantly reduced by OL-HDF. In view of these results, OL-HDF may become the first-line option in hemodialysis patients.

CONCISE METHODS

Study Design

The study design was previously reported.³⁰ The ESHOL study was a prospective, randomized, open-label clinical trial in patients with

ESRD under hemodialysis in Catalonia, Spain. All hemodialysis units in Catalonia, both in-hospital and out-of-hospital units, were invited to participate. All patients signed consent forms approved by the Hospital Ethics Committee. The registered protocol number is NCT 00694031.¹⁸

The primary objective was to assess the effect of postdilution OL-HDF compared with hemodialysis, either low-flux or high-flux, on all-cause mortality. The primary outcome variable was the time to occurrence of death from any cause. Key secondary outcomes were cardiovascular mortality, other causes of mortality, all-cause hospitalization, dialysis dose (Kt/V and urea reduction ratio), BP control and intradialysis tolerance (symptomatic hypotension episodes, arrhythmia, and thoracic pain), nutrition (dry body weight, normalized protein catabolic rate, albumin), anemia, and phosphate and β_2 -microglobulin serum levels.

Study Population

The study population was previously described.³⁰ Essentially, the inclusion criteria were patients aged >18 years with ESRD receiving thrice-weekly standard hemodialysis for >3 months. Exclusion criteria were as follows: active systemic diseases, liver cirrhosis, malignancy, immunosuppressive therapy, intradialysis dose (Kt/V<1.3), single needle dialysis, and temporary nontunnelized catheter.

Randomization and Dialysis Treatment Parameters

Patients were randomized 1:1 to continue on thrice-weekly hemodialysis or to start OL-HDF three times a week. A central computerized random-generator was utilized to allocate patients to each study group and randomization was stratified by center. The length of the recruitment period was 16 months and the study was completed in order to provide a follow-up of 3 years for all surviving patients.

Treatment Procedures

Synthetic high-flux dialyzers were used for OL-HDF (FX60: 59.7% and FX80: 8.6% [Fresenius Medical Care, Bad Homburg, Germany]; Polyflux 170H: 7.9%, Polyflux 210H: 10.3%, and Arylane H9: 1.5% [Gambro AB, Stockholm, Sweden]; or other dialyzers: 12.5%). Patients randomized to hemodialysis were treated with synthetic high-flux (FX60: 58.7%, FX80: 8.4%, Polyflux 170H: 10.4%, Polyflux 210H: 5.5%, Arylane H9: 0.9% and other dialyzers: 12.5%) or low-flux dialyzers (8.1%).

Both OL-HDF and hemodialysis were performed with ultrapure dialysis fluids, defined as <0.1 CFU/ml and <0.03 EU/ml. The length of dialysis sessions in each treatment modality was not modified.

When OL-HDF could not be performed temporarily for technical reasons, affected patients were treated with the same high-flux membranes. For patients on postdilution OL-HDF, a minimum of 18 L/session of replacement volume was requested. Patients not receiving the allocated treatment modality for >2 consecutive months were withdrawn from the study.

The composition of dialysate was the same in both groups, as was the reinfusate in OL-HDF (sodium 138–140 mmol/L, potassium 1.5–2.0 mmol/L, calcium 1.25–1.75 mmol/L, magnesium 0.5 mmol/L, chloride 106–109 mmol/L, bicarbonate 34–37 mmol/L, acetate 3–4 mmol/L, and glucose 1.0 g/L).

Study Variables

Before randomization, the Charlson comorbidity index score was calculated for each patient. The following parameters were recorded at baseline and every 3 months: dialyzer characteristics, dialysis time, Qb, Qd, vascular access, replacement volume, dry body weight, predialysis and postdialysis body weight, convective volume, and predialysis and postdialysis systolic and diastolic BP.

The following laboratory data were recorded at baseline and every 3 months: predialysis urea, creatinine, bicarbonate, sodium, potassium, C-reactive protein, uric acid, albumin, calcium, phosphate, intact parathyroid hormone, β_2 -microglobulin, hemoglobin, transferrin saturation index, and ferritin. Using predialysis and postdialysis BUN in a mid-week dialysis session, the urea reduction rate, dialysis dose (Kt/V by Daugirdas' second-generation single-pool variable volume formula) and normalized protein catabolic rate were calculated by standard formulas. All laboratory determinations were performed locally by standard procedures in certified laboratories. The doses of ESAs, iron supplements, antihypertensive drugs, and phosphate binders were also recorded at baseline and every 3 months.

Clinical monitoring included intradialysis symptoms (symptomatic hypotension, episodes of arrhythmia and thoracic pain), hospital admissions for any reasons, and withdrawals from the study and their causes. To calculate the number of dialysis sessions complicated by intradialysis symptoms, the last 12 sessions preceding the quarterly visit were considered.

Sample Size

According to the Catalan Registry of Renal Patients, 3-year patient survival in hemodialysis patients was 70%.¹ Because several retrospective studies have suggested a 35% reduction of mortality in patients on OL-HDF,¹² we expected a 3-year survival of 80% in patients on OL-HDF. When the sample size in each group is 296, with a total number of events required of 143, a 0.05 level two-sided log-rank test will have 80% power to detect the difference between an OL-HDF group proportion of 0.8 and a hemodialysis group proportion of 0.7 at time t, assuming a constant HR of 0.626. To compensate for dropouts, which were expected due to renal transplantation or loss to follow-up, we planned to enroll at least 400 patients per group.

Statistical Analyses

All data analyses were carried out according to a pre-established statistical analysis plan. All-cause mortality, as well as cardiovascular death, cachexia, infection, tumors, sudden death, and death from other causes were described by means of the Kaplan–Meier method. The log-rank test was used for hypothesis testing, and the HR and its 95% CI were estimated from the unadjusted Cox model. Additional multivariate Cox regression sensitivity analyses were conducted, adjusting by age, sex, diabetes, the Charlson comorbidity index (the original scale and also excluding diabetes), and the type of vascular access to assess the robustness of the study results. The NNT estimated after the switch from hemodialysis to OL-HDF was also calculated.

Time repeated measurements were analyzed using linear mixed models including treatment, time, and the treatment by time interaction term. Gaussian continuous variables were approached through mixed models for repeated measurements, adjusting by

the baseline value and, for non-Gaussian data (binomial and Poisson distribution variables), by penalized quasi-likelihood under restricted maximum likelihood models. Treatment inferences, effect estimates, and 95% CIs were taken from these models.

Two-sided significance tests were used throughout, and a *P* value of <0.05 was considered significant. All statistical analyses were performed using the SAS 9.2 statistical package.

ACKNOWLEDGMENTS

The following institutions and investigators participated in the ESHOL study: M. Pons, B. Insensé, C. Perez, and T. Feliz (CETIRSA, Barcelona); R. Ramos, M. Barbeta, and C. Soto (Hospital San Antonio Abad, Vilanova i la Geltru); J. Mora, A. Juan, and O. Ibrik (Fresenius Medical Care, Granollers); A. Foraster and J. Carreras (Diaverum Baix Llobregat, Hospitalet); F. Moreso, J. Nin, and A. Fernández (Fresenius Medical Care, Hospitalet); J. Soler, M. Arruche, C. Sánchez, and J. Vidiella (Fresenius Medical Care, Reus); F. Barbosa, M. Chiné, and S. Hurtado (Fresenius Medical Care Diagonal, Barcelona); J. Llibre, A. Ruiz, M. Serra, M. Salvó, and T. Poyuelo (CETIRSA, Terrassa); F. Maduell, M. Carrera, N. Fontseré, M. Arias, and Josep M. Campistol (Hospital Clínic, Barcelona); A. Merín and L. Ribera (Fresenius Medical Care Julio Verne, Barcelona); J.M. Galceran, J. Mòdol, E. Moliner, and A. Ramirez (Fundació Althaia, Manresa); J. Aguilera and M. Alvarez (Hospital Santa Tecla, Tarragona); B. de la Torre and M. Molera (Diaverum Bonanova, Barcelona); J. Casellas and G. Martín (Diaverum IHB, Barcelona); E. Andres and E. Coll (Fundació Puigvert, Barcelona); M. Valles and C. Martínez (Hospital Josep Trueta, Girona); E. Castellote (Hospital General, Vic); J.M. Casals, J. Gabàs, and M. Romero (Diaverum, Mataró); A. Martinez-Castelao and X. Fulladosa (Hospital Universitari Bellvitge, Hospitalet); M. Ramirez-Arellano and M. Fulquet (Hospital de Terrassa); A. Pelegrí, M. el Manouari, and N. Ramos (Diaverum Verge de Montserrat, Santa Coloma); J. Bartolomé (Centre Secretari Coloma, Barcelona); R. Sans (Hospital de Figueres); E. Fernández and F. Sarró (Hospital Arnau de Vilanova, Lleida); T. Compte (Hospital Santa Creu, Tortosa); F. Marco and R. Mauri (Diaverum Nephros, Barcelona); and J. Bronsoms (Clínica Girona). The clinical trials unit comprised J.A. Arnaiz, H. Beleta, and A. Pejenaute (UASP Farmacología Clínica, Hospital Clínic Barcelona). Statistical analyses were performed by F. Torres, J. Ríos, and J. Lara (Biostatistics Unit, School of Medicine, Universitat Autònoma de Barcelona; and Biostatistics and Data Management Platform, IDIBAPS, Hospital Clínic, Barcelona).

The Catalan Society of Nephrology has endorsed the ESHOL study. This study was partly supported by grants from Fresenius Medical Care and Gambro through the Catalan Society of Nephrology.

DISCLOSURES

None.

REFERENCES

1. Generalitat de Catalunya. Departament de Salut, Organització Catalana de Trasplantaments: Registre malalts renals de Catalunya. Informe estadístic 2005-2006. Available at: <http://biblio.idescat.cat/docs/pec/paae2008/gi04652006.pdf>. Accessed June 2012
2. Registro Español de Enfermos Renales: Dialysis and transplant report in Spain, 2006 (in English). *Nefrologia* 29: 525–533, 2009
3. Eknayan G, Beck GJ, Cheung AK, Daugirdas JT, Greene T, Kusek JW, Allon M, Bailey J, Delmez JA, Depner TA, Dwyer JT, Levey AS, Levin NW, Milford E, Ornt DB, Rocco MV, Schulman G, Schwab SJ, Teehan BP, Toto R; Hemodialysis (HEMO) Study Group: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 347: 2010–2019, 2002
4. Locatelli F, Martin-Malo A, Hannedouche T, Loureiro A, Papadimitriou M, Wizemann V, Jacobson SH, Czekalski S, Ronco C, Vanholder R; Membrane Permeability Outcome (MPO) Study Group: Effect of membrane permeability on survival of hemodialysis patients. *J Am Soc Nephrol* 20: 645–654, 2009
5. Canaud B, Flavier JL, Argilés A, Stec F, NGuyen QV, Bouloux C, Garred LJ, Mion C: Hemodiafiltration with on-line production of substitution fluid: Long-term safety and quantitative assessment of efficacy. *Contrib Nephrol* 108: 12–22, 1994
6. Locatelli F, Marcelli D, Conte F, Limido A, Malberti F, Spotti D: Comparison of mortality in ESRD patients on convective and diffusive extracorporeal treatments. The Registro Lombardo Dialisi E Trapianto. *Kidney Int* 55: 286–293, 1999
7. Maduell F, del Pozo C, Garcia H, Sanchez L, Hdez-Jaras J, Alberio MD, Calvo C, Torregrosa I, Navarro V: Change from conventional haemodiafiltration to on-line haemodiafiltration. *Nephrol Dial Transplant* 14: 1202–1207, 1999
8. Lomoy W, Becaus I, Billiow JM, Sierens L, Van Malderen P, D'Haenens P: On-line haemodiafiltration. Remarkable removal of β_2 -microglobulin. Long-term clinical observations. *Nephrol Dial Transplant* 15[Suppl 1]: 49–54, 2000
9. Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W: A comparison of on-line hemodiafiltration and high-flux hemodialysis: A prospective clinical study. *J Am Soc Nephrol* 11: 2344–2350, 2000
10. Wizemann V, Lotz C, Techert F, Uthoff S: On-line haemodiafiltration versus low-flux hemodialysis. A prospective randomized study. *Nephrol Dial Transplant* 15[Suppl 1]: 43–48, 2000
11. Carracedo J, Merino A, Nogueras S, Carretero D, Berdud I, Ramírez R, Tetta C, Rodríguez M, Martín-Malo A, Aljama P: On-line hemodiafiltration reduces the proinflammatory CD14+CD16+ monocyte-derived dendritic cells: A prospective, crossover study. *J Am Soc Nephrol* 17: 2315–2321, 2006
12. Canaud B, Bragg-Gresham JL, Marshall MR, Desmeules S, Gillespie BW, Depner T, Klassen P, Port FK: Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. *Kidney Int* 69: 2087–2093, 2006
13. Jirka T, Cesare S, Di Benedetto A, Perera Chang M, Ponce P, Richards N, Tetta C, Vaslaky L: Mortality risk for patients receiving hemodiafiltration versus hemodialysis. *Kidney Int* 70: 1524, author reply 1524–1525, 2006
14. Panichi V, Rizza GM, Paoletti S, Bigazzi R, Aloisi M, Barsotti G, Rindi P, Donati G, Antonelli A, Panicucci E, Tripepi G, Tetta C, Palla R; RISCVID Study Group: Chronic inflammation and mortality in haemodialysis: Effect of different renal replacement therapies. Results from the RISCVID study. *Nephrol Dial Transplant* 23: 2337–2343, 2008
15. 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* 4: 1944–1953, 2009
16. Grooteman MPC, van den Dorpel MA, Bots ML, Penne EL, van der Weerd NC, Mazairac AH, den Hoedt CH, van der Tweel I, Lévesque R, Nubé MJ, ter Wee PM, Blankestijn PJ; CONTRAST Investigators: Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *J Am Soc Nephrol* 23: 1087–1096, 2012
17. Ok E, Asci G, Toz H, Ok ES, Kircelli F, Yilmaz M, Hur E, Demirci MS, Demirci C, Duman S, Basci A, Adam SM, Isik IO, Zengin M, Suleymanlar G, Yilmaz ME, Ozkahya M; On behalf of the 'Turkish Online

- Haemodiafiltration Study': Mortality and cardiovascular events in on-line haemodiafiltration (OL-HDF) compared with high-flux dialysis: Results from the Turkish OL-HDF Study. *Nephrol Dial Transplant* 28: 192–202, 2013
18. Survival Study in Patients Undergoing On-line Hemodiafiltration (ESHOL): A randomized study to evaluate survival in patients undergoing on-line HDF. Available at: <http://clinicaltrials.gov/ct2/show/NCT00694031>. Accessed
 19. Foley RN, Parfrey PS, Sarnak MJ: Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol* 9[Suppl]: S16–S23, 1998
 20. Kim ST, Yamamoto C, Asabe H, Sato T, Takamiya T: Online haemodiafiltration: Effective removal of high molecular weight toxins and improvement in clinical manifestations of chronic haemodialysis patients. *Nephrology (Carlton)* 2[Suppl 1]: S183–S186, 1996
 21. Iseki K, Fukiyama K; Okawa Dialysis Study (OKIDS) Group: Clinical demographics and long-term prognosis after stroke in patients on chronic haemodialysis. *Nephrol Dial Transplant* 15: 1808–1813, 2000
 22. McMurray JJ, Uno H, Jarolim P, Desai AS, de Zeeuw D, Eckardt KU, Ivanovich P, Levey AS, Lewis EF, McGill JB, Parfrey P, Parving HH, Toto RM, Solomon SD, Pfeffer MA: Predictors of fatal and nonfatal cardiovascular events in patients with type 2 diabetes mellitus, chronic kidney disease, and anemia: An analysis of the Trial to Reduce Cardiovascular Events with Aranesp (darbepoetin-alfa) Therapy (TREAT). *Am Heart J* 162: 748–755, e3, 2011
 23. Locatelli F, Altieri P, Andrucci S, Bolasco P, Sau G, Pedrini LA, Basile C, David S, Feriani M, Montagna G, Di Iorio BR, Memoli B, Cravero R, Battaglia G, Zoccali C: Hemofiltration and hemodiafiltration reduce intradialytic hypotension in ESRD. *J Am Soc Nephrol* 21: 1798–1807, 2010
 24. Donauer J, Schweiger C, Rumberger B, Krumme B, Böhrer J: Reduction of hypotensive side effects during online-haemodiafiltration and low temperature haemodialysis. *Nephrol Dial Transplant* 18: 1616–1622, 2003
 25. Kaiser JP, Oppermann M, Götze O, Deppisch R, Göhl H, Asmus G, Röhrich B, von Herrath D, Schaefer K: Significant reduction of factor D and immunosuppressive complement fragment Ba by hemofiltration. *Blood Purif* 13: 314–321, 1995
 26. Haag-Weber M, Cohen G, Hörl WH: Clinical significance of granulocyte-inhibiting proteins. *Nephrol Dial Transplant* 15[Suppl 1]: 15–16, 2000
 27. Lornoy W, Becaus I, Billioud JM, Sierens L, van Malderen P: Remarkable removal of beta-2-microglobulin by on-line hemodiafiltration. *Am J Nephrol* 18: 105–108, 1998
 28. Odell RA, Slowiaczek P, Moran JE, Schindhelm K: β_2 -microglobulin kinetics in end-stage renal failure. *Kidney Int* 39: 909–919, 1991
 29. Tiranathanagul K, Praditpornsilpa K, Katavetin P, Srisawat N, Townamchai N, Susantitaphong P, Tungsanga K, Eiam-Ong S: On-line hemodiafiltration in Southeast Asia: A three-year prospective study of a single center. *Ther Apher Dial* 13: 56–62, 2009
 30. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Foraster A, Soler J, Galceran JM, Martinez-Castelao A; Online Hemodiafiltration Study Group from the Catalan Society of Nephrology: Design and patient characteristics of ESHOL study, a Catalanian prospective randomized study. *J Nephrol* 24: 196–202, 2011

See related editorial, "Has the Time Now Come to More Widely Accept Hemodiafiltration in the United States?," on pages 332–334.

This article contains supplemental material online at <http://jasn.asnjournals.org/lookup/suppl/doi:10.1681/ASN.2012080875/-/DCSupplemental>.