Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly

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Large cohort studies suggest that high convective volumes associated with online hemodiafiltration may reduce the risk of mortality/morbidity compared to optimal high-flux hemodialysis. By contrast, intradialytic tolerance is not well studied. The aim of the FRENCHIE (French Convective versus Hemodialysis in Elderly) study was to compare high-flux hemodialysis and online hemodiafiltration in terms of intradialytic tolerance. In this prospective, open-label randomized controlled trial, 381 elderly chronic hemodialysis patients (over age 65) were randomly assigned in a one-to-one ratio to either high-flux hemodialysis or online hemodiafiltration. The primary outcome was intradialytic tolerance (day 30–day 120). Secondary outcomes included health-related quality of life, cardiovascular risk biomarkers, morbidity, and mortality. During the observational period for intradialytic tolerance, 85% and 84% of patients in high-flux hemodialysis and online hemodiafiltration arms, respectively, experienced at least one adverse event without significant difference between groups. As exploratory analysis, intradialytic tolerance was also studied, considering the sessions as a statistical unit according to treatment actually received. Over a total of 11,981 sessions, 2,935 were complicated by the occurrence of at least one adverse event, with a significantly lower occurrence in online hemodiafiltration with fewer episodes of intradialytic symptomatic hypotension and muscle cramps. By contrast, health-related quality of life, morbidity, and mortality were not different in both groups. An improvement in the control of metabolic bone disease biomarkers and β2-microglobulin level without change in serum albumin concentration was observed with online hemodiafiltration. Thus, overall outcomes favor online hemodiafiltration over high-flux hemodialysis in the elderly.

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Renal replacement therapy (RRT) by diffusive-based hemodialysis (HD) is still hampered by intradialytic adverse events[1,2] and relatively poor outcomes for end-stage kidney disease (ESKD) patients.[3–5] Convective-based modalities have been proposed as an alternative capable of relieving most intradialytic adverse events and improving patient outcomes.[6–8] By ensuring isothermic dialysis through a spontaneous cooling effect, online hemodiafiltration (OLHDF) may reduce intradialytic hypotension (IDH).[9–11] OLHDF combines the use of ultrapure dialysis fluid with high-flux hemodialyzers, and enhances convective solute fluxes of middle and/or high molecular weight uremic toxins, and has thereby been shown in several studies to reduce mortality and morbidity.[12–15]

Whereas most large, retrospective or prospective randomized controlled trials have investigated the benefits of convective-based modalities on objectively measured end points (e.g., mortality), few studies have reported patient-perceived symptomatology related to dialysis sessions, demonstrating little or no advantage with OLHDF. In a randomized controlled trial, Locatelli *et al.*[16] reported

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a significant reduction in clinical symptomatic IDH incidence using OLHDF, but failed to show any improvement in subjective patient perception. More recently, Caplin *et al.*[17] also yielded no evidence that switching prevalent stable ESKD patients from high-flux HD (HFHD) to hemodiafiltration (HDF) greatly improved perceived intradialytic symptomatology. In addition, most studies have explored the effects of HDF versus HFHD in a relatively selective population that does not reflect the aging and comorbidity profile of today's ESKD population.[18,19]

In the FRENCHIE (French Convective versus Hemodialysis in Elderly) study, we aimed to explore the potential benefits of using OLHDF versus optimal HFHD in elderly ESKD patients. The primary objective was to focus on treatment tolerance, and secondary objectives were to analyze patient-reported outcome measures, intermediary outcomes (biomarkers of cardiovascular risk and nutritional status), and objectively measured outcomes (hospitalizations and mortality).

RESULTS

Patient characteristics

Between May 2005 and May 2011, 415 ESKD patients ≥65 years old were assessed for eligibility in 32 French dialysis facilities. Thirty-four patients were excluded: 5 did not meet inclusion criteria, 12 declined to participate, and 17 were excluded for other reasons. A total of 381 patients were randomized and followed up until their final visit no later than May 2013 (Figure 1). The mean ± SD and median (interquartile range) duration of follow-up were 19.65 ± 7.38 months and 23.92 (6.44) months.

Patient characteristics at baseline (both the randomized and primary outcome analysis populations) are summarized in Table 1 and did not significantly differ between study arms.

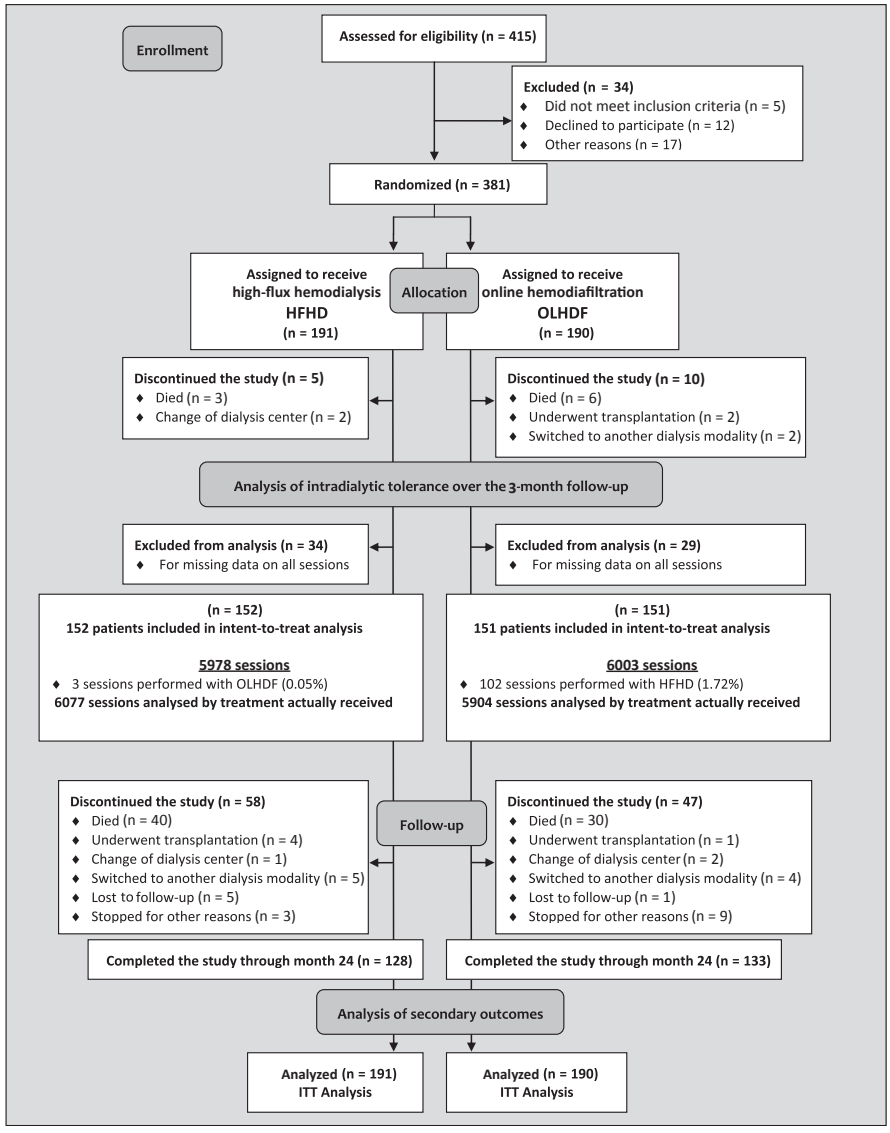

Figure 1 | Flow chart of study participants. ITT, intent-to-treat.

Table 1 | Baseline characteristics

Variable	Randomized population		Population of primary outcome analysis	
	High-flux HD (n = 191)	OLHDF (n = 190)	High-flux HD (n = 152)	OLHDF (n = 151)
Gender, male (n [%])	115 (60.21)	114 (60.00)	93 (61.18)	90 (59.60)
Age (yr)	76.11 (± 6.68)	76.35 (± 6.13)	76.41 (± 6.79)	76.61 (± 5.86)
BMI (kg/m^2)	26.26 (± 4.68)	26.27 (± 5.11)	26.26 (± 4.65)	26.29 (± 5.18)
BMI ≥ 30 kg/m^2 (n [%])	37 (21.39)	34 (19.65)	31 (21.09)	29 (19.73)
Etiology of ESRD (n [%])				
Vascular and hypertensive nephropathy	82 (43.62)	90 (48.13)	70 (46.05)	74 (49.01)
Glomerulonephritis	34 (18.09)	28 (14.97)	32 (21.05)	22 (14.57)
Diabetic nephropathy	58 (30.85)	53 (28.34)	41 (26.97)	42 (27.81)
Cystic renal disease	11 (5.85)	13 (6.95)	9 (5.92)	10 (6.62)
Interstitial nephropathy	18 (9.57)	20 (10.70)	15 (9.87)	16 (10.60)
Other cause	28 (14.89)	32 (17.11)	21 (13.82)	29 (19.21)
Diabetes mellitus (n [%])	73 (38.42)	74 (39.36)	56 (36.84)	63 (41.72)
Hypertension (n [%])	135 (71.05)	149 (79.26)	110 (72.37)	121 (80.13)
Cardiopathy disease history (n [%])	97 (51.05)	99 (52.66)	82 (53.95)	80 (52.98)
Arteriopathy disease history (n [%])	83 (43.68)	77 (40.96)	72 (47.37)	63 (41.72)
Dialysis vintage (yr)	4.63 (± 5.04)	5.00 (± 5.88)	4.76 (± 5.41)	4.93 (± 6.20)
Vascular access, arteriovenous fistula (n [%])	130 (68.06)	131 (68.95)	130 (85.53)	131 (86.75)
Antihypertensive medication (n [%])	101 (53.44)	106 (56.99)	73 (48.34)	82 (54.30)
ACE inhibitors and ARBs	48 (25.40)	53 (28.49)	33 (21.85)	37 (24.50)
Beta blockers	60 (31.75)	56 (30.11)	38 (25.17)	40 (26.49)
Calcium channel blockers	34 (17.99)	41 (22.04)	24 (15.89)	31 (20.53)
Erythropoietin stimulating agents (IU/kg/wk)	104.66 (± 107.80)	120.76 (± 134.28)	104.58 (± 108.09)	121.79 (± 143.40)
Hemoglobin (g/dl)	11.59 (± 1.25)	11.63 (± 1.35)	11.69 (± 1.24)	11.64 (± 1.41)
C reactive protein (mg/l)	11.51 (± 23.36)	12.11 (± 16.20)	10.06 (± 14.10)	11.64 (± 14.90)
Albumin (g/l)	39.06 (± 3.76)	38.93 (± 4.14)	39.01 (± 3.65)	38.62 (± 4.08)
Transthyretin (g/l)	0.25 (± 0.06)	0.25 (± 0.06)	0.25 (± 0.06)	0.24 (± 0.07)
β2-microglobulin (mg/l)	27.75 (± 7.97)	26.08 (± 6.69)	27.50 (± 7.40)	26.07 (± 6.99)
Total cholesterol (mmol/l)	4.55 (± 1.12)	4.42 (± 1.15)	4.59 (± 1.13)	4.42 (± 1.21)
LDL cholesterol (mmol/l)	2.64 (± 0.96)	2.52 (± 0.95)	2.67 (± 0.98)	2.52 (± 0.97)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; BMI, body mass index; ESRD, end-stage renal disease; HD, hemodialysis; LDL, low-density lipoprotein; OLHDF, online hemodiafiltration.
Values are described by proportions for categorical variables and mean (± SD) for quantitative variables.

HD treatment parameters from the first session (0 months) in allocated treatment to the last session (24 months) of the study are presented in Table 2. In the OLHDF group, throughout the study duration, the percentage of patients receiving pre-dilution and related infusions was less than 10% (8.38%, 9.09%, 7.10%, and 8.27% at 0, 6, 12, and 24 months, respectively). At 0 months, the 2 groups did not significantly differ regarding all dialysis prescriptions and treatment schedule except for dialysate flow and convection volume, which were significantly higher in the OLHDF group. Dialysate flow increased significantly in both groups throughout follow-up without no significant variation between groups ($P = 0.07$). In addition, a significant increase in blood flow and urea single-pool Kt/V during follow-up was observed in the OLHDF group, whereas no significant variation was reported in the HFHD group. When modeling urea single-pool Kt/V according to time, group, and time × group, and after adjustment for blood and dialysate flow rate, no dramatic change in P values was observed. The slight dialysis duration differences observed between groups might be attributable to sampling fluctuations, or minor errors in connection and disconnection timing reported in patient logs. However, these minor differences should not translate to any effect on dialysis modality, as they did not reach significance.

Intradialytic tolerance in first quarter of study

Records of intradialytic events started at day 30 after the stabilization period. Only 2 patients were switched during this interval: 1 moved to another dialysis center not performing HDF, and the other refused HDF treatment due to nonspecific discomfort and intolerance to the cooling effect of the method.

The main intent-to-treat analysis of intradialytic tolerance was performed in 152 and 151 patients in the HFHD and OLHDF groups, respectively (Table 3). During the observational period from day 30 to day 120, 84.9% and 84.1% of patients in the HFHD and OLHDF arms, respectively, experienced at least 1 adverse event, with no significant difference between groups (odds ratio [OR] = 0.94, confidence interval [CI] 95% = [0.51–1.76], $P = 0.85$).

As an exploratory analysis of the root cause of intradialytic intolerance, intradialytic tolerance was examined, considering the sessions as a statistical unit according to treatment actually received. The median number of dialysis sessions per month was 13.34 [10.05–14.50] in the HFHD group and 13.34 [10.15–15.05] in the OLHDF group ($P = 0.93$). Analysis was performed on a total of 6077 HFHD sessions and 5904 OLHDF sessions. Of 11,981 sessions, 2935 (24.5%) were complicated by the occurrence of at least 1 adverse event, with

Table 2 | Characteristics of treatment according to the HFHD and OLHDF groups during follow-up

Variable	0 mo Mean (± SD)	6 mo Mean (± SD)	12 mo Mean (± SD)	24 mo Mean (± SD)	Time *P* value	Group *P* value	Time × group *P* value
Duration of dialysis session (h)					0.30	0.84	0.26
HFHD	3.95 (± 0.36)	3.93 (± 0.33)	3.94 (± 0.36)	3.91 (± 0.34)	0.48		
OLHDF	3.91 (± 0.48)	3.92 (± 0.49)	3.98 (± 0.56)	3.98 (± 0.60)	0.17		
P value[a]	0.34	0.37	0.96	0.32			
Blood flow (ml/min)					**0.02**	**0.05**	0.08
HFHD	335.32 (± 42.15)	336.28 (± 42.23)	336.73 (± 39.73)	334.90 (± 41.56)	0.97		
OLHDF	337.54 (± 41.63)	341.22 (± 43.44)	344.68 (± 41.08)	349.51 (± 40.46)	**<0.01**		
P value[a]	0.58	0.14	0.06	**<0.01**			
Dialysate flow (ml/min)					**<0.01**	**<0.0001**	0.07
HFHD	509.09 (± 46.06)	510.08 (± 61.53)	517.30 (± 56.70)	523.81 (± 66.55)	**0.04**		
OLHDF	539.29 (± 76.04)	560.79 (± 101.62)	553.90 (± 98.75)	552.05 (± 104.53)	**<0.01**		
P value[a]	**<0.0001**	**<0.0001**	**<0.0001**	**<0.01**			
Intradialytic weight change (pre-post) (kg)					0.20	0.92	0.86
HFHD	2.14 (± 0.81)	2.22 (± 0.83)	2.11 (± 0.93)	2.12 (± 0.86)	0.29		
OLHDF	2.10 (± 0.82)	2.21 (± 0.94)	2.14 (± 0.91)	2.18 (± 0.94)	0.64		
P value[a]	0.76	0.65	0.93	0.63			
Ultrafiltration rate (ml/h/kg)					0.17	0.46	0.90
HFHD	7.91 (± 3.09)	8.15 (± 3.05)	7.72 (± 3.30)	7.93 (± 3.32)	0.40		
OLHDF	7.99 (± 3.32)	8.32 (± 3.30)	7.96 (± 3.57)	8.35 (± 4.03)	0.43		
P value[a]	0.77	0.76	0.55	0.33			
Urea single-pool Kt/V					**<0.01**	**<0.001**	0.18
HFHD	1.56 (± 0.36)	1.54 (± 0.27)	1.54 (± 0.31)	1.59 (± 0.36)	0.46		
OLHDF	1.62 (± 0.32)	1.62 (± 0.38)	1.69 (± 0.38)	1.74 (± 0.35)	**<0.001**		
P value[a]	0.12	0.13	**<0.01**	**<0.01**			
nPCR (g/kg/d)					0.17	0.69	0.22
HFHD	1.25 (± 0.33)	1.23 (± 0.34)	1.19 (± 0.33)	1.21 (± 0.38)	0.32		
OLHDF	1.25 (± 0.34)	1.18 (± 0.38)	1.23 (± 0.38)	1.24 (± 0.39)	0.12		
P value[a]	0.60	0.32	0.29	0.57			
Convection volume (l/session)					**0.0012**	**<0.0001**	**0.0005**
HFHD	1.99 (± 1.22)	2.11 (± 1.17)	1.94 (± 1.17)	2.00 (± 1.22)	0.99		
OLHDF[b]	19.32 (± 4.46)	20.95 (± 5.30)	21.93 (± 5.21)	22.53 (± 6.76)	**<0.0001**		
post-dilution infusion	19.86 (± 4.68)	20.76 (± 4.88)	21.75 (± 4.91)	22.48 (±6.26)			
pre-dilution & related infusion	37.58 (± 7.32)	42.62 (± 13.35)	44.08 (± 10.88)	42.59 (± 16.38)			
P value[a]	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**			
Erythropoietin stimulating agents (IU/kg/wk)					0.08	0.29	0.11
HFHD	104.66 (± 107.80)	90.42 (± 87.18)	95.39 (± 87.39)	80.57 (± 70.40)	0.63		
OLHDF	120.76 (± 134.28)	92.65 (± 84.43)	109.77 (± 117.12)	110.66 (± 99.77)	**0.01**		
P value[a]	0.14	0.60	0.36	0.14			

HFHD, high-flux hemodialysis; mo, months; OLHDF, online hemodiafiltration. $P < 0.05$ are in bold.
[a]*P* value of group effect at each time point.
[b]After correction for mode of dilution.[20]

a lower occurrence in OLHDF (23.1%; $P = 0.0004$) (Table 4). Compared with HFHD sessions, OLHDF sessions presented fewer episodes of asymptomatic hypotension ($P = 0.002$) and muscle cramps ($P = 0.03$). More arrhythmia episodes were reported in OLHDF sessions ($P = 0.01$), but the occurrence remained relatively low in both treatments (0.5‰ vs. 2.4‰ in HFHD and OLHDF sessions, respectively) compared with previous studies. No significant difference between HFHD and OLHDF sessions was evidenced in terms of headache, nausea, fever reaction (temperature > 39°C not bacterial [catheter or other]-related), or chest pain.

Health-related quality of life and long-term patient-reported outcome measures

At 0 months, the 2 groups did not differ for all health-related quality of life (HRQOL) component scores studied: burden of kidney disease ($P = 0.07$), physical composite score ($P = 0.78$), and mental composite score ($P = 0.73$). No difference in evolution over the follow-up was observed between the HFHD and OLHDF groups except for mental composite score ($P = 0.04$), which tended to be higher in the HFHD group at 24 months ($P = 0.06$) (Supplementary Figure S1).

Renal replacement treatment efficacy and biomarkers of cardiovascular risk

Treatment adequacy is summarized in Table 5 and Figure 2. At 0 months, the 2 groups were comparable for all parameters of dialysis adequacy. In both arms, a slight but significant decrease in post-dialysis body weight was observed during follow-up. However, after taking into account group and time effects, the reported variation did not reach significance ($P = 0.08$). Significantly lower pre-dialysis β2-microglobulin (β2m) level ($P < 0.01$) and higher β2m reduction rate ($P < 0.0001$) were observed in the OLHDF group over time

Table 3 | Primary outcomes: intent-to-treat analysis of intradialytic tolerance and patient-reported outcomes between the HFHD and OLHDF groups

Variable		HFHD (*N* = 152)		OLHDF (*N* = 151)		Odds ratio (CI 95%)	*P* value	Yule's Q
		n	%	*n*	%			
At least 1 event	No	23	15.13	24	15.89	1	0.85	
	Yes	129	84.87	127	84.11	0.94 [0.51;1.76]		−0.03
Asymptomatic hypotension	No	49	32.24	50	33.11	1	0.87	
	Yes	103	67.76	101	66.89	0.96 [0.59;1.55]		−0.02
Symptomatic hypotension	No	109	71.71	118	78.15	1	0.20	
	Yes	43	28.29	33	21.85	0.71 [0.42;1.20]		−0.17
Headache	No	139	91.45	139	92.05	1	0.85	
	Yes	13	8.55	12	7.95	0.92 [0.41;2.09]		−0.04
Muscle cramps	No	100	65.79	113	74.83	1	0.09	
	Yes	52	34.21	38	25.17	0.65 [0.39;1.06]		−0.21
Nausea	No	139	91.45	130	86.09	1	0.14	
	Yes	13	8.55	21	13.91	1.73 [0.83;3.59]		0.27
Vomiting	No	140	92.11	143	94.70	1	0.37	
	Yes	12	7.89	8	5.30	0.65 [0.26;1.65]		−0.21
Fever	No	147	96.71	146	96.69	1	0.99	
	Yes	5	3.29	5	3.31	1.01 [0.29;3.55]		0.005
Chest pain	No	151	99.34	146	96.69	1	0.14	
	Yes	1	0.66	5	3.31	5.17 [0.60;44.8]		0.68
Arrhythmia	No	149	98.03	141	93.38	1	0.06	
	Yes	3	1.97	10	6.62	3.52 [0.95;13.1]		0.56
Other event	No	81	53.29	82	54.30	1	0.86	
	Yes	71	46.71	69	45.70	0.96 [0.61;1.51]		−0.02

HFHD, high-flux hemodialysis; OLHDF, online hemodiafiltration.
Intent-to-treat analysis of intradialytic tolerance was performed based on the percentage of patients presenting with at least 1 adverse event occurring between day 30 and day 120 of follow-up.

(Figure 2). These differences remained significant over the 24-month follow-up, but no difference in variation was observed between the 2 groups. In the OLHDF arm, pre-dialysis phosphate level significantly decreased throughout the study ($P < 0.001$) compared with the HFHD arm, and the variation between the 2 groups was significant

Table 4 | Exploratory root cause analysis: intradialytic tolerance and patient-reported outcomes between the HFHD and OLHDF groups using sessions as a statistical unit

Variable		HFHD (*N* = 6077)		OLHDF (*N* = 5904)		Odds Ratio (CI 95%)	*P* value
		n	%	*n*	%		
At least 1 event	No	4505	74.13	4541	76.91	1	**0.0004**
	Yes	1572	25.87	1363	23.09	0.86 [0.79; 0.94]	
Asymptomatic hypotension	No	4824	79.38	4819	81.62	1	**0.002**
	Yes	1253	20.62	1085	18.38	0.87 [0.79; 0.95]	
Symptomatic hypotension	No	5972	98.27	5822	98.61	1	0.13
	Yes	105	1.73	82	1.39	0.80 [0.60; 1.07]	
Headache	No	6054	99.62	5886	99.70	1	0.49
	Yes	23	0.38	18	0.30	0.81 [0.43; 1.49]	
Muscle cramps	No	5944	97.81	5807	98.36	1	**0.03**
	Yes	133	2.19	97	1.64	0.75 [0.57; 0.97]	
Nausea	No	6056	99.65	5877	99.54	1	0.33
	Yes	21	0.35	27	0.46	1.32 [0.75; 2.34]	
Vomiting	No	6055	99.64	5893	99.81	1	0.07
	Yes	22	0.36	11	0.19	0.51 [0.25; 1.06]	
Fever	No	6072	99.92	5899	99.92	1	0.96
	Yes	5	0.08	5	0.08	1.03 [0.30; 3.56]	
Chest pain	No	6076	99.98	5898	99.90	1	0.09
	Yes	1	0.02	6	0.10	6.18 [0.74; 51.3]	
Arrhythmia	No	6074	99.95	5890	99.76	1	**0.01**
	Yes	3	0.05	14	0.24	4.81 [1.38; 16.8]	
Other event	No	5883	96.81	5742	97.26	1	0.15
	Yes	194	3.19	162	2.74	5.16 [1.76; 15.1]	

HFHD, high-flux hemodialysis; OLHDF, online hemodiafiltration.
Analysis of intradialytic tolerance according to actual treatment received at each session was performed based on the presence of at least one adverse event per session occurring between day 30 and day 120 of follow-up. $P < 0.05$ are in bold.

Table 5 | Treatment adequacy according to the HFHD and OLHDF groups during follow-up

Variable	0 mo Mean (± SD)	6 mo Mean (± SD)	12 mo Mean (± SD)	24 mo Mean (± SD)	Time *P* value	Group *P* value	Time × group *P* value
Systolic blood pressure (mm Hg)					0.49	0.64	0.18
HFHD	137.63 (± 23.63)	137.57 (± 24.26)	135.63 (± 23.37)	140.48 (± 23.08)	0.21		
OLHDF	138.56 (± 21.84)	137.91 (± 24.96)	136.33 (± 23.68)	134.92 (± 24.20)	0.43		
P value[a]	0.73	0.84	0.87	0.06			
Diastolic blood pressure (mm Hg)					0.28	0.14	0.50
HFHD	65.75 (± 14.12)	64.40 (± 15.80)	63.99 (± 15.71)	65.77 (± 15.64)	0.54		
OLHDF	64.53 (± 15.09)	62.91 (± 14.48)	62.95 (± 15.51)	61.27 (± 13.38)	0.26		
P value[a]	0.46	0.43	0.68	**0.04**			
Heart rate (bits/min)					0.32	0.41	0.30
HFHD	74.50 (± 12.43)	72.34 (± 11.93)	72.72 (± 12.20)	72.18 (± 12.10)	0.31		
OLHDF	74.40 (± 13.26)	74.39 (± 14.76)	73.36 (± 12.91)	75.07 (± 15.15)	0.30		
P value[a]	0.85	0.24	0.92	0.20			
Post-dialysis body weight (kg)					**<.0001**	0.38	0.08
HFHD	70.78 (± 14.44)	70.67 (± 14.04)	70.60 (± 14.05)	70.16 (± 14.22)	**<.0001**		
OLHDF	69.86 (± 14.49)	69.40 (± 14.12)	69.40 (± 14.34)	68.80 (± 13.47)	**<.0001**		
P value[a]	0.58	0.36	0.24	0.44			
Pre-dialysis sodium (mmol/l)					0.07	0.58	0.28
HFHD	138.16 (± 3.35)	138.14 (± 3.26)	137.96 (± 3.16)	138.23 (± 3.36)	0.83		
OLHDF	138.37 (± 3.44)	137.73 (± 3.59)	138.08 (± 3.41)	138.08 (± 3.62)	**0.02**		
P value[a]	0.59	0.19	0.76	0.54			
Pre-dialysis potassium (mmol/l)					0.16	0.77	0.40
HFHD	4.87 (± 0.71)	4.90 (± 0.63)	4.84 (± 0.59)	4.87 (± 0.67)	0.87		
OLHDF	4.80 (± 0.64)	4.93 (± 0.73)	4.84 (± 0.67)	4.78 (± 0.76)	0.07		
P value[a]	0.33	0.47	0.81	0.43			
Pre-dialysis bicarbonate (mmol/l)					0.45	0.56	0.95
HFHD	23.06 (± 2.77)	22.93 (± 2.64)	23.08 (± 2.92)	22.85 (± 2.42)	0.54		
OLHDF	22.88 (± 3.10)	22.81 (± 3.32)	23.06 (± 2.61)	22.90 (± 2.96)	0.84		
P value[a]	0.51	0.62	0.54	0.99			
Pre-dialysis calcium (mmol/l)					0.54	0.84	0.48
HFHD	2.22 (± 0.17)	2.21 (± 0.16)	2.23 (± 0.20)	2.20 (± 0.19)	0.63		
OLHDF	2.23 (± 0.17)	2.21 (± 0.16)	2.21 (± 0.17)	2.21 (± 0.17)	0.40		
P value[a]	0.54	0.72	0.29	0.78			
Pre-dialysis hemoglobin (g/dl)					0.95	0.74	0.62
HFHD	11.59 (± 1.25)	11.64 (± 1.37)	11.56 (± 1.25)	11.69 (± 1.12)	0.76		
OLHDF	11.63 (± 1.35)	11.54 (± 1.38)	11.59 (± 1.20)	11.55 (± 1.48)	0.81		
P value[a]	0.74	0.50	0.71	0.43			
Pre-dialysis TSAT (%)					**0.01**	0.37	0.64
HFHD	28.87 (± 11.84)	29.00 (± 13.02)	28.45 (± 12.35)	27.60 (± 11.56)	0.56		
OLHDF	28.56 (± 12.37)	28.26 (± 12.76)	27.54 (± 13.37)	25.82 (± 12.05)	**0.01**		
P value[a]	0.95	0.73	0.70	0.14			
Pre-dialysis ferritin (ng/ml)					**0.03**	0.45	0.51
HFHD	463.43 (± 514.43)	468.42 (± 455.85)	533.31 (± 850.66)	483.66 (± 299.08)	0.64		
OLHDF	488.84 (± 695.23)	527.39 (± 693.32)	468.16 (± 705.69)	537.95 (± 489.90)	**0.02**		
P value[a]	0.85	0.95	0.78	0.12			
Pre-dialysis PTH (pg/ml)					0.50	0.35	0.79
HFHD	289.03 (± 355.70)	280.96 (± 275.04)	283.00 (± 294.68)	283.53 (± 250.96)	0.76		
OLHDF	263.39 (± 263.32)	264.08 (± 256.24)	262.01 (± 258.33)	241.74 (± 210.52)	0.51		
P value[a]	0.82	0.53	0.30	0.26			

HFHD, high-flux hemodialysis; mo, months; OLHDF, online hemodiafiltration; PTH, parathyroid hormone; TSAT, transferrin saturation. $P < 0.05$ are in bold.
[a]*P* value of group effect at each time point.

($P = 0.01$). All other parameters including dialysis adequacy and iron status parameters did not differ between the groups during the study.

The variation of nutritional, inflammatory, and cardiovascular biomarkers in the 2 groups are summarized in Table 6 and Figure 3. At 0 months, the 2 groups were comparable for all these parameters. Albumin remained stable in both study arms over time, while a significant decrease in transthyretin was observed but only in the HFHD group ($P < 0.01$). We observed a slight but not significant increase over time in C-reactive protein (CRP) level, comparable in both groups (Figure 3). In addition, interleukin (IL) 6, tumor necrosis factor alpha, and IL-10 remained stable throughout follow-up. N-terminal pro b-type natriuretic peptide and cardiac troponin T increased significantly in both groups over time, but no significant variation was observed between groups.

Hospitalization and mortality

The results of hospitalization and mortality recorded between 0 and 24 months of follow-up are presented in Table 7. The rate of all-cause hospital admissions showed no relative risk

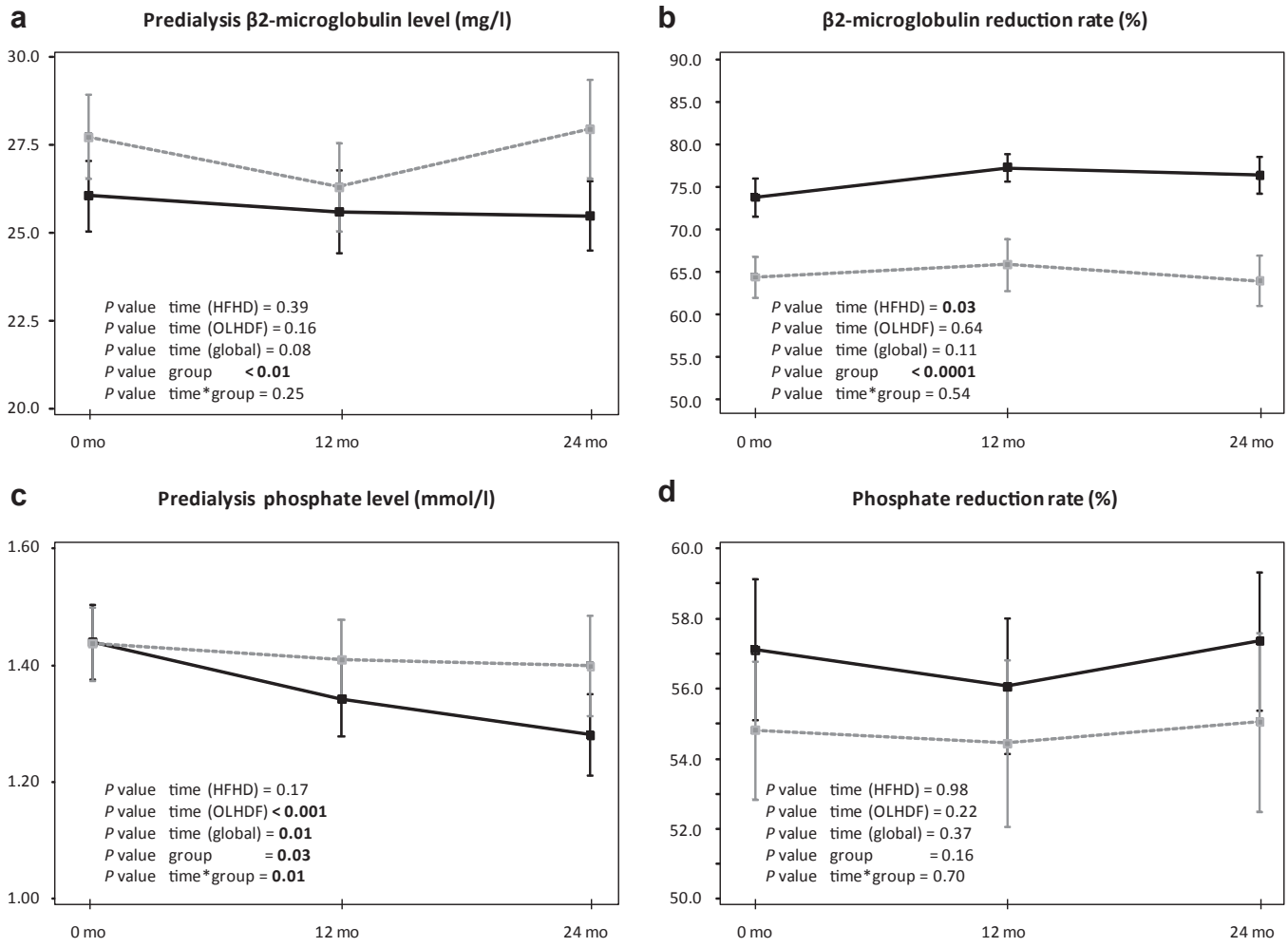

Figure 2 | Biological variables of treatment adequacy. Predialysis and reduction rates of (**a,b**) β2-microglobulin and (**c,d**) phosphate levels. High-flux hemodialysis (HFHD) is indicated in gray; online hemodiafiltration (OLHDF) is indicated in black.

difference between groups (incidence rate ratio = 0.89; 95% CI [0.76–1.04]). The rate of vascular access admissions showed a relative risk reduction of 47% favorable to the OLHDF group (incidence rate ratio = 0.53; 95% CI, 0.35–0.81).

All-cause and cardiovascular mortality at 24 months

Annual crude mortality rates were 22.5% (11.0% at 12 months) and 18.9% (8.9% at 12 months) at 24 months of follow-up in the HFHD and OLHDF groups, respectively. Kaplan-Meier survival analysis comparing study arms (HFHD vs. OLHDF not considering total ultrafiltered volume) for all-cause mortality is represented in Figure 4. All-cause mortality did not significantly differ between study arms (log-rank *P* value = 0.43). Likewise, no difference in cardiovascular mortality between groups was found (log-rank *P* value = 0.53).

Effect of total convective volume was also tested in the OLHDF group by splitting it into 2 categories by median value (<20 and ≥20 liters [L]/session). Mean (SD) values of convective volumes were 16.46 (± 2.99) L and 25.85 (± 6.14) L, respectively in each category. All-cause and cardiovascular mortality did not differ between OLHDF patients with convective volume below versus above 20 L.

DISCUSSION

The main objective of this prospective, multicenter, randomized clinical study was to explore the effects of renal replacement modality type (HFHD vs. OLHDF) on intradialytic tolerance and patient perception in elderly ESKD patients. Clinical tolerance of treatment modality was assessed over the first quarter (30–120 days) of the study (individual and global prevalence of intradialytic symptomatology), while long-term effects of RRT (clinical symptomatology, biomarkers, morbidity, and mortality) were monitored over 24 months of follow-up. Globally, our study did not demonstrate any beneficial effect of OLHDF over HFHD on the main outcome at the patient level by analyzing the proportion of patients presenting with at least 1 adverse event in the intent-to-treat analysis, while at the session level, in OLHDF, fewer symptomatic hypotensive episodes and cramps were noted. Over the 2-year study period,

Table 6 | Biological variables over time in patients receiving HFHD versus OLHDF

Variable	0 mo Mean (± SD)	12 mo Mean (± SD)	24 mo Mean (± SD)	Time *P* value	Group *P* value	Time × group *P* value
Transthyretin (g/l)				0.06	0.58	0.29
HFHD	0.25 (± 0.06)	0.25 (± 0.06)	0.24 (± 0.06)	**<0.01**		
OLHDF	0.25 (± 0.06)	0.24 (± 0.08)	0.24 (± 0.07)	0.35		
P value[a]	0.47	0.29	0.70			
Interleukin 6 (pg/ml)				0.47	0.14	0.12
HFHD	6.13 (± 9.18)	6.06 (± 7.88)	9.03 (± 20.99)	0.09		
OLHDF	7.42 (± 10.56)	8.47 (± 14.35)	13.14 (± 47.52)	0.64		
P value[a]	0.12	**0.03**	0.73			
Interleukin 10 (pg/ml)				0.92	0.22	0.38
HFHD	0.77 (± 2.16)	0.56 (± 0.26)	0.73 (± 0.82)	0.70		
OLHDF	1.16 (± 7.63)	1.00 (± 3.95)	0.82 (± 1.58)	0.50		
P value[a]	0.48	0.12	0.26			
TNF-α (pg/ml)				0.26	0.62	0.18
HFHD	26.87 (± 21.25)	23.53 (± 9.98)	24.67 (± 8.96)	0.11		
OLHDF	24.42 (± 10.31)	24.80 (± 11.34)	24.41 (± 10.06)	0.47		
P value[a]	0.35	0.64	0.39			
NT-ProBNP (ng/l)				**<0.0001**	0.07	0.06
HFHD	8496.09 (± 10578.53)	11,062.53 (± 14788.29)	12,310.74 (± 15866.04)	**<0.0001**		
OLHDF	7793.48 (± 10264.56)	9046.60 (± 17516.82)	12,611.20 (± 40984.06)	**<0.0001**		
P value[a]	0.56	**0.02**	0.10			
hs cTNT (ng/l)				**<0.0001**	0.32	0.31
HFHD	80.66 (± 51.13)	91.60 (± 75.07)	106.65 (± 149.31)	**<0.0001**		
OLHDF	78.61 (± 43.58)	81.64 (± 56.89)	90.40 (± 82.61)	**<0.01**		
P value[a]	0.71	0.16	0.44			

hs cTNT, high-sensitive cardiac troponin T; NT-ProBNP, N-terminal pro b-type natriuretic peptide; TNF-α, tumor necrosis factor alpha; HFHD, high-flux hemodialysis; mo, months; OLHDF, online hemodiafiltration. $P < 0.05$ are in bold.
[a]*P* value of group effect at each time point.

hospitalizations remained similar in both groups, as did HRQOL. Regarding mortality, no significant difference was observed between the HFHD and OLHDF arms, perhaps due to suboptimal convective dose.[12,20] Finally, inflammatory biomarkers remained unchanged over the study period regardless of the dialysis modality used. Nutritional biomarkers including normalized protein catabolic rate and albumin remained stable in the 2 arms, whereas a trend of decrease in transthyretin (prealbumin) was observed in HFHD-treated patients.

Several previous studies investigating the influence of dialysis modalities on symptomatic IDH have yielded conflicting results. Locatelli *et al.* observed a beneficial effect of a pure (hemofiltration) or mixed (HDF) convection versus diffusive (low-flux HD) technique on IDH, with a more pronounced effect in OLHDF associated with a slight but significant increase in systolic blood pressure.[6] Interestingly, the results of their analysis (based on sessions) concur with our exploratory root cause analysis using sessions as a statistical unit. The ESHOL trial also provided evidence of the effect of OLHDF on IDH episodes, which was apparently not due to major differences in sodium removal during sessions.[12] Vilar *et al.*[21] demonstrated similar benefits in a retrospective study. However, it is important to note that such findings are not universal since Locatelli *et al.*[16] reported in a previous trial no difference in treatment tolerance between low-flux HD, HFHD, and high-flux HDF. Caplin *et al.*[17] more recently corroborated this finding, demonstrating that switching to HDF did not improve intradialytic symptoms in patients established on HD with optimal dialysis conditions. However, they still demonstrated a trend in lower muscle cramp episodes with HDF, which concurs with the results of our exploratory root cause analysis of intradialytic intolerance. Conversely, this observation was not confirmed in another study.[21] In our study, we observed a very low rate of intradialytic arrhythmia. Surprisingly, a slight but significant increase was observed in OLHDF (2.4‰) versus HFHD (0.5‰) and could be related to factors not studied in this trial such as electrolyte transfer (sodium, potassium, calcium, magnesium, acetate, bicarbonate),[22–25] removal of cardiac medication (beta-blockers),[26–28] and history of cardiovascular disease. These high transfer rates between dialysate and blood compartment could result in a transient electrolyte gradient between extracellular fluid and the intracellular milieu. Rapid correction of acidosis is also known to act synergistically with magnesium and ionized calcium changes interfering with potassium kinetic and rapid membrane polarization changes. It is important to note that these arrhythmic episodes were transient, clinically detected, and mainly related to auricular extra beats and atrial fibrillation not leading to hospitalization or active intervention. These findings are corroborated by the lack of difference between dialysis modalities in arrhythmia episodes over the 2-year study period (see Table 7). In addition, fewer stroke episodes (although statistical significance was not reached) were observed in the OLHDF group. Hemodynamic effects of HDF are indeed difficult to ascertain in the context of short-term studies because they are associated with several confounders that were not assessed in our study

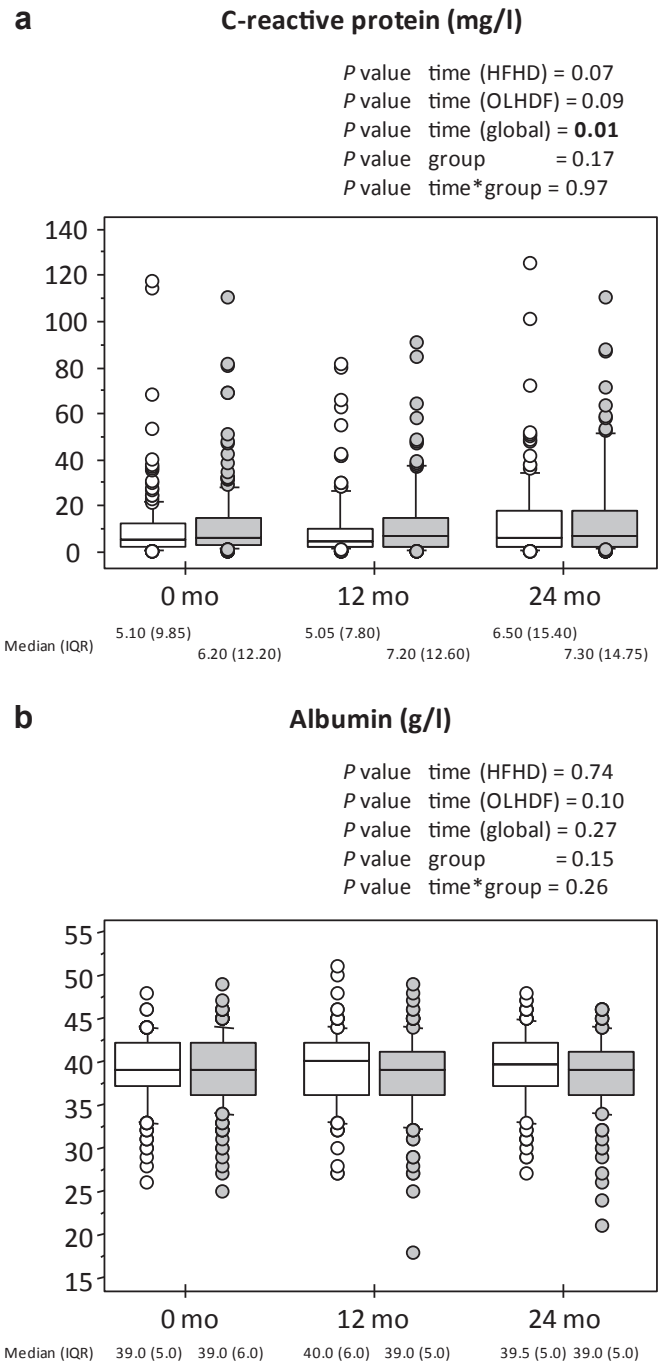

Figure 3 | Malnutrition and inflammation variables over time in patients receiving high-flux hemodialysis (HFHD; indicated in white) versus online hemodiafiltration (OLHDF; indicated in gray). (**a**) C-reactive protein and (**b**) albumin. IQR, interquartile range; mo, months.

such as sodium mass balance, thermal balance, and treatment time, but also due to the low incidence of symptomatic IDH (<2%) despite advanced age and comorbidities.[6] It should be noted that ultrafiltration rate, a surrogate of sodium mass removal rate, remained low in both study arms, averaging 7.8 ml/h/kg and 7.9 ml/h/kg for HFHD and OLHDF, respectively, over 2 years. A low ultrafiltration rate is of major importance in this context for 2 reasons: first, it facilitates the vascular refilling rate during a dialysis session and reduces the propensity for hypotensive episodes; second, it reflects good patient adherence to dietary salt restriction. Both of these factors are well known to affect hemodynamic stability and blood pressure control.[29–35] Finally, in our study, the differential drop-out rate between groups during the evaluation period of intradialytic tolerance (n = 3/6077 and n = 102/5904 sessions in the HFHD and OLHDF groups, respectively) could not be attributable to OLHDF intolerance because personal or medical decisions accounted for less than 10% of drop-outs in this group (Supplementary Table S3).

Over 2 years, HRQOL based on mental composite score and physical composite score but not burden of kidney disease remained virtually similar for OLHDF and HFHD. Improvement in HRQOL with HDF remains a matter of ongoing controversy. Similar to our findings, Mazairac *et al.* in the CONTRAST trial[36] could not demonstrate any benefit of convective therapy over low-flux HD using the same validated questionnaire and also observed a decline in patient satisfaction over time. Conversely, others have demonstrated a beneficial effect of HDF on HRQOL,[36,37] particularly a recent report by Karkar *et al.*[38] that describes improved social, physical, and professional activities in association with fewer episodes of hypotension, cramps, itching, fatigue, joint pain, and stiffness with OLHDF. A similar beneficial effect of HDF on patient satisfaction reported by Kantartzi *et al.*[39] must be regarded with caution due to differences in the questionnaire used and the comparative study group (low-flux HD and not HFHD). It is also important to note that QOL questionnaires (HRQOL, SF36 or EUROQOL, 5 dimensions) are not sufficiently specific or sensitive tools to explore the effects of RRTs on ESKD patients' perception. It has been shown recently that simpler and more specific questions (time of recovery after dialysis and patient-reported outcome measures) had more predictive value for ESKD patient outcomes.[40–43] In addition, it is noteworthy that the possibility of requiring assistance (from a family member or third party) in order to fill out the questionnaire, a potential bias in the analysis, was not recorded in our study.

The quality of RRT delivered to the entire studied cohort is quite remarkable and needs to be emphasized. Regardless of the RRT modality (HFHD vs. OLHDF), the majority of ESKD patients were on target for major (e.g., extracellular fluid volume, blood pressure control, urea Kt/V, phosphate, anemia, normalized protein catabolic rate, and albumin) and minor (e.g., sodium, potassium, HCO_3, β2m, iron status, and lipids) dialysis adequacy markers. The lower pre-dialysis β2m[37,44,45] achieved here in OLHDF confirms the higher removal mass of this technique in comparison with HFHD with respect to middle molecules.[46,47] It is also known that removal rates of small–molecular weight solutes (e.g., urea and creatinine) are slightly increased with HDF. This is confirmed here by higher (~10%) urea Kt/V values achieved with OLHDF. Conflicting results with serum predialysis β2m concentrations are reported particularly in the Turkish and

Table 7 | Hospitalization and mortality data recorded between 0 and 24 months of follow-up

	All (N = 381) (623.93 patient-years at risk)		HFHD (n = 191) (311.10 patient-years at risk)		OLHDF (n = 190) (312.83 patient-years at risk)		
	No. of events	No. of events/100 patient-years	No. of events	No. of events/100 patient-years	No. of events	No. of events/100 patient-years	IRR
All-cause hospitalizations	**655**	**104.98**	**346**	**111.22**	**309**	**98.78**	**0.89 [0.76; 1.04]**
Hospitalizations for:							
Heart failure	19	3.05	12	3.86	7	2.24	0.58 [0.19; 1.60]
Ischemic heart disease	56	8.98	30	9.64	26	8.31	0.86 [0.49; 1.51]
Mesenteric thrombosis	7	1.12	3	0.96	4	1.28	1.33 [0.22; 9.05]
Stroke	24	3.85	15	4.82	9	2.88	0.60 [0.23; 1.45]
Arrhythmia	35	5.61	16	5.14	19	6.07	1.18 [0.57; 2.45]
Peripheral artery disease	57	9.14	26	8.36	31	9.91	1.19 [0.68; 2.08]
Sudden death	16	2.56	9	2.89	7	2.24	0.77 [0.24; 2.33]
Infection	114	18.27	52	16.72	62	19.82	1.19 [0.81; 1.75]
Tumor	24	3.85	7	2.25	17	5.43	2.41 [0.95; 6.89]
Trauma	30	4.81	13	4.18	17	5.43	1.30 [0.59; 2.91]
Cachexia	17	2.73	10	3.21	7	2.24	0.70 [0.22; 2.03]
Carpal tunnel syndrome surgery	7	1.12	3	0.96	4	1.28	1.33 [0.22; 9.05]
Vascular access dysfunction	103	16.51	67	21.54	36	11.51	0.53 [0.35; 0.81]
Parathyroidectomy	5	0.80	3	0.96	2	0.64	0.66 [0.05; 5.79]
Other	141	22.60	80	25.72	61	19.50	0.76 [0.53; 1.07]
All-cause hospitalizations without palliative care or follow-up care	646	104	343	110	303	97	0.88 [0.75; 1.03]
Deaths	**79**	**12.66**	**43**	**13.82**	**36**	**11.51**	**0.83 [0.52; 1.33]**

Bold characters highlight all-cause hospitalizations and deaths.

ESHOL OLHDF trials.[13] Some methodological concerns have been addressed in both of these studies concerning dosing methods (specificity and variability), frequency of β2m measurements, and role of residual kidney function. Now, it must be reminded that predialysis β2m concentrations depend on 2 factors, β2m generation and removal rates. In the case of HDF, β2m concentrations are directly related to convective volume.[48–50] Considering the mortality risk associated with β2m,[51] it must be emphasized that predialysis β2m concentrations should preferably be lower than 27 mg/l in ESKD patients.[51]

Long-term laboratory data are reassuring in confirming the safety of HDF. In our study, OLHDF was associated with an excellent preservation of nutritional status as depicted by IPAQSS (Indicators for Improvement of Service Quality and Safety) indicators such as stable body mass index, albumin, and normalized protein catabolic rate.[52] In addition, transthyretin remained constant during the study for

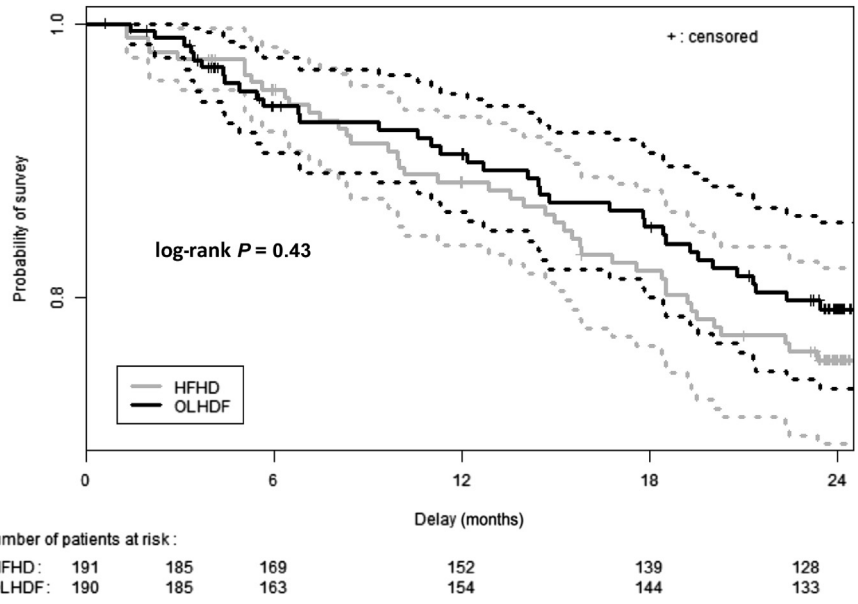

Figure 4 | Kaplan-Meier curve for 24-month survival in the intention-to-treat population. HFHD, high-flux hemodialysis; OLHDF, online hemodiafiltration.

OLHDF while decreasing for HFHD. Interestingly, no significant difference in CRP, pro- and anti-inflammatory cytokines between HFHD and OLHDF was observed over the 2-year follow-up period. Conversely, den Hoedt *et al.*[53] reported in the CONTRAST trial a decline in albumin (annual decrease of 0.8 g/l) in conjunction with a decrease in body mass index and a worsening of inflammatory markers over time. This trend was not observed in our study despite the fact that patients were older than 65 years and the prevalence of diabetes and cardiovascular history was higher. In our study, the lack of difference in albumin and inflammatory markers between RRT modalities confirms that convective therapy does not enhance albumin or nutrient losses, which in turn may exacerbate the malnutrition inflammation and atherogenesis syndrome frequently associated with ESKD patients. This is in line with recent results from the REDERT study.[54] Other authors have even reported a benefit of OLHDF, with a significant and long-lasting reduction in predialysis CRP with stable albumin values.[50] All these findings including ours clearly demonstrate that OLHDF is a safe and well-tolerated RRT in the long term.

According to safety, improvement of dialysis adequacy, and absence of malnutrition and inflammatory effect of OLHDF, it could be postulated that OLHDF would improve survival. Although numerous observational studies[14] and interventional studies[12,15] have demonstrated an improvement of survival rate for HDF patients, this beneficial effect was not formally confirmed in this randomized controlled trial. However, when including these data with the ESHOL, CONTRAST, and Turkish studies in an individual participant data meta-analysis, significant improvement in both all-cause and cardiovascular mortality was observed. It is notable that annual crude mortality appears to be much better in this elderly population, regardless of the modality used, than in the pair-matched population of the DOPPS study and similar to the low mortality rates observed in Japan.[55] This low mortality rate does not seem to be related to selection for patients substantially healthier than the overall dialysis population, because the comorbidities of the REIN register (e.g., diabetes and history of cardiovascular events) reported by Mercadal *et al.*[14] and those of EuCliD (European Clinical Database)[56] are similar to those observed in our population of the same age. Furthermore, Mercadal *et al.*'s study analyzed incident patients, whereas we analyzed prevalent patients. Because mortality risk is not monotonic over time, the patients in this study could be affected by survivor bias. Other unmeasured confounding factors associated with the ability to achieve and tolerate high-efficiency extracorporeal blood purification cannot be ruled out. However, in the 2014 REIN registry, the percentage of fistula in prevalent patients over 65 years old was 77.9%, (78.7% in the French data from EuCliD), which is higher than in our cohort. The median Kt/V was 1.4, and 79% of patients had Kt/V greater than 1.2. In addition, 17%, 24%, and 59% of patients treated in dialysis facilities had 0, 1, or $\geq$2 comorbidities, respectively. This low mortality rate might be due in part to the highly efficient treatment in the HFHD and OLHDF groups and more likely due to the health authority (Haute Autorité de Santé) implementing control of best clinical practices in hemodialysis facilities.[52] Finally, this low mortality rate may mitigate the true beneficial effects of convective therapy. It is worth noting that the beneficial effects of quality control and national data registry (REIN) on CKD dialysis patient outcomes have been illustrated recently, at both the patient and facility levels, by demonstrating the superiority of HDF over HFHD.[14]

Our study has several limitations that have certainly hampered expected outcomes. Due to randomization stratified by a center providing both HFHD and OLHDF and several other reasons (e.g., elderly patients, water treatment system, monitoring capabilities, and competitive trials), recruitment of patients has been difficult and insufficient to reach the required number, leading to slight overestimation of the expected difference between the 2 groups. Therefore, with the main analysis being underpowered at the patient level, we cannot conclude any clinical benefit. In contrast, at the session level, some significant differences were noted, suggesting variability in patient tolerance over time that could be related to factors including weekly number of sessions and dialysis weight loss.[57]

Otherwise, the total ultrafiltered volume, a major driving force of convective therapy benefits, averaged 21 L per session, a value close to the threshold for clinical benefit.[15,58–60] Second, intradialytic hypotensive episodes were defined as a decrease in systolic blood pressure of 20 mm Hg according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines.[61] However, after the initiation of this study, Flythe *et al.* demonstrated that nadir-based definitions of hypotension best capture the association between intradialytic hypotension and mortality when unadjusted and after adjustment for potential confounders.[3] Here again, the poor association between decrease in systolic blood pressure and mortality may mitigate our results. Third, this study is underpowered for detecting a clinically important difference in all-cause mortality considering the relatively low annual crude mortality rate of our ESKD population. Indeed, the ESHOL trial[12] required more than 900 patients to demonstrate any benefit of OLHDF on mortality rate. But the recent meta-analysis of individual participant data was ultimately able to demonstrate that OLHDF, especially if applied at a sufficient dose, was associated with a survival benefit.[15,59]

In conclusion, the FRENCHIE study is in accordance with previous randomized controlled trials in the field. It confirms the safety and efficacy of OLHDF in a multicenter approach and tends to generalize these benefits to an elderly and more fragile population. In agreement with previous reports, including the individual participant data meta-analysis, our results suggest that convective volume is a crucial determinant to achieve better outcomes even in well-treated elderly ESKD patients. Laboratory follow-up tends to confirm that by

combining the use of ultrapure dialysis fluid and HDF methods, nontraditional cardiovascular risk factors (including β2m as in indicator of middle-molecule uremic toxins) and mineral abnormalities could be reduced without impairing nutritional and inflammatory status. The results obtained here, in a prevalent HD population treated using optimal HD conditions with ultrapure water, blood flow, and rate of solute transfer, should be extended with caution in other dialysis populations. Further studies adequately powered and better designed would certainly be helpful in confirming these findings. A European collaborative network has already been initiated in this field and will help to elucidate the true benefits of and appropriate indications for HDF.

METHODS

Study design

The FRENCHIE study was a prospective, open-label, randomized controlled, multicenter trial (ClinicalTrials.gov Identifier: NCT01327391, registered at "Ministère de la Santé et des Solidarités" after approval by the Montpellier University Hospital ethics committee). Eligible patients were randomly assigned at a 1:1 ratio to receive either HFHD or OLHDF for 2 years. The randomization sequence was centralized and computed in permuted blocks by the statistician using SAS software (SAS Institute, Cary, NC) with stratification by center. Therefore, it was impossible for investigators and patients to know which intervention patients would be assigned to until enrollment had been confirmed. The primary outcome was intradialytic tolerance from day 30 to day 120. The secondary outcomes included biological markers of cardiovascular risk, all-cause and cardiovascular hospitalizations, and all-cause and cardiovascular mortality during 2 years of follow-up.

The planned duration of the recruitment period was initially 1 year, but because of difficulties in enrolling dialysis facilities providing both dialysis modalities and in elderly patients meeting the selection criteria, this period was extended for an additional 5 years.

The study was conducted according to the principles of the Declaration of Helsinki and in compliance with the International Conference on Harmonization's Good Clinical Practice regulations. All patients provided written informed consent.

Patient selection

Patients were eligible for inclusion if they were ≥65 years old, with no significant diuresis (<100 ml/24 h) and/or residual kidney function (<2 ml/min/1.73 m^2), on HFHD for ≥3 months and considered stabilized, with 3-times-weekly HD sessions and hemoglobin within 9 to 13 g/dl. Patients with severe malnutrition (serum albumin <20 g/l), unstable clinical condition, unipuncture or failed vascular access flow, or known problems of coagulation were not included.

There was no run-in period before entering the active study phase, and randomly selected patients were assigned to HFHD or switched to OLHDF.

Treatment modalities and procedures

Only high-flux membrane hemodialyzers were used (Supplementary Table S1). Treatments were based on 3-times-weekly dialysis sessions, 3 to 4 hours per session, with a blood flow of 350 to 400 ml/min and a dialysate flow of 500 to 600 ml/min. Both treatment modalities were performed with the same ultrapure bicarbonate-buffered dialysate. OLHDF treatments were mainly performed in postdilution mode, but pre-dilution and related infusion were authorized according to patient profile (e.g., access type and flow, hemorheologic conditions) and local practices under strict safety operational conditions of the referring physician.

The ultrafiltration flow rate was set according to each individual patient's interdialytic weight gain. The routine anticoagulation protocol was unchanged for the study and was individualized for each patient. Dialysis efficacy was assessed using standard best practices, and diffusive dialysis dose was estimated using urea single-pool Kt/V.[62] Routine patient care was performed according to best clinical practices and national health authority rules.

At 0 months, information on demographics, comorbidities, dialysis treatment, and medication was obtained through nephrologist reports. At 0, 6, 12, and 24 months, clinical events, medication, dialysis treatment, and routine laboratory analyses were also recorded.

Outcomes

Intradialytic tolerance. Dialysis-related adverse events occurring during dialysis sessions between days 30 and 120 of treatment (in order to let the patients stabilize onto allocation treatment) were precisely recorded according to time period per session for each patient (Supplementary Table S2).[63] The main outcome was the proportion of patients presenting with at least 1 adverse event during this period in an intent-to-treat analysis. In addition, for root cause analysis, the tolerance was also studied at the session level as a statistical unit according to treatment actually received.

Health-related quality of life as surrogate for patient-reported outcome measures during interdialytic period. HRQOL was evaluated at 0, 6, 12, and 24 months using the Kidney Disease Quality of Life Short Form (KDQOL-SF) questionnaire (French version 1.2).[64,65] This questionnaire consists of generic (SF-36) and kidney disease–specific (KDQOL) portions. The 8 domains of the SF-36 can be summarized in 2 summary scores, the physical composite and the mental composite score. The kidney-disease specific portion consists of 44 questions that can be condensed into 12 domains with a range of 0 to 100, with higher scores indicating a better health status. The analysis only focused on burden of chronic kidney disease and RRT, with physical composite and mental composite score components as surrogates for long-term treatment tolerance and consequence.

Laboratory parameters. Routine laboratory analyses including serum urea, creatinine, sodium, potassium, bicarbonates, proteins, calcium, phosphorus (all being evaluated before and after dialysis), iron, transferrin, ferritin, and parathyroid hormone were locally performed at 0, 6, 12, and 24 months. Specific biomarkers including serum β2m, albumin, transthyretin (prealbumin), low-density lipoprotein and high-density lipoprotein cholesterol, high-sensitive C reactive protein, IL-6, IL-10, tumor necrosis factor alpha, high-sensitive cardiac troponin T and N-terminal pro b-type natriuretic peptide assessing cardiovascular risk were performed on samples collected at 0, 12, and 24 months, centrifuged, aliquoted, frozen, and analyzed in a central laboratory.

Serum β2m, albumin, transthyretin, and high-sensitive C reactive protein were determined by immunoturbidimetry (Cobas 8000; Roche Diagnostics, Meylan, France). Total and HDL cholesterol were assessed by enzymatic colorimetry (Cobas 8000). Plasma IL-6, IL-10, and tumor necrosis factor alpha were measured by enzyme-linked

immunosorbent assay (ThermoFisher Scientific, Courtaboeuf, France). The cardiac troponin T and N-terminal pro b-type natriuretic peptide levels were determined by electro-chemiluminescence immunoassay (Cobas 8000).

Hospitalization and morbidity. All hospital admissions for any reason during the study period were reported in the patient medical record, then notification was sent to the data monitoring center.

Mortality. Mortality was recorded during the entire study. Dates of death were documented and causes of death were categorized as either cardiovascular (myocardial infarction, congestive heart failure, stroke, arrhythmia, and sudden death) or non-cardiovascular (infection, neoplasm, and other or unknown causes).

Sample size estimation

According to the registry of Montpellier dialysis center ESKD patients, at least 1 adverse event (Supplementary Table S1) occurs during dialysis sessions (on a 3-month basis) in 90% of patients. We expected a 10% reduction in patients presenting with at least 1 adverse event with the use of OLHDF. With an α error of 0.05 and a β error of 0.10, and taking account 15% of annual mortality and 10% dropouts (lost to follow-up or other cause including transplantation), the sample size has been estimated at 300 patients per study arm.

Statistical methods

Categorical variables were expressed as number and percentages, and quantitative variables were expressed as mean and SD. The Shapiro-Wilk test was used to test the normality of continuous variables.

In the main analysis, intradialytic tolerance was studied, at the patient level, in an intent-to-treat population. An exploratory analysis of intradialytic tolerance, considering the sessions as a statistical unit according to treatment actually received, was also performed to better understand the root cause of intradialytic intolerance. Logistic regressions were used. The ORs and 95% CIs were reported. Yule's Q was also calculated to evaluate the effect size. The Mann-Whitney U test was performed to compare the number of dialysis sessions by month.

An intent-to-treat analysis was also performed for all secondary outcomes.

Linear mixed models were performed to analyze the association between dialysis modality and changes in biological markers, characteristics of treatment, and treatment adequacy over the 2-year follow-up. If necessary, transformations were performed to normalize response parameters. Time, dialysis modality (OLHDF vs. HFHD), and dialysis modality $\times$ time interactions were modeled as fixed effects. The dialysis modality $\times$ time interaction was tested to evaluate the differences in changes between OLHDF and HFHD over the 2-year follow-up. Tests of the dialysis modality and time interactions were also reported separately for each modality of treatment (within-group variations) and at each time point. The model included time, dialysis modality, and time–dialysis modality interaction.

The associations between dialysis modality and risk of all-cause or cardiovascular mortality were described using the Kaplan-Meier method and tested for statistical significance using the log-rank test.

Significance was set at $P < 0.05$. All analyses were performed with SAS Enterprise Guide, version 4.3.

DISCLOSURE

During the trial period, BC was an employee of the University Hospital Center of Montpellier (head of nephrology department) and is now a full-time employee of Fresenius Medical Care. All the other authors declared no competing interests.

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SUPPLEMENTARY MATERIAL

Table S1. Treatment modalities and procedures.
Table S2. Definition of intradialytic tolerance recorded at each session between day 30 and day 120 of follow-up.
Table S3. Causes of drop-out during the evaluation period of intradialytic tolerance between day 30 and day 120.
Figure S1. Health-related quality of life (HRQOL) evaluated at 0, 6, 12, and 24 months using the Kidney Disease Quality of Life Short Form (KDQOL-SF) questionnaire (French version 1.2).
Supplementary material is linked to the online version of the paper at www.kidney-international.org.

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APPENDIX

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