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Mortality remains high for hemodialysis patients. Online hemodiafiltration (OL-HDF) removes more middle-sized uremic toxins but outcomes of individual trials comparing OL-HDF with hemodialysis have been discrepant. Secondary analyses reported higher convective volumes, easier to achieve in larger patients, and improved survival. Here we tested different methods to standardize OL-HDF convection volume on all-cause and cardiovascular mortality compared with hemodialysis. Pooled individual patient analysis of four prospective trials compared thirds of delivered convection volume with hemodialysis. Convection volumes were either not standardized or standardized to weight, body mass index, body surface area, and total body water. Data were analyzed by multivariable Cox proportional hazards modeling from 2793 patients. All-cause mortality was reduced when the convective dose was unstandardized or standardized to body surface area and total body water; hazard ratio (95% confidence intervals) of 0.65 (0.51–0.82), 0.74 (0.58–0.93), and 0.71 (0.56–0.93) for those receiving higher convective doses. Standardization by body weight or body mass index gave no significant survival advantage. Higher convection volumes were generally associated with greater survival benefit with OL-HDF, but results varied across different ways of standardization for body size. Thus, further studies should take body size into account when evaluating the impact of delivered convection volume on mortality end points.

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The mortality for patients with chronic kidney disease treated by dialysis (CKD5d) remains high. Intuitively, a greater amount of dialysis or achieving a critical threshold might be expected to improve patient survival. This was supported by the National Co-operative Dialysis Study, which reported that time averaged urea concentration determined short term patient outcomes, and defined a critical threshold for adequacy of hemodialysis (HD) treatments, based on total dialysis urea clearance,[1] which was then normalized to body water as a sessional Kt/Vurea[2] and linked to time averaged urea concentration.[3,4] Further observational studies reported higher patient survival rates with a delivered sessional Kt/Vurea >1.0,[5,6] and by general agreement HD Kt/Vurea targets were increased to 1.2.[7] These studies led to a randomized prospective HD study[8] which reported that higher urea clearances did not beneficially improve patient survival. However, subsequent *post-hoc* analysis of the HD study showed an association between increasing serum beta-2 microglobulin concentrations, a marker of middle-sized azotemic toxins, and

Table 1 | Patient demographics comparing hemodialysis and online hemodiafiltration

Mode	HD	OI-HDF	OI-HDF	OI-HDF
OI-HDF dose		Lowest	Middle	Highest
Convection volume (l)	NA	18.0 (16.0–18.8)	21.0 (20.2–22.0)	25.7 (24.4–27.4)
Number	1393	433	447	435
Age (yr)	64.4 (14.8)	64.2 (14.3)	61.5 (14.8)	65.2 (13.7)
Female sex (%)	528 (38)	218 (50)	159 (36)	114 (26)
CVD (%)	499 (36)	157 (36)	130 (29)	168 (39)
Diabetes (%)	402 (29)	138 (32)	116 (26)	128 (29)
Dialysis vintage (mo)	34 (15–65)	32 (14–69)	33 (17–65)	29 (13–62)
Systolic BP (mmHg)	137.5 (22.8)	137.9 (21.4)	135.8 (21.1)	137.8 (23.4)
Diastolic BP (mmHg)	73.5 (13.6)	73.8 (11.8)	75.7 (13.1)	72.5 (13.9)
Vascular access, AVF	1175 (84)	368 (85)	397 (89)	372 (86)
Dialysis session duration (min)	233 (20)	226 (23)	234 (14)	240 (18)
Blood flow (ml/min)	335 (66)	304 (50)	334 (61)	387 (58)
Dialysis single-pool Kt/V	1.50 (0.30)	1.46 (0.28)	1.53 (0.29)	1.63 (0.32)
Hemoglobin (g/dl)	11.7 (1.6)	11.7 (1.5)	11.8 (1.4)	11.8 (1.5)
Beta-2 microglobulin (mg/l)	27.7 (11.9)	27.6 (11.7)	26.2 (9.7)	26.6 (12.2)
Albumin (g/dl)	3.98 (0.41)	3.89 (0.40)	3.99 (0.39)	4.10 (0.40)
Creatinine (mg/dl)	8.42 (2.63)	8.26 (2.47)	8.46 (2.44)	8.47 (2.53)
Body surface area (m^2)	1.77 (0.22)	1.72 (0.23)	1.77 (0.20)	1.80 (0.20)
BMI post dialysis (kg/m^2)	25.2 (4.6)	24.7 (5.0)	24.9 (4.6)	25.8 (4.8)
Weight (kg)	68.7 (15.4)	66.2 (14.6)	68.9 (13.7)	71.5 (14.5)
Total body water (l)	35.1 (6.5)	34.6 (6.7)	35.3 (6.2)	35.0 (6.2)

AVF, arteriovenous fistula; BMI, body mass index; BP, blood pressure; CVD, cardiovascular disease; HD, hemodialysis; NA, not applicable; OI-HDF, online hemodiafiltration. Pre-dialysis hemoglobin and biochemical variables. Results expressed as number, percentage (%), or mean (s.d.) or median (interquartile range). History of CVD and diabetes mellitus (diabetes).

mortality[9] supporting results from previous observational cohort studies.[10,11] The effect of removal of middle-sized uremic toxins was explored by the Membrane Permeability Outcome trial, which compared high flux and low flux dialyzers.[12] There was no benefit for high flux dialysis in the population as a whole, but there was an advantage for those patients with a serum albumin ≤40 g/l and for diabetic patients on *post-hoc* analysis.[12] More recently several trials of hemodiafiltration have been reported, with variable results.[13–15]

Dialysis dosing based on urea has been traditionally normalized to total body water used as surrogate of urea distribution volume.[2] However, as prospective studies comparing different dialysis doses based on urea kinetic modeling have failed to demonstrate any survival advantage,[8,9] there have been several concerns about scaling dialysis dose to total body water. First, this scaling parameter may lead to a lower delivered dose of dialysis to women by overestimating Kt/Vurea[16] and on the other hand, a greater dose to the morbidly obese.[17] Body water is typically calculated from anthropomorphic equations, but newer techniques using multifrequency bioimpedance[18] show that body water depends on body composition, as fat contains less water than muscle.[19] Second, urea kinetics do not reflect those of middle-sized uremic toxins. Third, urea generation adjusted to total body water does not account for differences in lean and fat mass metabolism,[20,21] or patient physical activity and metabolic rate,[22,23] and so, dialysis dose is not scaled to the metabolic rate.[24,25] Dialysis dose is traditionally measured as Kt/Vurea and adjusted to total body water, whereas other measurements, such as glomerular filtration rate and left ventricular mass are indexed to body surface area. We determined how the impact of different methods of standardizing individual patient OI-HDF convective dose impacted on overall patient survival and cardiovascular mortality compared with patients treated by conventional HD.

RESULTS

The mean patient age was 64 ± 15 years, 62% male, 29% diabetic, and 35% had a past history of cardiovascular disease. Patients had a median dialysis vintage of 33 (15–64) months, 85% was dialysed using an arteriovenous fistula, and mean treatment session time was 233 min. In the original reports, 597 of the 2793 (21.4%) patients were lost to follow-up. We were able to collect follow-up data on 2708 (97%) of the original patients. During a median follow-up of 2.5 years (1.9–3.0), 769 patients died, with 292 deaths from cardiovascular causes. We divided the OI-HDF cohort into three groups according to the volume of convective therapy delivered (Table 1).

Univariable analyses showed that those receiving the highest convective volume of OI-HDF had a statistically significantly lower risk of all-cause mortality as compared with HD, independent of method of standardization (Table 2). The multivariable model showed that all-cause mortality was reduced when convective dose was unstandardized or standardized to body surface area (BSA) and total body water (TBW); hazard ratio 0.65 (0.51–0.82), 0.68 (0.48–0.98), and 0.63 (0.44–0.91) for those receiving the higher convective clearances. Standardization by body weight or body mass index (BMI) gave no significant survival advantage (Figure 1).

Table 2 | Hazard ratio and 95% confidence intervals for all-cause mortality by delivered convection volume with standard hemodialysis as a reference using different methods to standardize convection volume to patient size

	Lower third	Middle third	Upper third
Method of standardization			
Unstandardized	0.90 (0.73; 1.12)	0.99 (0.81; 1.21)	0.66 (0.52; 0.83)
BSA-standardized	0.89 (0.72; 1.10)	0.92 (0.74; 1.13)	0.71 (0.57; 0.90)
BMI-standardized	0.93 (0.76; 1.15)	0.82 (0.67; 1.00)	0.76 (0.60; 0.96)
Weight-standardized	0.80 (0.64; 1.00)	0.92 (0.75; 1.13)	0.79 (0.64; 0.99)
TBW-standardized	1.00 (0.81; 1.22)	0.82 (0.67; 1.02)	0.71 (0.57; 0.89)

BMI, body mass index; BSA, body surface area; TBW, total body water.
Values are hazard ratios and 95% confidence intervals. Thresholds for the thirds were 19.55 and 23.07 for unstandardized; 19.14 and 23.10 for BSA-standardized, 19.49 and 24.10 for BMI-standardized, 19.66 and 25.51 for weight-standardized, and 19.26 and 23.70 for TBW-standardized convection volume. BSA was standardized per 1.73 m^2, BMI was standardized to 25 kg/m^2, weight was standardized to 70 kg, and TBW was standardized to 35 l.

Similarly for cardiovascular mortality, there was a survival advantage for the individuals receiving the highest convective volume compared with those patients treated by HD (Table 3). Standardizing for body size, the reduction in cardiovascular mortality risk was restricted to BSA and TBW. Adding in patient demographics, co-morbidity, and baseline biochemical variables, then the benefit for higher convective volumes reducing cardiovascular risk was again limited to BSA and TBW and not weight or BMI (Figure 2). Thus, aiming for a convective volume of >23.1 L per session for a patient with a BSA of 1.73 m^2 or an estimated total body water of 35 L (Table 2).

We analyzed the data comparing OL-HDF with both low flux and high flux HD (Supplementary Table S1 online). There was a survival advantage for the highest delivered OL-HDF volume group compared with high flux HD in the unstandardized, and TBW-standardized models. Compared with the low flux HD patients, higher convective OL-HDF patients were associated with a statistically significant reduction in all-cause mortality when standardized for weight and BSA.

In an analysis excluding individuals with renal transplantation during follow-up, we demonstrated that both all-cause mortality and cardiovascular mortality were significantly improved when convection volume was either unstandardized or standardized by BSA and TBW (Supplementary Table S2 online). We then analyzed whether the survival advantage was for both larger and smaller patients (Supplementary Table S3 online), as typically in clinical practice women and smaller men are prescribed less dialysis treatment. All-cause mortality was reduced in both

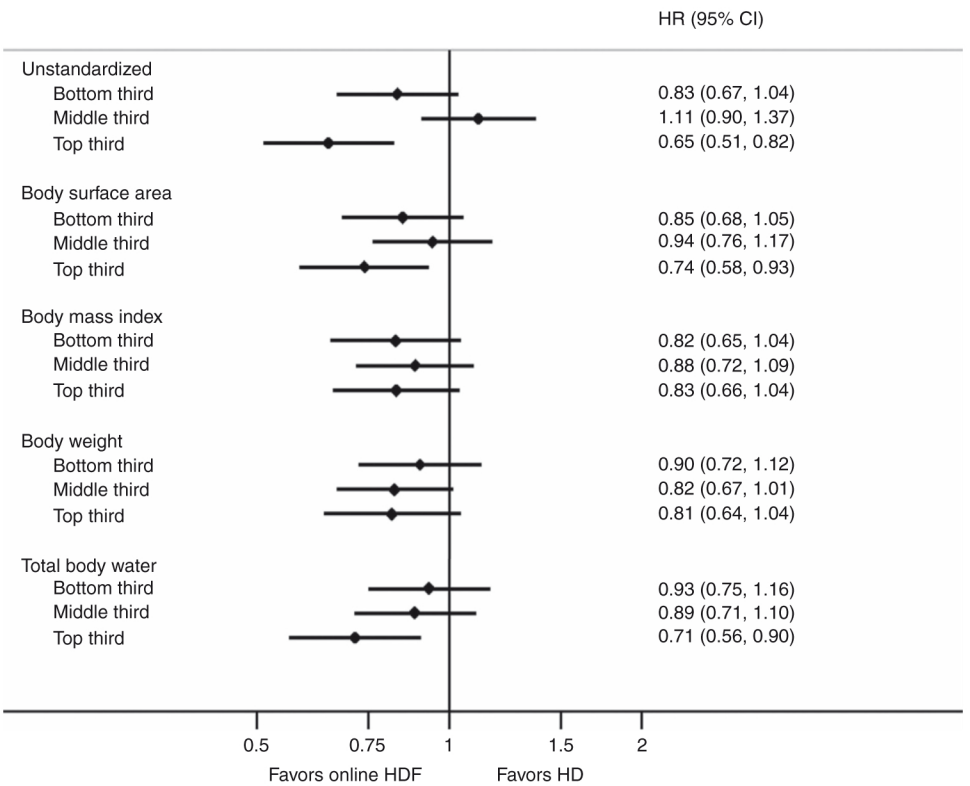

Figure 1 | Hazard ratios (HRs; boxes) and 95% confidence intervals (CIs; bars) for all-cause mortality in patients receiving online hemodiafiltration versus hemodialysis by convection volume, using different methods to standardize convection volume.

Table 3 | Hazard ratio and 95% confidence intervals for cardiovascular mortality by delivered convection volume with standard hemodialysis as a reference using different methods to standardize convection volume to patient size

	Lower third	Middle third	Upper third
Method of standardization			
Unstandardized	0.95 (0.68; 1.33)	0.79 (0.56; 1.12)	0.62 (0.43; 0.89)
BSA-standardized	0.95 (0.68; 1.32)	0.75 (0.53; 1.06)	0.68 (0.48; 0.98)
BMI-standardized	0.89 (0.63; 1.24)	0.71 (0.51; 0.99)	0.75 (0.52; 1.09)
Weight-standardized	0.77 (0.54; 1.11)	0.79 (0.57; 1.11)	0.79 (0.56; 1.11)
TBW-standardized	1.03 (0.75; 1.42)	0.70 (0.49; 1.00)	0.63 (0.44; 0.91)

BMI, body mass index; BSA, body surface area; TBW, total body water.
Values are hazard ratios and 95% confidence intervals. Thresholds for the thirds were 19.55 and 23.07 for unstandardized; 19.14 and 23.10 for BSA-standardized, 19.49 and 24.10 for BMI-standardized, 19.66 and 25.51 for weight-standardized, and 19.26 and 23.70 for TBW standardized convection volume. BSA was standardized per 1.73 m^2, BMI was standardized to 25 kg/m^2, weight was standardized to 70 kg, and TBW was standardized to 35 l.

smaller and larger patients who received the higher OL-HDF convective dose, apart from those patients with a small BSA.

DISCUSSION

Our analysis of the pooled data from the individual patients recruited into the four recent major prospective clinical trials comparing Ol-HDF with HD showed an association between higher convective doses and improved dialysis patient survival, in keeping with previous observational studies,[26] and also those that reported no survival benefit for lower volume hemodiafiltration treatments.[27]

Although greater convective volume exchange was associated with improved overall and cardiovascular survival, this policy is not practical in routine clinical practice, as individual patients vary widely in size, so an absolute target threshold volume would be difficult to achieve for all patients. We therefore standardized the convection volumes delivered to various anthropometric parameters, fitting better with patient metabolic characteristics, and also to exclude possible statistical confounding bias that larger patients have larger exchange volumes. Traditionally HD treatment adequacy is adjusted according to total body water,[2] although more recently it has been proposed to scale HD dosing to body surface area,[24] as surrogate of metabolic rate and metabolic rate according to organ mass.[22–24] We also scaled the convective dose to weight and BMI that are routinely available measurements. Whereas the suggested survival advantage for higher convective dose was maintained after standardizing

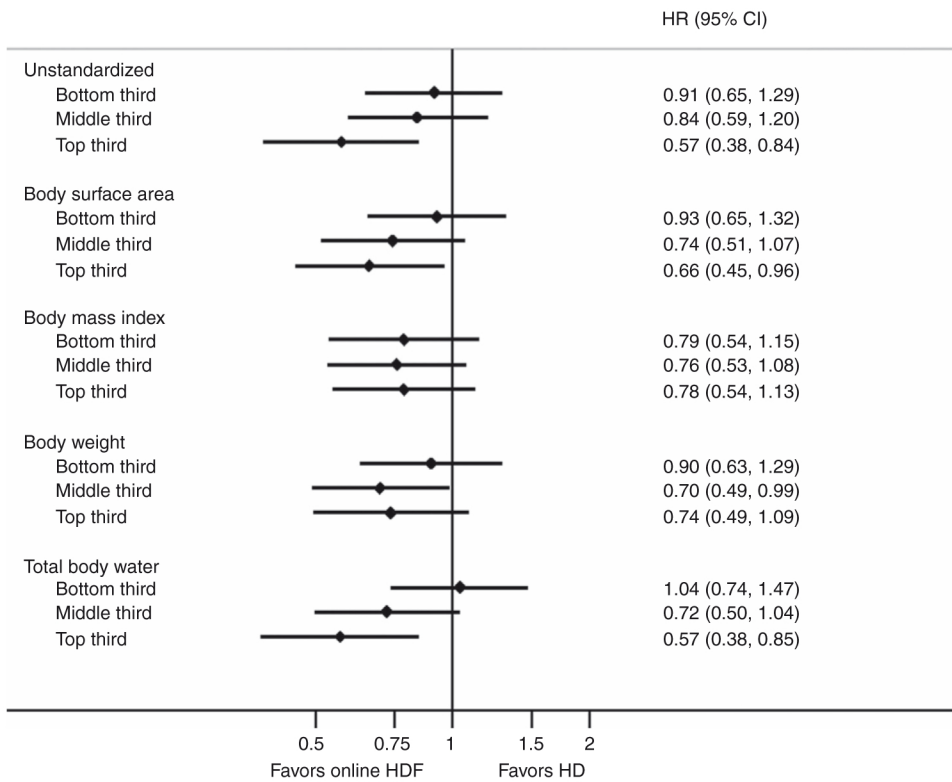

Figure 2 | Hazard ratios (HRs; boxes) and 95% confidence intervals (CI; bars) for cardiovascular mortality in patients receiving online hemodiafiltration versus hemodialysis by convection volume, using different methods to standardize convection volume.

patients for body surface area and total body water, there was no advantage when standardizing for weight or for BMI. This finding is in keeping with comparative studies from animal models matching metabolic rate and glomerular filtration rate.[22] The survival advantage associated with higher convective volume for patients standardized for body surface area and total body water remained after adjusting for age, sex, diabetes, cardiovascular mortality, baseline serum albumin, and creatinine. We also found that the survival advantage was maintained on subgroup analysis; for those who had received higher convective volume clearances with Ol-HDF compared with those treated by high flux HD, and also after excluding patients who were transplanted.

Chronic kidney disease is associated with protein energy wasting and, as such, body composition may differ from that of the general population,[28,29] with a greater proportional increase in body fat as weight increases.[30] As BMI disproportionally increased with abdominal girth and fat weight,[17] then standardization for body weight and BMI fail to take into account muscle mass, as increasing body weight and BMI are more associated with increasing body fat. Whereas body surface area and total body water, to a lesser extent, more closely reflect lean body mass in dialysis patients.[17] Dialysis patients are relatively sedentary, and greater muscle mass generally associates with greater physical activity and, as such, increased protein break down and metabolic rate.[31] Re-analysis of the HD study showed that patients with greater body surface area, and by analogy muscle mass,[32] benefited from a greater dose of dialysis when their dialysis prescription was adjusted for body surface area.[24,33] This would support our analysis that the associated survival advantage for higher convective doses are observed when the convective dose is adjusted according to body surface area or total body water, surrogate estimates of lean body mass, rather than body size estimates more related to fat mass.[34] This suggested effect on improving survival compared with HD was sustained after adjusting for age, sex, diabetes, cardiovascular co-morbidity, baseline serum albumin, and creatinine; all factors, which are recognized to be associated with changes in body composition.

Similarly when we looked at cardiovascular mortality, there was a reduction in risk of cardiac death for those patients receiving the highest tertile of convective exchange. To exclude confounding by larger patients having better survival and also receiving more convection, we again standardized convective dose to body size, this was statistically significant only when the convective volume was standardized for body surface area and total body water. Importantly the survival advantage for higher volume convective exchanges was sustained when comparing smaller and larger patients.

The suggested reduction in cardiovascular risk could be secondary to a reduction in hypotensive episodes during Ol-HDF treatments compared with HD,[35] but some of the benefit in reducing intra-dialytic hypotension may reflect increased thermal cooling with higher convective volume Ol-HDF.[36] However, greater convective volumes may also increase the removal of potential azotemic toxins.[37] In addition, there are potential differences in sodium balance between convective and diffusive techniques, although clinical studies have failed to demonstrate clinically significant differences in body water following Ol-HDF and HD treatments.[38,39]

There have been debates as how best to prescribe the dose of dialysis for patients with chronic kidney disease, as smaller patients require proportionally more dialysis than larger patients on a weight or BMI basis.[40] Some have argued that dialysis dosage should take into consideration metabolic rate,[21–23] which is related to physical activity and muscle mass as a source of protein-derived uremic toxins, whereas others have proposed that dialysis dosing should be adjusted to body surface area.[24] As body composition varies between individuals not only with age, sex, and co-morbidities,[41] but also particularly at the extremes of the normal range,[17] then future prospective studies are required to formally investigate the benefits of delivering a threshold dose of Ol-HDF in a wide range of patients, differing not only in age, sex, ethnicity, and diabetes, but also deliberately including patients of varying sizes. Although bioimpedance assessments are not infallible,[42] they could potentially help to determine body water and body composition and allow for future studies to determine an individualized target threshold.

In clinical practice, once Ol-HDF has been successfully established, then clinicians could steadily increase the convective dose to achieve a target threshold designed to improve patient survival. As body height and weight are readily available, then adjusting convective volumes for BSA would appear to be the more simple approach in clinical practice.[43] Adjusting the target for Ol-HDF treatments by BSA would then allow comparison between studies, and also allow future prospective studies to determine whether there is a critical threshold for improved patient survival.

The results of our analysis of the individual pooled data suggest an increased survival advantage for those patients receiving greater Ol-HDF convective dosing. To exclude confounding by patient size, we standardized the dose to body size, and this suggested that the survival advantage was greatest when adjusted for body surface area and total body water and, as such, more associated with lean body mass, whereas there was no advantage when patients were standardized for body weight or BMI, which are more associated with body fat mass.

MATERIALS AND METHODS

We undertook an analysis of individual patients data pooled from four systematically identified large multicenter randomized controlled trials that assessed the effects of online post-dilutional hemodiafiltration with standard HD on mortality in adult patients undergoing chronic HD. A detailed description of the study designs, patient eligibility criteria, and treatment procedures of each of the studies has been reported elsewhere.[13–15,25,44]

Body surface area was calculated using the equation of Gehan and George,[45] and total body water using the anthropomorphic derived equation of Watson *et al.*[46]

Study population

CONTRAST recruited 714 patients treated by HD for >2 months in dialysis centers in the Netherlands, Canada, and Norway comparing Ol-HDF and low flux HD.[13] Ol-HDF was targeted to a suggested convection volume of 6 l/h, averaging 21 l per session. ESHOL included 906 patients treated by HD for >3 months in Catalonia,[15] with a minimum of 18 l substitution fluid/session requested for Ol-HDF treatments. The French HDF study included 391 patients treated by HD for ≥1 month, with no specified convection volume target[25,44] (Supplementary Figure S1 online). The Turkish HDF study recruited 782 patients[14] with a minimum target of 15 l substitution fluid/session for Ol-HDF treatments. In all studies, patients were randomized to either continuing with high flux HD, apart from the CONTRAST study, or switching to Ol-HDF. The majority of patients dialysed with high flux dialyzers, but membrane composition varied between individual centers and was standardized. All patients in the original studies provided signed informed consent.

Study end point and follow-up

The primary outcome variables in the present analyses were all-cause mortality and cardiovascular mortality. Follow-up procedures differed between the four studies, and, as such, censoring of patients who discontinued randomized treatment could have introduced selection bias in the individual study analysis.[13–15,44] To improve study power and to reduce the potential effect of selection bias due to informative censoring, additional follow-up data on (time to) all-cause mortality and cardiovascular mortality was obtained for those patients who had discontinued randomized treatment and were considered alive in the previously published analyses.[13–15,44]

Statistical analysis

Hazard ratios and 95% confidence intervals comparing the effect of online HDF versus HD on the study end points in thirds of the actual (on-treatment) delivered convection volume were estimated using Cox proportional hazards models with a random effect for study. Five different methods of standardizing individual patient Ol-HDF convective dose were used, with method 1 not being standardized, and methods 2–5 being standardized by 1.73 m^2 body surface area, 25 kg/m^2 BMI, 70 kg body weight, and 35 l of total body water, respectively. Models were unadjusted or adjusted for the potential confounding effects of age, sex, baseline serum albumin, creatinine, history of diabetes, and history of cardiovascular disease. All analyses were performed using the statistical program R (version 2.15.3; https://www.r-project.org/) and a two-sided P-value of <0.05 conferred significance.

DISCLOSURE

MPCG research funded by Fresenius Medical Care, the Netherlands BV; lectures funded by Fresenius Medical Care BV, Sanofi-Aventis; travel refund/congress registration fees: Baxter. FL was the principal investigator of the "MPO" study and of the "Italian Convective trial". FM was the principal investigator of the "ESHOL" study. EO was the principal investigator of Turkish HDF Study; is a member of the scientific advisory committee of Fresenius Medical Care, Turkey. The remaining authors declared no competing interests.

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