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Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials

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ABSTRACT

Background. Mortality rates remain high for haemodialysis (HD) patients and simply increasing the HD dose to remove more small solutes does not improve survival. Online haemodiafiltration (HDF) provides additional clearance of larger toxins compared with standard HD. Randomized controlled trials (RCTs) comparing HDF with conventional HD on all-cause and cause-specific mortality in end-stage kidney disease (ESKD) patients reported inconsistent results and were at high risk of bias. We conducted a pooled individual participant data analysis of RCTs to provide the most reliable evidence to date on the effects of HDF on mortality outcomes in ESKD patients.

Methods. Individual participant data were used from four trials that compared online HDF with HD and were designed to examine the effects of HDF on mortality endpoints. Bias by

informative censoring of patients was resolved. Hazard ratios (HRs) and 95% confidence intervals (95% CI) comparing the effect of online HDF versus HD on all-cause and cause-specific mortality were calculated using the Cox proportional hazard regression models. The relationship between convection volume and the study outcomes was examined by delivered convection volume standardized to body surface area.

Results. After a median follow-up of 2.5 years (Q1–Q3: 1.9–3.0), 769 of the 2793 participants had died (292 cardiovascular deaths). Online HDF reduced the risk of all-cause mortality by 14% (95% CI: 1%; 25%) and cardiovascular mortality by 23% (95% CI: 3%; 39%). There was no evidence for a differential effect in subgroups. The largest survival benefit was for patients receiving the highest delivered convection volume [>23 L per 1.73 m² body surface area (BSA) per session], with a multivariable-adjusted HR of 0.78 (95% CI: 0.62; 0.98) for all-cause mortality and 0.69 (95% CI: 0.47; 1.00) for cardiovascular disease mortality.

Conclusions. This pooled individual participant analysis on the effects of online HDF compared with conventional HD indicates that online HDF reduces the risk of mortality in ESKD patients. This effect holds across a variety of important clinical subgroups of patients and is most pronounced for those receiving a higher convection volume normalized to BSA.

Keywords: clinical trial, epidemiology, ESKD, haemodiafiltration, haemodialysis

INTRODUCTION

Approximately 10% of the general population suffers from kidney damage, and a proportion will progress into end-stage kidney disease (ESKD). ESKD ranks among the most severe chronic non-communicable diseases [1]. Haemodialysis (HD) has become the standard renal replacement therapy for patients with ESKD, with >2 million patients now treated worldwide. The survival probability of patients with ESKD at 1, 2 and 5 years after diagnosis is around 81, 68 and 39%, respectively [2]. Five-year survival in the UK is just marginally above that for ovarian cancer, but markedly less than that for colon cancer, and much lower than that for acute myocardial infarction or stroke [3]. Therefore, there is an unmet and urgent medical need to improve the prognosis for ESKD patients.

Simply increasing urea clearance with standard HD has not been shown to improve survival [4], but secondary analyses suggested that survival depended on clearance of the so-called middle molecules [5]. Online haemodiafiltration (HDF) more effectively removes these larger middle molecules than HD [6]. Since 2012, several trials that compared HDF with standard HD have been conducted [7–10]. Two trials showed no statistical significant beneficial effect for HDF on mortality [7, 8], whereas one trial reported a reduction in all-cause mortality with an estimated relative risk reduction of 30% [9]. All trials did report in *post hoc* analyses that patients with the highest delivered convection volume had a considerably lower risk of all-cause mortality than those receiving HD. The cut point above which a lower relative risk was found varied between the trials (17, 23 and 22 L per session, respectively), as did the level of multivariable adjustment for potential confounders. In addition, the trials presented the convection volume in litres per session without taking body size into account. From a clinical perspective, a convection volume of 22 L per session is clearly different for a small individual of 50 kg than for tall, large patient of 100 kg, suggesting that adjusting for body size is required. Furthermore, trials were highly criticized for selection bias because of informative censoring of participants due to non-fatal events, such as renal transplantation, leading to a potential overestimation of the effect of HDF [11, 12]. Individual trials are usually not powered for subgroup analyses and analyses using published data on subgroups have substantial limitations because of the inability to systematically adjust for potential confounders. A pooled individual participant data (IPD) analytic approach is most suitable for assessing subgroup

effects with sufficient power and adequate adjustment for potential confounders [13].

To provide the most reliable evidence to date on the effects of online HDF when compared with standard HD on all-cause mortality and cause-specific mortality in ESKD patients, we conducted a pooled IPD analysis of recent trials that compared online HDF with HD and were designed to examine the effects of HDF on mortality endpoints, taking informative censoring and body size into account.

MATERIALS AND METHODS

Study design

A pooled IPD analysis was undertaken using data from systematically identified large multicentre randomized controlled trials (RCTs) that assessed the effects of online HDF versus HD on mortality endpoints in adult patients undergoing chronic HD [14]. To ensure adequate event follow-up and reasonable power for mortality endpoints, studies had to be designed to examine the effects of HDF on mortality endpoints. Moreover, since not all convective dialysis therapies are equal, we avoided making invalid comparisons by only considering RCTs that compared modern convective therapies, i.e. online HDF with HD [15].

Study populations

A detailed description of the study design, patient eligibility criteria and treatment procedures of each of the studies meeting the inclusion criteria has been provided elsewhere [7–9, 10]. CONTRAST included 714 patients treated by HD for >2 months in dialysis centres in the Netherlands, Canada and Norway [7]. Online HDF was performed with a suggested target convection volume of 6 L/h, i.e. generally 24 L/per session. ESHOL included 906 patients treated by HD for >3 months in Spain [9], with a minimum of 18 L/session of convection volume requested for online HDF treatments. The French HDF study included 391 patients treated by HD for at least 1 month, with no target online HDF convection volume specified (Supplementary data, Figure S1) [10]. The Turkish HDF study included 782 patients [8], with a minimum target of 15 L/session convection volume for online HDF treatments. In all studies, patients were 1:1 randomized to either continuation of HD or to switch to online HDF, generally in a thrice-weekly treatment schedule. In CONTRAST, patients in the control group were dialysed using low-flux membranes, and in the other three studies, high-flux membranes were used. The risk of bias was assessed using the Cochrane risk of bias tool (Supplementary data, Figure S2) [16].

Study endpoint and follow-up

The primary outcome was all-cause mortality. Secondary outcomes were mortality from cardiovascular causes, infections and sudden death. Follow-up procedures differed across studies. CONTRAST patients who discontinued randomized treatment due to renal transplantation, modality switch to peritoneal dialysis, moving to a non-participating centre or other reasons continued to be followed for the primary and

main secondary outcomes. However, mortality follow-up data were incomplete for 355 (39%) of patients in the ESHOL study, for 43 (11%) patients in the French HDF study and for 199 (25%) patients in the Turkish HDF study because they were censored as alive at the time they discontinued randomized treatment. Such censoring introduces selection bias if censoring is associated with the allocated treatment and the risk of outcome [12]. Thus, for the present study, additional follow-up data on all-cause mortality and cause-specific mortality (ESHOL and French HDF study only) were collected and obtained for 352 of the 355 (99%) ESHOL patients, 41 of the 43 (95%) French study patients and 148 of the 199 (74%) Turkish study patients who were censored as alive.

Statistical analysis

Hazard ratios (HRs) and 95% confidence intervals (95% CI) comparing the effect of online HDF versus HD on the study endpoints were estimated using the Cox proportional hazards models with a random effect for study. Further analyses were conducted on age (<65 versus ≥65 years), sex, history of diabetes, history of cardiovascular diseases (CVD), albumin levels (<4 versus ≥4 g/dL), dialysis vintage (<30 versus ≥30 months) and mode of vascular access (arteriovenous fistula versus other). The distribution of convection volume differed across studies because of differences in study methodology, clinical practice and patient characteristics. The dose–response association between online HDF and clinical outcomes was examined in thirds of the actual (on-treatment) delivered, 1.73 m² body surface area (BSA)-standardized, convection volume. BSA was estimated using the formula from Gehan and George as recommended by the European Best Practice Guidelines: $[BSA (m^2) = 0.0235 \times \text{baseline height (cm)}^{0.42246} \times \text{baseline weight (kg)}^{0.51456}]$. Standardization of delivered convection volume was done by dividing by patient BSA $[1.73 \times (\text{patient convection$

volume/patient BSA)]. The association between convection volume and mortality was additionally adjusted for age, sex, baseline serum albumin, creatinine, history of diabetes and history of CVD. Complete case analyses were conducted as a primary analysis. In a secondary analysis, incomplete (time to) event data ($n = 63$ for all-cause mortality and $n = 202$ for cause-specific mortality) were imputed using multiple imputation ($m = 10$) using multivariate imputation by chained equations (MICE). The imputation model included fixed effects for study, patient characteristics, clinical parameters, (time to) transplantation and (time to) event. All analyses were performed using R (version 2.15.3) and a two-sided P-value of <0.05 conferred significance.

RESULTS

Of the 2793 patients included, 38% were women. The mean age was 64 (standard deviation 15) years, 29% had diabetes mellitus and 35% a history of CVD. At the start of the study, patients had been established on dialysis for a median of 33 (Q1–Q3: 15–64) months and 85% had vascular access through an arteriovenous fistula (Table 1 and Supplementary data, Table S1).

Online HDF and all-cause and cause-specific mortality

During a median follow-up of 2.5 years (Q1–Q3: 1.9–3.0), 769 patients died, including 292 CVD deaths, 112 sudden deaths and 150 deaths from infections (Table 2 and Supplementary data, Table S2). Online HDF reduced the risk of all-cause mortality by 14% (95% CI: 1%; 25%), and reduced the risk of cardiovascular mortality by 23% (95% CI: 3%; 39%). The risk of sudden death or death from infections was not significantly different between the treatment arms. There was no evidence

Table 1. Baseline characteristics of study participants

	Overall	CONTRAST	ESHOL	French study	Turkish study
N (% HDF)	2793 (50)	714 (50)	906 (50)	391 (50)	782 (50)
Age (years)	64.1 (14.7)	64.1 (13.7)	65.4 (14.4)	76.2 (6.4)	56.5 (13.9)
Female sex	1045 (37)	269 (38)	300 (33)	154 (39)	322 (41)
History of CVD	989 (37)	313 (44)	298 (33)	196 (50)	182 (23)
Diabetes mellitus	814 (30)	170 (24)	226 (25)	146 (37)	272 (35)
Dialysis vintage (months)	33 (15–64)	24 (12–48)	28 (12–59)	38 (17–71)	50 (24–83)
Systolic BP (mmHg)	137.4 (22.4)	147.8 (21.6)	136.4 (23.9)	138.1 (22.8)	128.2 (16.0)
Diastolic BP (mmHg)	73.7 (13.3)	75.7 (12.2)	72.0 (15.1)	65.1 (14.6)	78.1 (8.2)
Vascular access, AVF (%)	2376 (85)	567 (79)	779 (86)	283 (72)	747 (96)
Duration of dialysis session (min)	233 (20)	226 (23)	235 (19)	236 (25)	237 (9)
Blood flow (mL/min)	337 (66)	301 (40)	386 (63)	336 (42)	294 (45)
Dialysis single-pool Kt/V	1.52 (0.31)	1.39 (0.22)	1.66 (0.31)	1.59 (0.34)	1.43 (0.27)
Haemoglobin (g/dL)	11.7 (1.6)	11.8 (1.3)	12.0 (1.4)	11.3 (2.4)	11.4 (1.5)
Phosphorus (mg/dL)	4.46 (1.53)	5.08 (1.53)	4.66 (1.47)	4.25 (1.63)	4.83 (1.46)
B-2-microglobulin (mg/L)	27.2 (11.6)	31.5 (14.0)	24.3 (9.7)	24.9 (10.2)	26.4 (8.7)
BMI after dialysis (kg/m ²)	25.2 (4.7)	25.4 (4.8)	24.9 (4.5)	26.3 (4.9)	24.9 (4.8)
Body surface area (m ²)	1.76 (0.22)	1.85 (0.21)	1.73 (0.19)	1.71 (0.32)	1.73 (0.18)
Albumin (g/dL)	3.98 (0.41)	4.04 (0.38)	4.09 (0.43)	3.90 (0.39)	3.84 (0.37)
C-reactive protein (mg/L)	3.48 (0.90–8.60)	3.93 (1.38–10.36)	6.30 (4.90–13.00)	5.00 (1.85–12.60)	0.87 (0.37–1.90)
Creatinine (mg/dL), pre-dialysis	8.39 (2.57)	9.74 (2.89)	8.02 (2.37)	7.41 (2.17)	8.05 (2.17)
Cholesterol (mmol/L)	4.11 (1.24)	3.68 (0.96)	NA	4.14 (1.63)	4.50 (1.09)

Values are n (%) for categorical variables, and mean (SD) or median (Q1–Q3) for continuous variables.

BP, blood pressure; AVF, arteriovenous fistula; BMI, body mass index.

Table 2. Risk ratio and HR and 95% CI of all-cause mortality and cause-specific mortality

Cause	HD			HDF			HR (95% CI) for HDF versus HD
	<i>n</i>	Events	Events/100 PY	<i>n</i>	Events	Events/100 PY	
All-causes	1369	410	12.10	1	359	10.45	0.86 (0.75; 0.99)
Cardiovascular disease	1302	164	4.84	1	128	3.73	0.77 (0.61; 0.97)
Infections	1302	77	2.27	1	73	2.13	0.94 (0.68; 1.30)
Sudden death	1302	56	1.65	1	56	1.63	0.99 (0.68; 1.43)

PY, person years.

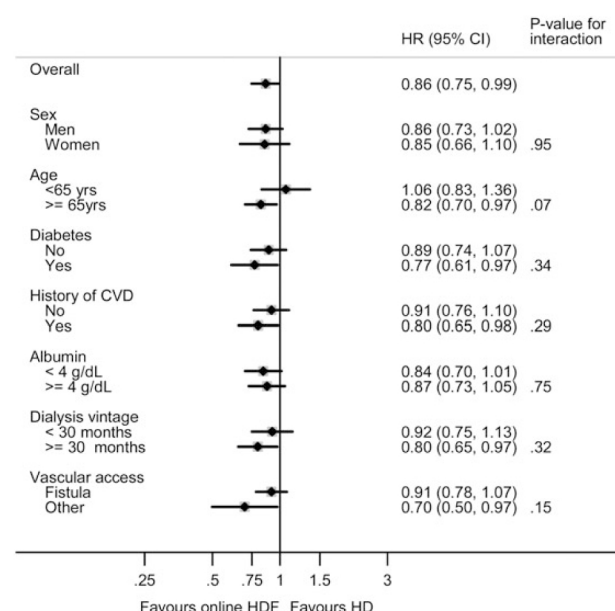


FIGURE 1: HRs (boxes) and 95% CI (bars) for all-cause mortality in patients receiving online HDF versus HD, overall and in subgroups.

for a differential effect of online HDF in any of the subgroups considered for any of the study endpoints (Figures 1 and 2, and Supplementary data, Figures S3 and S4). Trial-specific mortality findings before and after obtaining additional mortality follow-up indicate that censoring of patients who discontinued randomized treatment increased the magnitude (but not the direction) of the association between HDF and mortality (Supplementary data, Table S3). Analyses in which incomplete data on follow-up data were imputed did not materially alter the findings; the HRs (95% CI) comparing HDF with HD were 0.86 (0.75; 1.00) for all-cause mortality, 0.78 (0.62; 0.98) for cardiovascular mortality, 0.99 (0.69; 1.44) for sudden death and 0.96 (0.70; 1.31) for death from infections.

Convection volume and mortality outcomes

Patients with the highest delivered convection volume (>23 L per 1.73 m² BSA per session) had a considerably lower risk of all-cause mortality than those receiving HD [HR: 0.78 (95% CI: 0.62; 0.98)] (Table 3). Similarly, the risk of CVD mortality in patients with the highest delivered convection volume was 31% (95% CI: 0%; 53%) lower than in patients receiving HD. There were no statistically significant reductions in the risk of death from infections or sudden death associated with higher

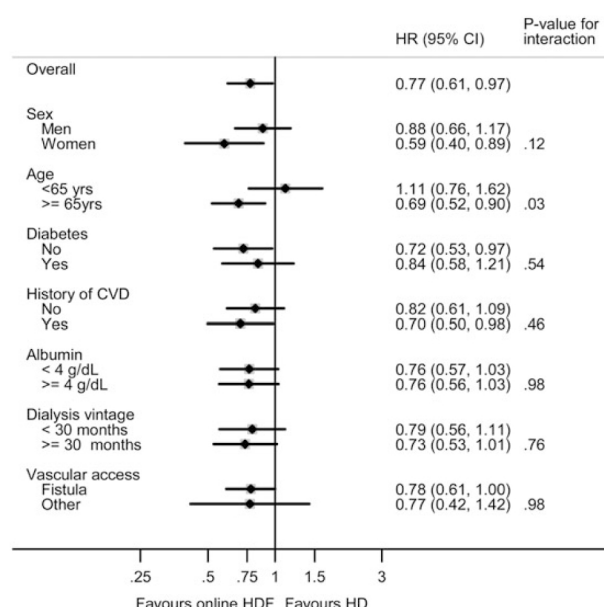


FIGURE 2: HRs (boxes) and 95% CI (bars) for cardiovascular mortality in patients receiving online HDF versus HD, overall and in subgroups.

Table 3. HR and 95% CIs for all-cause mortality and cause-specific mortality by delivered BSA-standardized convection volume in litres per 1.73 m² per treatment with standard HD as a reference

Cause	Online HDF: BSA-adjusted convection volume (L/session)		
	<19	19–23	>23
All-causes			
Unadjusted	0.91 (0.74; 1.13)	0.88 (0.72; 1.09)	0.73 (0.59; 0.91)
Adjusted	0.83 (0.66; 1.03)	0.93 (0.75; 1.16)	0.78 (0.62; 0.98)
Cardiovascular			
Unadjusted	1.00 (0.71; 1.40)	0.71 (0.50; 1.01)	0.69 (0.48; 0.98)
Adjusted	0.92 (0.65; 1.30)	0.71 (0.49; 1.03)	0.69 (0.47; 1.00)
Infections			
Unadjusted	1.50 (0.93; 2.41)	0.96 (0.56; 1.65)	0.56 (0.30; 1.08)
Adjusted	1.50 (0.92; 2.46)	0.97 (0.54; 1.74)	0.62 (0.32; 1.19)
Sudden death			
Unadjusted	1.24 (0.80; 1.91)	0.91 (0.57; 1.47)	0.60 (0.35; 1.03)
Adjusted	1.09 (0.69; 1.74)	1.04 (0.63; 1.70)	0.69 (0.39; 1.20)

Values are HRs and 95% CI.

Adjusted for age, sex, albumin, creatinine, history of cardiovascular diseases and history of diabetes.

convection volumes. Figure 3 enables estimation of the convection volume required for a patient with a given height and weight to achieve a 1.73 m² BSA-standardized sessional convection volume of 23 L.

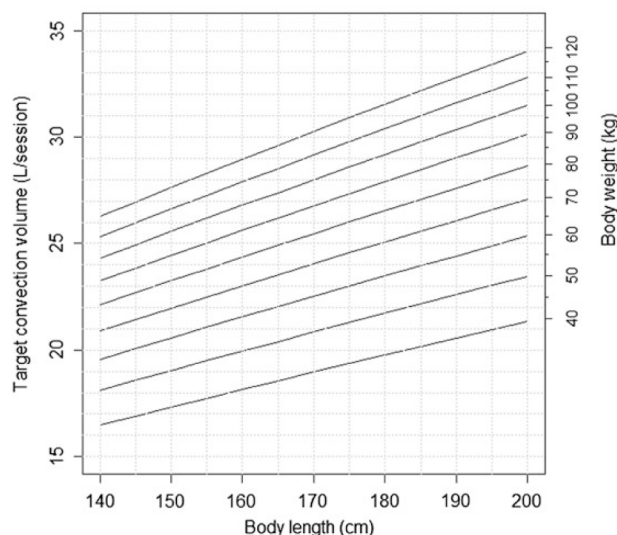


FIGURE 3: Convection volume per session needed for an individual patient to have a BSA-adjusted convection volume of at least 23 L or above, based on measurements of height and weight of the patient. The formula used was: Convection volume needed = $(23 \times \text{individual BSA}) / 1.73$. Here $\text{BSA (m}^2\text{)} = 0.0235 \times \text{height (cm)}^{0.42246} \times \text{weight(kg)}^{0.51456}$.

DISCUSSION

This pooled IPD analysis of RCTs showed that online HDF reduced the risk of all-cause mortality and cardiovascular mortality compared with HD in patients with ESKD requiring HD. There was no evidence to suggest that the beneficial effect of online HDF differed across patient subgroups. However, the survival benefit of online HDF seems to largely depend on the delivered convection volume per session, with patients achieving high volumes benefitting most.

What this study adds

A number of observational studies and RCTs have suggested that HDF is beneficial, but they were too small, prone to residual confounding and affected by selection bias [11, 14, 17]. Where analyses on published data of studies cannot address these issues adequately, we intentionally restricted our analyses to the studies included here for two main reasons. First, to ensure high quality of event adjudication, reasonable power for mortality endpoints and low risk of bias, studies had to be designed to examine the effect of online HDF on mortality endpoints. Secondly, not all convective dialysis therapies are equal [15], to avoid making invalid comparisons between different approaches to give convective treatment and to provide evidence on modern convective therapies, we did not include studies applying any convective therapy and only considered RCTs that compared online HDF with HD. Two trials meeting these inclusion criteria, however, were criticized for informative censoring bias [11, 12]. Selection bias due to informative censoring of patients who discontinued randomized treatment in these studies was eliminated by actively pursuing the vital status of those participants who were censored alive. This enabled us

to provide the most reliable evidence to date on the effects of online HDF when compared with standard HD on all-cause mortality and cause-specific mortality in ESKD patients. Furthermore, the present analysis was better powered than the individual trials to study whether, compared with HD, the effect of online HDF differed across certain patient populations. In this sufficiently powered IPD analysis, free from selection bias due to informative censoring, online HDF beneficially improves survival and reduces cardiovascular mortality consistently across a variety of important clinical subgroups of patients.

Importance of the dose of convection volume

Few studies have examined the association between delivered convection volume and mortality outcomes. The prospective cohort Dialysis Outcome Practice Patterns Study (DOPPS) reported that the mortality risk was 35% lower in European ESKD patients receiving a minimum of 15 L/session of replacement fluid (equalling ~17 L of convection volume) than in the control population receiving standard HD, even after adjustment for age, comorbidities, urea clearance and local practice patterns [18]. A second prospective observational study of >700 ESKD patients over 3 years period also suggested that high-volume HDF was associated with lower mortality risk [19]. The present combined analysis confirms this finding and suggests a substantial survival benefit when a convection volume of at least 23 L/session (BSA standardized) is delivered. Because almost all patients were treated in a thrice-weekly schedule, this dose equals at least 69 L/week. One possible criticism is that this dose and effect relation is in fact due to a selection bias, i.e. that high dose is only achievable in healthy patients, with low mortality risk. While extensive statistical adjustments did not materially alter the main findings, residual confounding may always remain, and only a new RCT targeting different convection volumes would in theory be required to definitively determine a dose–response effect.

In all studies included in this IPD, the convection volume delivered varied considerably (Supplementary data, Figure S5). The main determinants of delivered convection volume were session treatment time, blood flow rate through extracorporeal circuit and percentage of flow ultrafiltered [20, 21]. The CONTRAST investigators showed that centre practice patterns rather than patient-related factors determined the delivered convection volume [20, 21]. Indeed, in ESHOL dialysis, staff was specifically trained to achieve high convection volumes [9]. As the convection volumes in that study were much higher than in the others, it is tempting to speculate that this training increased the likelihood of obtaining higher volumes in clinical practice. These facts are confirmed in a recent study that involved 387 patients and showed that high-volume HDF (>21 L/session of substitution fluid) was routinely achieved in >80% of patients provided best practices were followed and appropriate dialysers used [22].

Safety

Safety of HDF is an obvious concern as large amounts of dialysate are infused directly into the patient. This makes assurance of chemical and microbiological quality of the infusate of utmost importance [6]. Previously, the CONTRAST

investigators reported that the production of infusate of sustained adequate microbiological quality is possible [23], and also that C-reactive protein and interleukin-6 levels were lower in the HDF group argues against HDF inducing a chronic inflammatory state [24]. Our IPD analysis of the four studies did not show any difference in mortality due to infectious complications.

Clinical relevance

Our IPD analysis is relevant to a broad spectrum of ESKD patients, health-care workers, regulatory and insurance bodies, and industry. Almost all patients in the present analysis were treated by the standard thrice-weekly schedule of 4 hourly sessions. Although European regulatory authorities have allowed online HDF to be used in clinical practice, it is not equally accepted elsewhere. At present, 18% (~70 000 patients) of all dialysis patients in Europe receive online HDF, whereas in Japan, it is ~8% (35 000 patients) and in the USA, virtually zero [25]. The results of our present analysis give further support to the notion that by applying online HDF, a superior treatment could be offered with no additional safety concerns.

Strengths and limitations

This is the largest IPD study on the effects of online HDF compared with conventional HD to date, addressing many of the biases in previous studies, and providing the most reliable evidence on the effects of online HDF on survival in patients with ESKD. Some limitations, however, need to be acknowledged. First, while all designed to assess the effect of online HDF on mortality endpoints, differences between trials in terms of study design and methodology, and inclusion and exclusion criteria of patients remain. We accounted for these differences in our statistical models, and conducted a wide range of subgroup analyses which illustrated that our findings were robust for factors that may modify the observed relationships. Second, the included trials were not designed to assess the impact of delivered convection volume with online HDF and mortality outcomes. The analyses on convection values should therefore be interpreted as an observational analysis in which residual confounding cannot be excluded. A new RCT targeting different convection volumes would be needed to definitively examine the dose–response effect shown in this study. Thirdly, the available studies recruited patients on a three-weekly 4 h treatment schedule, and the role of online HDF in more intensified regimens (i.e. daily, nocturnal, prolonged) is not established in long-term studies, although short-term results appear quite promising [26, 27]. Finally, our analysis is limited to adult patients. There are some studies reporting that daily online HDF may have significant beneficial effects on nutrition, anaemia and growth acceleration in children [28].

CONCLUSION

This large-scale IPD analysis on the effects of online HDF compared with conventional HD indicates that online HDF reduces the risk of mortality in ESKD patients, especially if applied sufficiently dosed (greater than ~23 L/session, i.e. greater than ~69

L/week). The precise mechanisms for this effect remain to be elucidated. A next study should address the hypothesis of whether online HDF, when consistently dosed as mentioned above, results in improvement in meaningful clinical endpoints (Supplementary data, Table S4). Such a study should also evaluate cost-effectiveness and domains of patient's well-being. Ideally, it should allow subgroup analyses to establish whether certain patient groups are especially likely to benefit. In the absence of such a trial, our analysis based on individual patient data provides the best level of evidence to date for the superiority of online HDF as the treatment of choice for ESKD patients.

CONFLICT OF INTEREST STATEMENT

None declared.

(See related article by Daugirdas. Lower cardiovascular mortality with high-volume hemodiafiltration: a cool effect? *Nephrol Dial Transplant* 2016; 31: 853–856)

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