Haemodiafiltration versus haemodialysis for kidney failure: an individual patient data meta-analysis of randomised controlled trials

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Summary

Background High-dose haemodiafiltration has been shown, in a randomised clinical trial, to result in a 23% lower risk of mortality for patients with kidney failure when compared with conventional high-flux haemodialysis. Nevertheless, whether treatment effects differ across subgroups, whether a dose–response relationship with convection volume exists, and the effects on cause-specific mortality remain unclear. The aim of this individual patient data meta-analysis was to compare the effects of haemodiafiltration and standard haemodialysis on all-cause and cause-specific mortality.

Methods On July 17, 2024, we searched MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials for randomised controlled trials, published from database inception, comparing online haemodiafiltration versus haemodialysis designed to measure mortality outcomes. The primary outcome was all-cause mortality. Hazard ratios were generated using Cox proportional hazards regression models reporting hazard ratios and 95% CIs. Subgroup analyses based on predefined patient characteristics and dose–response analyses using natural splines for convection volume were performed. This analysis is registered with PROSPERO (CRD42024511514).

Findings Five trials (n=4153 patients; 2070 receiving haemodialysis and 2083 receiving haemodiafiltration) were eligible for inclusion in this analysis. After a median follow-up of 30 months (IQR 24–36), all-cause mortality occurred in 477 patients (23·3%) treated with haemodiafiltration compared with in 559 patients (27·0%) treated with haemodialysis (hazard ratio 0·84 [95% CI 0·74–0·95]). No evidence of a differential effect across subgroups was noted. A graded relationship between convection volume and mortality risk was apparent: as the volume increased, the mortality risk decreased.

Interpretation Compared with haemodialysis, online haemodiafiltration reduces all-cause mortality in people with kidney failure. Results do not differ across patient and treatment characteristics and the risk reduction appears to be dose-dependent. In conclusion, the present analysis strengthens the notion that haemodiafiltration can be considered as a superior alternative to the present standard (ie, haemodialysis).

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Introduction

Kidney failure is associated with a mortality rate of around 50% within 5 years of the first need for dialysis.[1,2] Convection-based haemodialysis treatments that remove a greater spectrum of uraemic molecules than diffusive therapy might lead to an improvement in survival estimates. The 2015 guidelines from the Kidney Disease Outcomes Quality Initiative concluded that the methodological limitations of existing clinical trials prevented the drawing of conclusions about whether haemodiafiltration for patients with kidney failure should be recommended instead of haemodialysis.[3] In a previous individual patient data meta-analysis, published in 2016, online haemodiafiltration, specifically for patients receiving high-dose convection volumes (ie, a convection volume of ≥23 L per dialysis session), was shown to lower all-cause, cardiovascular, and infection-related mortality.[4] These findings constituted the rationale for a randomised controlled trial, CONVINCE,[5] which reported, in 2023, a significant reduction of 23% in all-cause mortality in patients with kidney failure treated with high-dose (≥23 L convection volume) haemodiafiltration compared with those treated with conventional high-flux haemodialysis.[6] Although CONVINCE provided robust evidence of the mortality benefit of high-dose hemodiafiltration over conventional high-flux haemodialysis, the decision of how those results should affect everyday clinical practice is up to the nephrology community and to health-care authorities.[7–12] However, addressing some outstanding questions could facilitate this process.

First, whether any patient subgroups (eg, specific age groups, those with diabetes, or those with previous cardiovascular disease) are especially likely to benefit from haemodiafiltration remains unclear. An individual trial

Research in context

Evidence before this study

Haemodialysis for kidney failure is associated with a mortality rate of approximately 50% at 5 years. Previous evidence on clinical outcomes from haemodiafiltration compared with haemodialysis reported divergent results on all-cause mortality, and only limited conclusions could be drawn on subgroup effects or dose–response relationships. In 2023, the CONVINCE trial reported a reduction in all-cause mortality in favour of high-dose haemodiafiltration, raising questions around implications for clinical practice, but clinical implementation should not be viewed based on the results of a single trial, and rather on all available evidence.

Added value of this study

This collaborative individual patient data meta-analysis of five large randomised controlled trials, including more than 4000 patients, showed that online haemodiafiltration, compared with conventional haemodialysis, reduces all-cause mortality and cardiovascular mortality, in particular cardiac mortality. This effect does not change with patient or treatment characteristics. A graded relationship between achieved haemodiafiltration convection volume and mortality risk was apparent: the higher the convection volume, the greater the benefit.

Implications of all the available evidence

Online haemodiafiltration reduces the risk of all-cause mortality, cardiovascular mortality, and cardiac mortality. When updated evidence on cost-effectiveness and on patient-reported outcomes is added to this information, it then proves a solid basis for recommendations for a change in clinical practice.

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See **Online** for appendix

might be insufficiently powered for subgroup analyses, and so might potentially be at risk of spurious or chance findings.[13,14] Second, the CONVINCE trial was powered to address all-cause mortality as a primary outcome, but did not have the sample size to formulate reliable conclusions on cause-specific mortality outcomes. CONVINCE diverged from other trials[4] by showing no evidence of a reduction in cardiovascular mortality with haemodiafiltration.[6] By considering all available evidence, differences in cause-specific mortality between haemodiafiltration and haemodialysis can be ascertained. Third, present evidence suggests that a minimum of 23 L per session convection volume is necessary for the beneficial effects of haemodiafiltration to be obtained.[4] However, emphasising that this threshold of 23 L per session represents a statistical stratification (ie, grouping into tertiles) of convection volume is important.[4] The actual delivered convection volume in previous trials varies considerably from the delivered convection volumes in clinical practice.[6,15–18] Therefore, to better understand the relationship between convection volumes and outcomes would be relevant.

The aim of this individual patient data meta-analysis is to present an overview of the existing evidence from randomised controlled trials comparing haemodiafiltration versus haemodialysis that were designed to assess all-cause mortality in patients with kidney failure. We aimed to provide more precise estimates of the effects of haemodiafiltration compared with haemodialysis across various subgroups, to assess cause-specific mortality, and to provide insight into the continuous relationship between achieved convection volume and mortality risks.

Methods

Search strategy and selection criteria

This study is registered at PROSPERO (CRD42024511514) and reported according to the PRISMA individual participant data statement (appendix pp 1–3).[19] We conducted searches of MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials from database inception to July 17, 2024 (appendix pp 4–5), drawing on the search terms used in a previous Cochrane review including haemodiafiltration, haemodialysis, and kidney failure.[20] No restrictions on publication date or languages were applied. Randomised controlled trials were eligible for inclusion if they compared online haemodiafiltration versus both low-flux and high-flux haemodialysis for the treatment of kidney failure in adults (ie, those aged 18 years and older). We included trials if they were powered to measure all-cause mortality after a follow-up of at least 1 year and when the principal investigator provided individual patient data for baseline characteristics, procedural, and outcome data. Reasons for exclusion after full-text review are provided in the appendix (pp 6–11).

Data analysis

RWMV screened the title, abstracts, and keywords of all retrieved records with support. Full-text articles were then reviewed for eligibility. Disagreements were reconciled by consensus mediated by another author (MLB). Previous meta-analyses and reference lists of included studies were checked for studies meeting the eligibility criteria. Data were scrutinised for accuracy before and after being combined in a single database. Risk of bias in included trials was assessed by RWMV (and MLB) according to the Cochrane risk of bias tool.[21]

The primary outcome for this meta-analysis, assessed in the intention-to-treat population, was all-cause mortality. Secondary outcomes were cardiovascular mortality, infection-related mortality including COVID-19, infection-related mortality excluding COVID-19, sudden death, and transplantation rate. We further stratified cardiovascular mortality as cardiac mortality (ie, myocardial infarction,

coronary revascularisation, unstable angina, and sudden death); non-cardiac mortality (ie, non-haemorrhagic stroke, peripheral arterial disease, and peripheral arterial revascularisation); and unclassified cardiovascular mortality. Subgroup differences were evaluated on the basis of the interaction test. Prespecified subgroups included age (<65 years *vs* ≥65 years), sex (male *vs* female), history of diabetes (yes *vs* no), history of cardiovascular disease (yes *vs* no), duration of dialysis treatment (<30 months *vs* ≥30 months), mode of vascular access (arteriovenous fistula *vs* other), and achieved convention volume (<19 L per session, 19–23 L per session, or >23 L per session). We did not conduct subgroup analysis by race or ethnicity because not all included studies collected race or ethnicity data.

We synthesised the data according to Cochrane methods for individual patient data meta-analyses,[22] and calculated hazard ratios (HRs) and 95% CIs to compare the effect of online haemodiafiltration versus haemodialysis on mortality outcomes by means of a random effects Cox proportional hazards model with a random effect for study. We prespecified a dose–response analysis to examine the relationship between achieved convection volume and all-cause mortality using a Cox proportional hazards model. We further explored non-linear associations by fitting models with natural splines of convection volume, using different degrees of freedom (maximum n=10). Model comparison was performed using the Akaike Information Criterion, which enabled identification of the optimal model fit by balancing goodness-of-fit and simplicity. An overview of this model comparison is given in the appendix (p 12).

A complete-case approach was used for all analyses, but some trials were missing data for several baseline variables. As previously reported,[4] follow-up procedures differed across studies, which led to incomplete all-cause mortality follow-up data for 355 (39%) of 906 patients in the ESHOL study,[18] 43 (11%) of 381 patients in the French haemodiafiltration study,[15] and 199 (25%) of 782 patients in the Turkish haemodiafiltration study,[17] because these patients were censored alive at the time they discontinued randomised treatment. Additional follow-up data on all-cause mortality (all trials) and cause-specific mortality (ESHOL and French haemodiafiltration studies only) were obtained for 352 (99%) of the 355 ESHOL patients, 41 (95%) of the 43 French study patients, and 148 (74%) of the 199 Turkish study patients who had been censored alive. This additional data collection has led to additional data from 10 patients in the French haemodiafiltration study (n=391) being reported here, but not in the original publication.[15] The other two studies, (CONTRAST[16] and CONVINCE[6]) had no missing outcome data. The total incomplete (time to) event data was n=63 for all-cause mortality and n=202 for cause-specific mortality. Missing information (ie, variables and outcome) was imputed using multiple imputation (m=10) with multivariate imputation by chained equations (appendix pp 13–14). The imputation model included fixed effects for study, patient characteristics, clinical parameters, (time to) kidney transplantation, and (time to) event. Finally, a Fine–Gray competing risk survival model was used to investigate the influence of covariates on the risk of mortality, considering kidney transplantation as a competing risk. All analyses were performed using R (version 2.15.3).

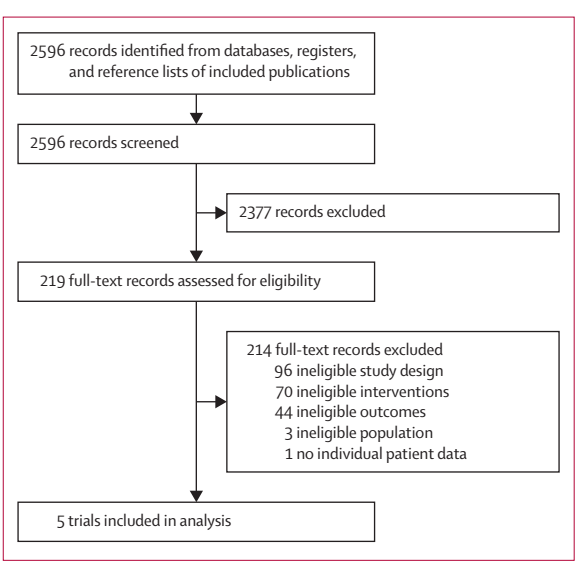

Figure 1: **Study selection diagram**

Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The search identified 2596 records, of which five randomised controlled trials including 4153 patients were eligible and whose principal investigators provided individual patient data (figure 1). The reasons for exclusion of the records screened in the full-text review are provided in the appendix (pp 4–5). A detailed description of the study design, patient eligibility criteria, and treatment procedures of each of the individual studies meeting the inclusion criteria has been provided elsewhere.[6,15–18] In brief, CONTRAST[16] included 714 patients treated with haemodialysis for at least 2 months, in dialysis centres in the Netherlands, Canada, and Norway, before randomisation. Online haemodiafiltration was performed with a suggested target convection volume of 24 L per session. ESHOL[18] included 906 patients treated with high-flux haemodialysis for longer than 3 months in Spain, with a minimum of 18 L per session of convection volume requested for online haemodiafiltration treatments. The Turkish haemodiafiltration study[17] included 782 patients, with a minimum target of 15 L per session convection volume for online haemodiafiltration treatments

	CONTRAST (n=714)	CONVINCE (n=1360)	ESHOL (n=906)	French study (n=391)	Turkish study (n=782)
Number of patients treated with haemodiafiltration	358 (50·1%)	683 (50·2%)	456 (50·3%)	195 (49·9%)	391 (50·0%)
Number of patients treated with haemodialysis	356 (49·9%)	677 (49·8%)	450 (49·7%)	196 (50·1%)	391 (50·0%)
Age, years	66·8 (54·9–74·8)	64·0 (54·0–72·0)	68·0 (56·0–77·0)	76·2 (71·2–81·1)	58·1 (48·1–67·1)
Female	269 (37·7%)	504 (37·1%)	300 (33·1%)	154 (39·4%)	322 (41·2%)
Male	445 (62·3%)	856 (62·9%)	606 (66·9%)	237 (60·6%)	460 (58·8%)
History of cardiovascular disease	313 (43·8%)	612 (45·0%)	298 (32·9%)	196 (50·1%)	182 (23·3%)
Diabetes	170 (23·8%)	481 (35·4%)	226 (24·9%)	146 (37·3%)	272 (34·8%)
Dialysis vintage, months	24·0 (12·0–48·0)	32·6 (15·1–71·6)	28·0 (12·0–59·0)	37·7 (17·0–70·6)	49·7 (24·3–83·2)
Systolic blood pressure, mm Hg	147·8 (21·6)	141·4 (22·1)	136·4 (23·9)	138·1 (22·8)	128·2 (16·0)
Diastolic blood pressure, mm Hg	75·7 (12·2)	72·7 (14·7)	72·0 (15·1)	65·1 (14·6)	78·1 (8·2)
Vascular access, arteriovenous fistula	567 (79·4%)	1115 (82·0%)	779 (86·0%)	283 (72·4%)	747 (95·5%)
Duration of dialysis session, min	240·0 (210·0–240·0)	240·0 (240·0–246·0)	240·0 (235·0–240·0)	240·0 (240·0–240·0)	239·8 (234·5–240·0)
Blood flow, mL per min	300·0 (280·0–325·0)	360·0 (350·0–400·0)	380·0 (350·0–400·0)	338·0 (300·0–358·0)	290·0 (266·7–319·1)
Dialysis single-pool, Kt/V	1·39 (0·22)	1·64 (0·31)	1·66 (0·31)	1·59 (0·34)	1·43 (0·27)
Haemoglobin, g/dL	11·80 (1·25)	11·28 (1·21)	11·98 (1·43)	11·61 (1·30)	11·43 (1·49)
Phosphorus, mg/dL	5·08 (1·53)	4·92 (1·47)	4·66 (1·47)	4·46 (1·36)	4·83 (1·46)
B-2 microglobulin, mg/L	31·78 (14·69)	..	24·26 (9·67)	26·99 (7·38)	26·36 (8·72)
BMI after dialysis, kg/m²	25·39 (4·80)	27·41 (5·65)	24·95 (4·53)	26·29 (4·89)	24·91 (4·76)
Body surface area, m²	1·85 (0·21)	1·86 (0·22)	1·73 (0·19)	1·76 (0·19)	1·74 (0·18)
Albumin, g/dL	4·04 (0·38)	..	4·09 (0·43)	3·90 (0·39)	3·84 (0·37)
C-reactive protein, mg/L	3·93 (1·38–10·36)	4·5 (2·0–10·4)	6·30 (4·90–13·00)	5·00 (1·85–12·60)	0·87 (0·37–1·90)
Pre-dialysis creatinine, mg/dL	9·74 (2·89)	8·36 (2·31)	8·02 (2·37)	7·64 (1·75)	8·05 (2·17)
Cholesterol, mmol/L	3·68 (0·96)	..	..	4·14 (1·63)	4·50 (1·09)
Convection volume, L per session*	19·8 (17·2–23·0)	24·9 (23·5–27·0)	24·2 (22·3–26·0)	19·9 (16·8–24·0)	19·6 (18·7–20·6)

Data are n (%), median (IQR), or mean (SD). *Only for patients receiving haemodiafiltration.

Table 1: **Baseline characteristics of study participants**

	Haemodialysis			Haemodiafiltration			Hazard ratio (95% CI) for haemodiafiltration *vs* haemodialysis
	n	Events	Events per 100 person-years	n	Events	Events per 100 person-years	
All-cause mortality (primary outcome)	2046	559	11·18	2050	477	9·37	0·84 (0·74–0·95)
Cardiovascular mortality	1979	202	4·04	1972	160	3·14	0·78 (0·64–0·96)
Cardiac causes	1979	117	2·34	1972	80	1·57	0·67 (0·50–0·89)
Non-cardiac causes	1979	32	0·64	1972	39	0·77	1·20 (0·75–1·91)
Unclassified	1979	53	1·06	1972	41	0·83	0·78 (0·52–1·17)
Infection-related mortality, including COVID-19	1677	118	2·36	1691	96	1·89	0·80 (0·61–1·04)
Infection-related mortality, excluding COVID-19	1677	97	1·94	1691	81	1·59	0·82 (0·61–1·10)
Sudden death	1979	98	1·96	1972	84	1·65	0·84 (0·63–1·12)
Transplantation	2070	162	2·80	2083	193	2·98	1·14 (0·92–1·41)

Table 2: **Primary and secondary outcomes**

compared with high-flux haemodialysis. The French haemodiafiltration study[15] included 391 patients treated by high-flux haemodialysis for at least 1 month, with no target online haemodiafiltration convection volume specified. CONVINCE included 1360 patients from eight European countries treated with high-flux haemodialysis, and considered high-dose haemodiafiltration as having at least 23 L per session convection volume.[6]

The characteristics of the 4153 patients (2070 patients treated with haemodialysis and 2083 patients treated with haemodiafiltration) are shown in table 1. The median age of included patients was 65·5 years (IQR 54·2–74·8). 1549 (37·3%) patients were female, 1295 (31·5%) had diabetes, and 1601 (39·5%) had a history of cardiovascular disease. Patients had a dialysis vintage of 33·0 months (IQR 14·9–66·0), and

3491 (84·1%) patients had an arteriovenous fistula for vascular access. The median achieved convection volume for patients receiving haemodiafiltration was 23·0 (interquartile interval 19·8–25·6). The risk of bias of the included studies was generally low (appendix pp 15–16). All studies were open-label and participants, personnel, and assessors were not masked to treatment allocation. Two studies initially had a high risk of attrition bias due to a high number of patients discontinuing the study during follow-up,[17,18] but due to the additional data collection efforts this risk decreased.[4]

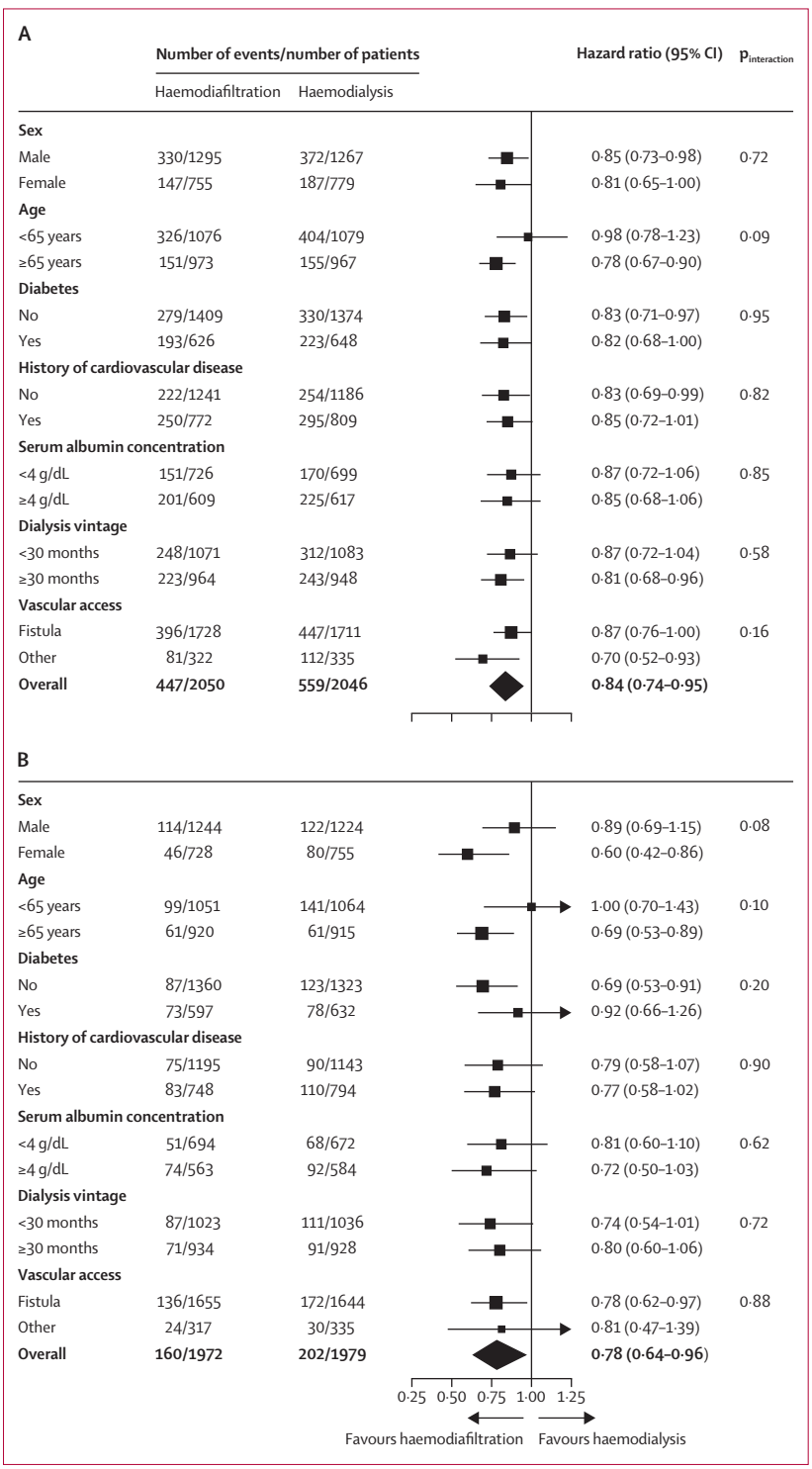

Figure 2: **All-cause mortality (A) and cardiovascular mortality (B) in patients treated with online haemodiafiltration versus haemodialysis**

Over a median follow-up of 30 months (IQR 24–36), all-cause mortality occurred in 477 (23·3%) of 2050 patients in the haemodiafiltration group (9·37 events per 100 patient-years) and in 559 (27·3%) of 2046 patients in the haemodialysis group (11·18 events per 100 patient years; HR 0·84 [95% CI 0·74–0·95]; table 2). Significant between-study heterogeneity (p<0·0001) was found for all-cause mortality. No evidence that treatment effects differed by participant subgroups was noted (figure 2).

362 deaths were attributed to cardiovascular disease, which occurred in 160 (8·1%) of 2083 patients in the haemodiafiltration group and in 202 (9·8%) of 2070 patients in the haemodialysis group (HR 0·78 [95% CI 0·64–0·96]; table 2). Significant between-study heterogeneity was found for cardiovascular mortality. This reduction in the risk of cardiovascular mortality was primarily driven by a reduction in death due to cardiac causes, a reduction that was not observed for non-cardiac causes (table 2). No evidence that treatment effects on mortality from cardiovascular causes differed by participant subgroups was noted (figure 2).

The results for all outcomes (table 2) based on the imputed dataset or competing risk analyses did not differ from the primary analyses (appendix pp 15–16).

In the multivariable-adjusted analyses, when analyses were restricted to patients whose treatment sessions achieved convection volumes greater than 23 L compared with those in the haemodialysis group, the adjusted HR for all-cause mortality was 0·63 (95% CI 0·50–0·79; table 3). Similarly, the risk of cardiovascular mortality in patients with the highest delivered convection volume was lower than in patients receiving haemodialysis. The risk of infection-related mortality was lower for patients receiving haemodiafiltration than for patients receiving haemodialysis.

Using achieved convection volume as a continuous measure, an association between convection volume and all-cause mortality risk was observed for patients assigned to haemodiafiltration (the higher the haemodiafiltration dose, the greater the benefit; figure 3).

Discussion

This analysis provides compelling evidence that treatment with high-dose haemodiafiltration, as compared with conventional haemodialysis, reduces the risk of all-cause mortality and cardiovascular mortality in patients with kidney failure. The numbers needed to treat to prevent one event were 26 patients for all-cause mortality, and 48 patients for cardiovascular mortality. The beneficial effect of haemodiafiltration was not

dependent on patient subgroups defined by single patient characteristics. The risk of mortality was especially reduced when high convection volumes were delivered. Finally, the nature of the relationship between convection volume and outcome appears to be dose-dependent (ie, the higher the convection volume, the greater the benefit).

We had the unique opportunity to combine the individual data of all published eligible trials that aimed (and were sufficiently powered) to address all-cause mortality, and additional efforts were made to obtain additional follow-up data to limit potential bias due to censoring of live patients. Considering the available evidence, this meta-analysis shows that haemodiafiltration, compared with haemodialysis, reduces the risk of all-cause and cardiovascular mortality, which expands the results of recent systematic reviews based on published aggregated data.[23–26] Two of these reviews[23,24] suggest that further increasing the sample size of future randomised controlled trials is unlikely to change these conclusions. Individual patient data meta-analyses allow more powerful and uniformly consistent analyses (as well as better characterisation of subgroups and outcomes) than meta-analysis based on aggregate data extracted from published trial reports.[27] No specific subgroups that were especially likely to benefit could be identified from univariate subgroup analyses, which is consistent with previous reports. Nevertheless, in clinical practice, individual patients are likely to have unique characteristics, including comorbidities; therefore, individualised treatment effect prediction provides a new and comprehensive approach to assess the presence of heterogeneity in treatment effects taking multiple characteristics into account.[28]

The present individual patient data meta-analysis suggests that the beneficial effects on all-cause and cardiovascular mortality (specifically cardiac mortality) are especially evident when higher convection volumes are delivered. Of note, causes of mortality are reported by physicians and independent adjudication was not performed in all trials. Establishing a single cause of mortality in a patient receiving haemodialysis can be challenging, if not unrealistic. However, a treatment benefit on cardiac mortality aligns with established concepts of how the mechanisms driving the beneficial effects of haemodiafiltration are multifaceted.[29] The signal that infection-related mortality is reduced when high convection volumes are delivered should be interpreted as hypothesis-generating. Reducing uremic toxins or increasing clearance of inflammatory cytokines might help to reduce the immune dysregulation associated with chronic kidney disease.

Finally, we assessed the nature of the relationship between convection volume (dose of the treatment) and all-cause mortality. Our analyses showed that two splines explained this relationship, showing a dose-dependent relation within the investigated dose range. The studied dose range reflects what is generally achievable in daily clinical practice in Europe for post-dilution haemodiafiltration. Practices can vary in other regions, where adjustments based on body size (ie, anthropometric characteristics) might be advised.[30] Predilution modality, which is common in Asian countries, typically delivers a convection volume at twice the volume commonly used in post-dilution haemodiafiltration in post-dilution mode to achieve similar solute clearances. In a previous study, we have

	Standard haemodialysis n=2070	Haemodiafiltration convection volume, L per session		
		<19 (n=370)	19–23 (n=641)	>23 (n=959)
All-cause mortality				
Unadjusted	Reference	0·92 (0·74–1·15)	0·93 (0·78–1·11)	0·70 (0·59–0·83)
Adjusted*	Reference	0·85 (0·67–1·08)	1·06 (0·87–1·29)	0·63 (0·50–0·79)
Cardiovascular mortality				
Unadjusted	Reference	0·98 (0·68–1·41)	0·76 (0·56–1·04)	0·74 (0·55–0·98)
Adjusted*	Reference	0·99 (0·68–1·44)	0·84 (0·60–1·16)	0·58 (0·40–0·85)
Cardiac cardiovascular death				
Unadjusted	Reference	0·71 (0·39–1·28)	0·58 (0·37–0·92)	0·74 (0·52–1·06)
Adjusted*	Reference	0·75 (0·41–1·37)	0·65 (0·40–1·04)	0·62 (0·40–0·97)
Infection-related mortality, including COVID-19				
Unadjusted	Reference	1·14 (0·70–1·85)	0·95 (0·63–1·44)	0·57 (0·39–0·82)
Adjusted*	Reference	1·02 (0·59–1·77)	1·22 (0·73–2·03)	0·51 (0·28–0·93)
Infection-related mortality, excluding COVID-19				
Unadjusted	Reference	1·21 (0·74–1·99)	1·04 (0·68–1·61)	0·51 (0·34–0·78)
Adjusted*	Reference	1·02 (0·59–1·77)	1·22 (0·73–2·03)	0·51 (0·28–0·93)

*Adjusted for age, sex, creatinine, history of cardiovascular disease, and history of diabetes.

Table 3: **All-cause and cause-specific mortality by convection volume (with standard haemodialysis as a reference)**

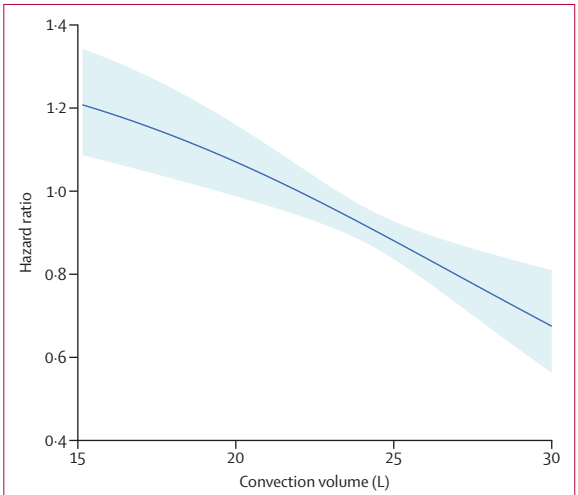

Figure 3: **Dose–response curve of the relation between convection volume plotted against hazard ratios of all-cause mortality, based on data from patients treated with haemodiafiltration**
The shaded area represents the 95% CI.

reported that high-dose convection volumes were achievable in nearly all patients and could be maintained over time.[31] In the present analysis, convection volume was not standardised to body size. The ideal scaling metric (eg, body size, bodyweight, BMI, body surface area, or total body water) remains undefined.[32]

Trial data do not fully represent populations in everyday clinical practice. However, real-world data (ie, collected from patients with kidney failure undergoing haemodialysis, during routine clinical practice) appears to confirm the existence of beneficial effects of haemodiafiltration on clinical outcomes,[33–35] and no safety concerns were observed in either trial or real-world settings. These findings have also been shown in the registries of three regions (France, Australia–New Zealand, and Japan).[35–37] In all included studies, treatment sessions were prescribed in a thrice weekly schedule with an average of 4 h per session, which is considered the standard in most regions. As such, we provide no comparison with any alternative schedules, such as more frequent sessions or longer sessions.

This individual patient data meta-analysis contains information that could be supportive to committees considering haemodialysis options, and should be reviewed and evaluated by best practice guideline committees.[23] Quality of life and health economic considerations were not included in this analysis, but the results of the CONVINCE trial on these topics will be presented in separate papers. In centres already offering haemodiafiltration on a limited scale, further expansion might not be difficult; however, in centres not offering haemodiafiltration, implementation might need investment in new equipment and staff training.

This analysis has limitations. First, due to the small number of included studies, identifying systematic patterns across individual studies was not feasible; therefore, publication bias could not be assessed. We have observed differences in trial methods and in completeness of information across the trials, although additional efforts were made to resolve any potential biases (ie, additional data collection on the missing data).[4] This heterogeneity across the studies is illustrated in the significant between-study heterogeneity, indicating differences across the included studies. The overall results should be interpreted as an average across these study populations, which might have a different true underlying average effect. We have limited the information in this Article to mortality endpoints, and did not include other patient-oriented endpoints such as hospitalisations or, importantly, health-related quality of life, which is crucial for decision making by patients and health-care professionals.[38] Furthermore, the present analysis is limited to the comparison of standard haemodialysis versus online haemodiafiltration as offered in the most often used schedule (thrice weekly for 4 h per session), which means that more frequent treatment sessions or the use of other membranes were not tested in this analysis. Finally, awareness of the considerable environmental impact of dialysis is increasing.[8] Comparison of the treatments from the environmental impact perspective was not possible in this analysis because of insufficient relevant data (eg, kg of waste produced and water and energy usage per session), but such estimates have been presented recently.[39]

In conclusion, this analysis strengthens the argument that haemodiafiltration is a superior alternative to standard haemodialysis, which constitutes the first time in decades that a change in the principles of the haemodialysis process has been found to be clinically meaningful. Nephrology expert panels and health-care authorities must now determine how can these findings translate into wider adoption of haemodiafiltration into everyday clinical practice, which might potentially lead to new and improved standards of care for patients requiring kidney replacement therapy.

Contributors

All authors conceived the idea for this meta-analysis. RWMV, MLB, and PJB wrote the protocol. RWMV reviewed all abstracts, selected full-text articles, and assessed the risk of bias. MLB served as a tiebreaker. RWMV conducted the meta-analysis. RWMV, CH, and MLB have accessed and verified the data. All authors had access to the data. RWMV, MLB, and PJB wrote the first draft of the manuscript. All authors reviewed, revised, and approved the final version of the manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

AD reports honoraria for lectures from Fresenius Medical Care, travel support by Nipro Corporation, and is a committee member of the European Renal Association Renal Nutrition Working Group. BC is a former employee of Fresenius Medical Care and Chief Executive Officer of MTX Consult. CB is an employee at B Braun. GS reports honoraria for lectures from Fresensius Medical Care. JH serves on the Board of Directors of NorrDia. MW reports consulting fees from Freeline. PJB reports honoraria for lectures from Fresenius Medical Care, and funding within the HORIZON 2020 programme (grant agreement 754803); payments to participating organisations and people within the CONVINCE study were handled by the University Medical Center Utrecht. All other authors declare no competing interests.

Data sharing

Requests for use of the individual patient data can be directed to the corresponding author. Requests will be discussed and decided upon by the CONVINCE Scientific Committee.

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