ORIGINAL ARTICLE

Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure

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*A list of the CONVINCE scientific committee investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on June 16, 2023, at NEJM.org.

This is the *New England Journal of Medicine* version of record, which includes all *Journal* editing and enhancements. The Author Accepted Manuscript, which is the author's version after external peer review and before publication in the *Journal*, is available at PubMed Central.

N Engl J Med 2023;389:700-9.
DOI: 10.1056/NEJMoa2304820

ABSTRACT

BACKGROUND

Several studies have suggested that patients with kidney failure may benefit from high-dose hemodiafiltration as compared with standard hemodialysis. However, given the limitations of the various published studies, additional data are needed.

METHODS

We conducted a pragmatic, multinational, randomized, controlled trial involving patients with kidney failure who had received high-flux hemodialysis for at least 3 months. All the patients were deemed to be candidates for a convection volume of at least 23 liters per session (as required for high-dose hemodiafiltration) and were able to complete patient-reported outcome assessments. The patients were assigned to receive high-dose hemodiafiltration or continuation of conventional high-flux hemodialysis. The primary outcome was death from any cause. Key secondary outcomes were cause-specific death, a composite of fatal or nonfatal cardiovascular events, kidney transplantation, and recurrent all-cause or infection-related hospitalizations.

RESULTS

A total of 1360 patients underwent randomization: 683 to receive high-dose hemodiafiltration and 677 to receive high-flux hemodialysis. The median follow-up was 30 months (interquartile range, 27 to 38). The mean convection volume during the trial in the hemodiafiltration group was 25.3 liters per session. Death from any cause occurred in 118 patients (17.3%) in the hemodiafiltration group and in 148 patients (21.9%) in the hemodialysis group (hazard ratio, 0.77; 95% confidence interval, 0.65 to 0.93).

CONCLUSIONS

In patients with kidney failure resulting in kidney-replacement therapy, the use of high-dose hemodiafiltration resulted in a lower risk of death from any cause than conventional high-flux hemodialysis. (Funded by the European Commission Research and Innovation; CONVINCE Dutch Trial Register number, NTR7138.)

Kidney failure is a severe and common chronic noncommunicable disease that is increasing in incidence worldwide.[1,2] Hemodiafiltration and hemodialysis are two accepted, commonly used therapies for patients with this disease, with practice differences across continents that may favor one method over the other, although hemodialysis is more often used overall.

Among the four randomized, controlled trials that have investigated whether hemodiafiltration offers survival benefits as compared with hemodialysis, three were inconclusive,[3-5] whereas the fourth showed a survival benefit for hemodiafiltration.[6] However, concerns about attrition during follow-up in these trials were raised by observers in the scientific and nephrology communities.[7,8] A meta-analysis of individual participant data from the four trials suggested a survival benefit with hemodiafiltration when a convection volume was delivered at a high dose, with a putative threshold of at least 23 liters per session in postdilution mode.[9] Analyses of dose dependency were not predefined; thus, the risk of confounding according to the medical indication for treatment exists. The results of study-level meta-analyses, including additional studies with various dialysis methods, were inconclusive as well.[10] In light of such uncertainty, we initiated a pragmatic, open-label, randomized, controlled trial to investigate whether high-dose hemodiafiltration offers survival benefits as compared with conventional high-flux hemodialysis.[11,12]

Methods

Trial Design and Oversight

The design of the CONVINCE trial has been published previously,[11,12] as described in the trial protocol, which is available with the full text of this article at NEJM.org. The trial aimed to assess benefits and harms of high-dose hemodiafiltration as compared with conventional high-flux hemodialysis regarding death from any cause, cause-specific mortality, cardiovascular events, hospitalizations, patient-reported outcomes, and cost-effectiveness. Patients were treated at 61 centers in eight European countries (see Section S1 of the Supplementary Appendix, also available at NEJM.org).

The trial, which was funded by the European Commission Research and Innovation, Horizon 2020, was conducted in accordance with the principles of the Declaration of Helsinki and the respective laws and regulations of the participating countries. Written informed consent was obtained according to these principles, along with the provisions of the General Data Protection Regulation Directive and local regulations. The trial was initiated by the investigators and was designed and overseen by a steering committee consisting of academic investigators and employees of dialysis providers independent of financial contributors. The scientific committee, whose membership did not include representatives of financial contributors, had final responsibility for the interpretation of the data, the preparation of the manuscript, and the decision to submit the manuscript for publication.

The trial was monitored by an academic contract research organization, Julius Clinical, according to standard operating procedures. During the trial, representatives of the research organization made at least one visit to each site where at least one patient had been enrolled and made more frequent visits to sites where more than 31 patients had been enrolled. Periodic contacts were made virtually or by telephone. The presence of a signed informed consent form was verified, and information from case-record forms was verified against data in electronic health care records. All reported events were reviewed for completeness and accuracy by the safety physician employed by the research organization. This review involved data regarding any events, the corresponding narrative, and coded disease category. Vital status was verified for all patients.

An independent data and safety monitoring board, which consisted of two nephrologists and one biostatistician, monitored the trial progress, the primary outcome, and safety data at regular intervals. Two formal interim analyses were performed according to the Haybittle–Peto stopping criterion.[13,14] Data collection was performed by the individual trial centers. The first author vouches for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Adult patients (≥18 years of age) were eligible for inclusion if they had received a diagnosis of kidney failure (stage V), had been treated with hemo-

A Quick Take is available at NEJM.org

dialysis for at least 3 months, were candidates for high-dose hemodiafiltration (a convection volume of ≥23 liters in postdilution mode per session), were willing to undergo dialysis sessions three times a week, and had an understanding of the trial procedures and an ability to adhere to the trial protocol, including completion of patient-reported outcome assessments. Written informed consent was provided by the patient or a designated guardian in accordance with local regulations.

Exclusion criteria were severe nonadherence to the dialysis procedure and accompanying prescriptions, especially the frequency and duration of dialysis treatment; a life expectancy less than 3 months; previous hemodiafiltration treatment less than 90 days before screening; anticipated kidney transplantation from a living donor within 6 months after screening; evidence of any other disease or medical condition that may interfere with the planned treatment, affect patient compliance, or place the patient at high risk for treatment-related complications; participation in any other study, as discussed with and decided by the scientific committee; or unavailability for trial visits for 3 months or more.

RANDOMIZATION, PROCEDURES, AND FOLLOW-UP

Patients who met the inclusion criteria were randomly assigned in a 1:1 ratio to receive either high-dose hemodiafiltration or continuation of high-flux hemodialysis. Trial-group assignments were made by means of centralized block randomization stratified according to center. The trial intervention was high-dose hemodiafiltration with on-line production of substitution fluid and ultrapure bicarbonate-based dialysis fluid at a convection volume of at least 23 liters per session in postdilution mode. Convection volume (i.e., total ultrafiltration volume) is the sum of the substitution volume and the net ultrafiltration volume (i.e., the treatment-induced weight loss as calculated to estimate dry weight). Steps that were taken to achieve high-dose hemodiafiltration targets (including a stepwise adjustment over 2 to 3 weeks) are detailed in the protocol.[11] Convection volumes and reasons why high-dose targets could not be reached were recorded on the electronic case record form. The comparison group received conventional hemodialysis by means of high-flux dialysis membranes and ultrapure bicarbonate-based dialysis fluid. All the participating centers had experience with hemodiafiltration, so continuous delivery of hemodiafiltration in compliance with local quality regulations could be expected.

Our trial was pragmatic, meaning that all data were collected as part of routine clinical practice. This design may have led to missing information with respect to some variables (Section S4). Additional data — including patients' disease characteristics, laboratory values, medications, and dialysis-specific measurements — are provided in Section S5. For patients who were receiving high-dose hemodiafiltration, we collected data at each follow-up visit regarding achieved convection volume and the number of treatment sessions not performed as high-dose hemodiafiltration in the previous 3 months.[11]

OUTCOMES

The primary outcome of the trial was death from any cause. Key secondary outcomes were cause-specific mortality, composite fatal and nonfatal cardiovascular events, kidney transplantation, and recurrent hospitalizations for any cause and for causes related to infection.[11] Cardiovascular events were defined as death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, therapeutic coronary procedure (coronary-artery bypass graft, percutaneous transluminal coronary angioplasty, or stenting), therapeutic carotid procedure (endarterectomy or stenting), and vascular intervention (revascularization, percutaneous transluminal angioplasty, or stenting), or peripheral limb amputation.

Reasons for hospitalization (e.g., infection-related or cardiovascular) were recorded during the trial period. Since all the patients had stage V disease, the trial population had a wide variety of frequent adverse events. Thus, the ethics committee approved our request to restrict the reporting of adverse events only to serious events regarding the primary and secondary outcomes. Findings with respect to patient-reported outcomes and cost-effectiveness are not reported here.

STATISTICAL ANALYSIS

We determined that the enrollment of 1800 patients would provide the trial with 90% power to determine a risk reduction of 25% in the intervention group, with a two-sided type I error of 5% and a follow-up of 2.5 years. During the con-

duct of the trial, additional exploratory estimates were generated on the basis of the observed patient enrollment, the anticipated duration of follow-up, and the observed blinded estimates of mortality (Section S3).[11] We analyzed the treatment characteristics over the course of the trial using linear mixed models for repeated measures. The trial site was included as a random effect for all models except the one for serum creatinine, where it was included as a fixed effect. Models were adjusted for baseline value, treatment group, trial visit, and interaction between treatment group and trial visit to estimate the marginal means in each group and overall mean difference between the groups, with 95% confidence intervals.

We applied Cox proportional-hazards models to estimate hazard ratios and corresponding 95% confidence intervals for the primary and key secondary outcomes involving single events. For recurrent outcomes of hospitalizations for any cause and for cause-specific reasons, the Andersen–Gill model was applied. The trial site was included as a random effect in these models. Data were censored on the date of the last trial visit (March 27, 2023). For secondary outcomes or subgroup analyses, no adjustment for multiplicity was made, so confidence intervals cannot be used to replace hypothesis testing.

We explored heterogeneity in treatment effect on the primary outcome through subgroup analyses using multiplicative interaction terms. Predefined subgroup analyses were conducted according to age group (under 50 years, 50 to 65 years, and over 65 years), biologic sex, cardiovascular disease history, diabetes at baseline, daily residual urinary output (<1000 ml or ≥1000 ml), vascular access (fistula or graft or catheter), and dialysis vintage (<2 years, 2 to 5 years, and >5 years).

For the primary outcome, we performed competing risk analyses with kidney transplantation as the competing event. Cause-specific Cox proportional-hazard regression and Fine–Gray models were used to estimate the cause-specific hazard ratio and subdistribution hazards, respectively. We graphically assessed the model assumption of proportionality using a log cumulative hazard plot and by examining the scaled Schoenfeld residuals. The proportional-hazards assumption was met for all outcomes. Finally, a sensitivity analysis in which the trial site was removed as a random effect was conducted to assess the robustness of the primary outcome. In light of the coronavirus disease 2019 (Covid-19) pandemic, we stratified the analyses regarding infection-related hospitalization and death according to Covid-19 infection. All analyses were performed with the use of RStudio software, version 2023.3.0.386.

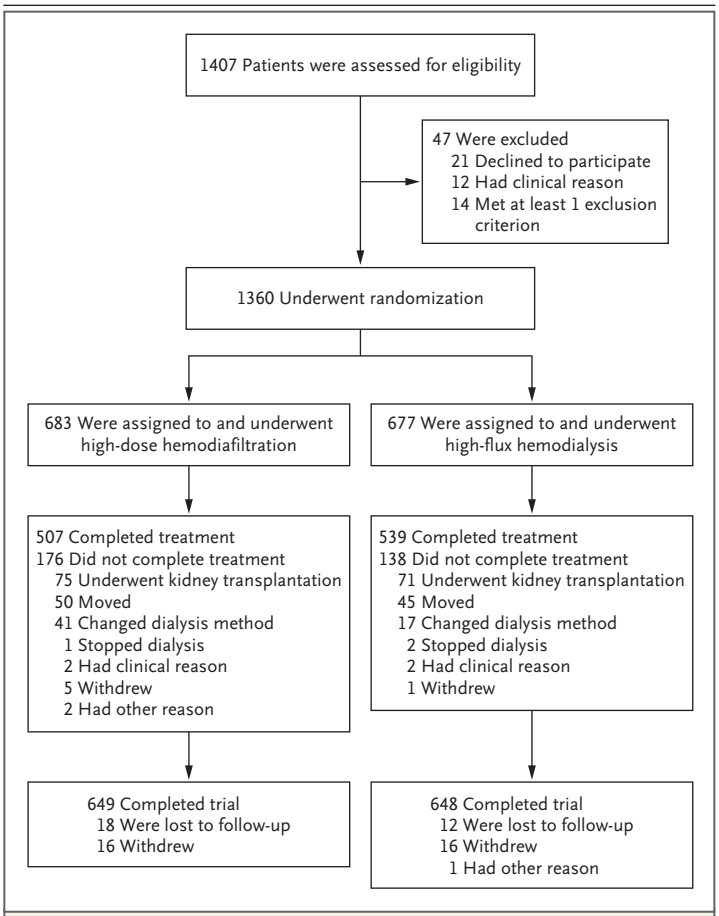


Figure 1. Patient Enrollment and Follow-up.

From November 2018 through April 2021, a total of 1360 patients underwent randomization to receive either high-dose hemodiafiltration or high-flux hemodialysis. The median follow-up was 30 months (interquartile range, 27 to 38).

RESULTS

PATIENTS

From November 2018 through April 2021, a total of 1360 patients underwent randomization (with 683 patients assigned to receive high-dose hemodiafiltration and 677 to receive high-flux hemodialysis) (Fig. 1). The characteristics of the patients,

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	High-Dose Hemodiafiltration (N = 683)	High-Flux Hemodialysis (N = 677)
Age — yr	62.5±13.5	62.3±13.5
Female sex — no. (%)	247 (36.2)	257 (38.0)
Region — no. (%)		
Western Europe	223 (32.7)	218 (32.2)
Eastern Europe	234 (34.3)	233 (34.4)
Southern Europe	226 (33.1)	226 (33.4)
Cardiovascular disease — no. (%)†		
Any	296 (43.3)	316 (46.7)
Coronary heart disease‡	130 (19.0)	147 (21.7)
Diabetes mellitus — no. (%)	230 (33.7)	251 (37.1)
Smoking — no./total no. (%)		
Never	360/683 (52.7)	318/673 (47.3)
Current	98/683 (14.3)	109/673 (16.2)
Past	225/683 (32.9)	246/673 (36.6)
Alcohol consumption — no./total no. (%)		
Never	357/679 (52.6)	343/674 (50.9)
Current	175/679 (25.8)	199/674 (29.5)
Past	147/679 (21.6)	132/674 (19.6)
Body-mass index — no. (%)§	27.4±5.6	27.5±5.7
Body-surface area — m^2¶	1.86±0.22	1.86±0.22
Blood pressure before dialysis — mm Hg		
Systolic	141±22	141±22
Diastolic	73±14	72±15
Heart rate before dialysis — beats/min	72±11	72±12
Laboratory values		
Hemoglobin — g/dl	11.3±1.2	11.3±1.2
Serum creatinine — mg/dl‖	7.4±2.5	7.3±2.3
Serum urea — mg/dl	70.6±30.5	71.4±32.7
Median C-reactive protein (IQR) — mg/liter	5 (2–11)	4 (2–10)
Serum phosphate — mg/dl	4.9±1.5	4.9±1.4
Blood flow — ml/min**	369±54	367±56
Median residual urinary output (IQR) — ml/24 hr	850 (500–1300)	800 (444–1200)
Dialysis		
Median vintage (IQR) — mo	35 (16–78)	30 (14–67)
Median duration of session (IQR) — min	240 (240–248)	240 (240–245)
Median single-pool Kt/V (IQR)††	1.61 (1.45–1.83)	1.61 (1.42–1.80)
Vascular access — no. (%)		
Fistula	558 (81.7)	557 (82.3)
Catheter	90 (13.2)	94 (13.9)
Graft	35 (5.1)	26 (3.8)
Previous kidney transplantation — no. (%)	93 (13.6)	79 (11.7)

* Plus–minus values are means ±SD. Details regarding missing data (which were omitted from calculations of means and medians) are provided in Section S4 in the Supplementary Appendix. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for serum phosphate (as inorganic phosphorus) to millimoles per liter, multiply by 0.3229. IQR denotes interquartile range.

† Cardiovascular disease (including coronary heart disease) was defined as a history of any one or more of the following conditions: angina, myocardial infarction, coronary stent or dotter procedure and coronary-artery bypass graft, congestive heart failure, atrial fibrillation, transient ischemic attack, cerebrovascular accident, abdominal aortic aneurysm or intermittent claudication; placement of pacemaker or internal defibrillator; carotid endarterectomy; stent or

Table 1. (Continued.)

dotter procedure, bypass surgery, or amputation of the arteries of the lower limbs; and stent or dotter procedure of the renal arteries.
‡ Coronary heart disease was defined as a history of any one or more of the following: angina, myocardial infarction, coronary stent or dotter procedure, and coronary-artery bypass graft.
§ The body-mass index is the weight in kilograms divided by the square of the height in meters.
¶ The body-surface area was calculated by means of the Du Bois formula.
‖ The serum creatinine value is the geometric mean of measurements taken before and after dialysis.
** Blood flow was measured through an extracorporeal circuit.
†† The single-pool urea Kt/V for hemodialysis is a dimensionless measure of the adequacy of small-molecule removal provided by a single dialysis treatment. In this measure, K represents the urea clearance by the dialyzer, t represents the treatment time, and V represents the urea distribution volume.

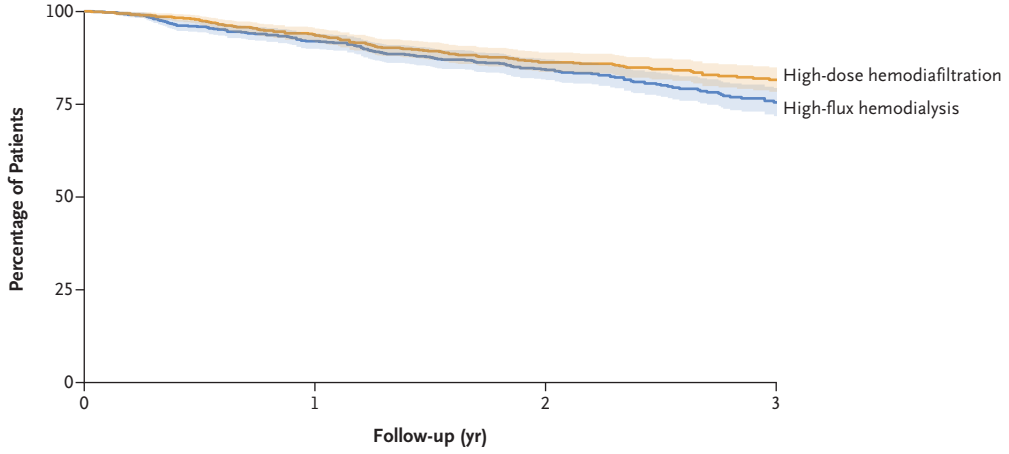
including demographic features, coexisting illnesses, laboratory values, and medications — were well balanced at baseline (Table 1 and Table S1). The median follow-up was 30 months (interquartile range, 27 to 38) for the patients in the two treatment groups. Loss to follow-up occurred in 18 patients (2.6%) in the hemodiafiltration group and in 12 (1.8%) in the hemodialysis group. The target volume of at least 23±1 liters per session for high-dose convection was achieved in 92% of delivered hemodiafiltration sessions, whereas the mean convection volume among the patients

Table 2. Primary and Secondary Outcomes.*

Variable	High-Dose Hemodiafiltration (N=683)		High-Flux Hemodialysis (N=677)		Hazard Ratio (95% CI)†
	no. (%)	*no. of events/ 100 patient-yr (95% CI)*	*no. (%)*	*no. of events/ 100 patient-yr (95% CI)*	
Primary outcome					
Death from any cause	118 (17.3)	7.13 (5.90–8.54)	148 (21.9)	9.19 (7.77–10.79)	0.77 (0.65–0.93)
Secondary outcomes					
Death					
Cardiovascular	31 (4.5)	1.87 (1.27–2.66)	37 (5.5)	2.30 (1.62–3.17)	0.81 (0.49–1.33)
Noncardiovascular	87 (12.7)	5.26 (4.21–6.48)	111 (16.4)	6.89 (5.67–8.30)	0.76 (0.59–0.98)
Infection-related					
Including Covid-19	38 (5.6)	2.30 (1.62–3.15)	54 (8.0)	3.35 (2.52–4.37)	0.69 (0.49–0.96)
Excluding Covid-19	23 (3.4)	1.39 (0.88–2.09)	33 (4.9)	2.05 (1.41–2.88)	0.68 (0.42–1.10)
Fatal or nonfatal cardiovascular outcome‡	136 (19.9)	9.05 (7.60–10.71)	126 (18.6)	8.48 (7.07–10.10)	1.07 (0.86–1.33)
Kidney transplantation	75 (11.0)	4.80 (3.77–6.01)	71 (10.5)	4.72 (3.69–5.96)	1.01 (0.71–1.44)
Recurrent hospitalization — no.§					
For any nonfatal cause	998	61.34 (57.59–65.27)	895	56.36 (52.73–60.18)	1.11 (0.98–1.25)
Infection-related					
Including Covid-19	234	14.32 (12.54–16.28)	219	13.92 (12.14–15.88)	1.06 (0.86–1.30)
Excluding Covid-19	152	9.34 (7.92–10.95)	156	9.82 (8.34–11.49)	0.97 (0.74–1.26)

* All the listed analyses were prespecified except for the categories involving hospitalization or death from coronavirus disease 2019 (Covid-19).
† No adjustment for multiplicity was made, so the 95% confidence intervals should not be used in place of hypothesis testing.
‡ The composite outcome of fatal or nonfatal cardiovascular events includes death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, therapeutic coronary procedure (coronary-artery bypass grafting, percutaneous transluminal coronary angioplasty, or stenting), therapeutic carotid procedure (endarterectomy or stenting), vascular intervention (revascularization or percutaneous transluminal angioplasty or stenting), or peripheral limb amputation.
§ In this category, patients may have had more than one recurrent event, so percentages of patients are not provided.

A Overall Survival



No. at Risk				
High-dose hemodiafiltration	683	625	519	194
High-flux hemodialysis	677	612	501	170
No. of Events				
High-dose hemodiafiltration	0	44	92	110
High-flux hemodialysis	0	54	105	140

B Risk of Death

Subgroup	High-Dose Hemodia-filtration	High-flux Hemodialysis	High-Dose Hemodia-filtration	High-flux Hemodialysis	Hazard Ratio (95% CI)
	no. of events/no. of patients		*rate/100 person-yr*		
Death from any cause					
Age					
<50 yr	2/121	8/119	0.64	2.57	0.25 (0.06–1.05)
50 to 65 yr	49/264	43/250	7.61	7.13	1.05 (0.75–1.49)
>65 yr	67/298	97/308	9.59	13.92	0.68 (0.53–0.89)
Sex					
Male	83/436	97/420	7.94	9.82	0.81 (0.65–1.01)
Female	35/247	51/257	5.74	8.17	0.70 (0.47–1.02)
Preexisting cardiovascular disease					
No	43/387	66/361	4.40	7.52	0.58 (0.42–0.79)
Yes	75/296	82/316	11.06	11.17	0.99 (0.76–1.28)
Preexisting diabetes					
No	54/453	76/426	4.72	7.24	0.65 (0.48–0.87)
Yes	64/230	72/251	12.50	12.81	0.97 (0.72–1.31)
Residual urinary output					
<1000 ml/24 hr	12/52	17/52	9.23	12.32	0.76 (0.37–1.59)
≥1000 ml/24 hr	6/30	3/26	6.67	4.05	1.59 (0.56–4.45)
Vascular access					
Fistula	97/558	123/557	7.16	9.23	0.77 (0.64–0.94)
Graft or catheter	21/125	25/120	6.98	8.93	0.78 (0.45–1.34)
Dialysis vintage					
<2 yr	37/267	51/281	5.59	7.56	0.73 (0.53–1.00)
2 to 5 yr	34/207	49/207	6.94	9.96	0.70 (0.46–1.06)
>5 yr	46/207	48/188	9.18	10.86	0.85 (0.64–1.15)
Death from cardiovascular causes					
Preexisting cardiovascular disease					
No	12/387	14/361	1.23	1.59	0.76 (0.35–1.64)
Yes	19/296	23/316	2.80	3.13	0.89 (0.48–1.65)

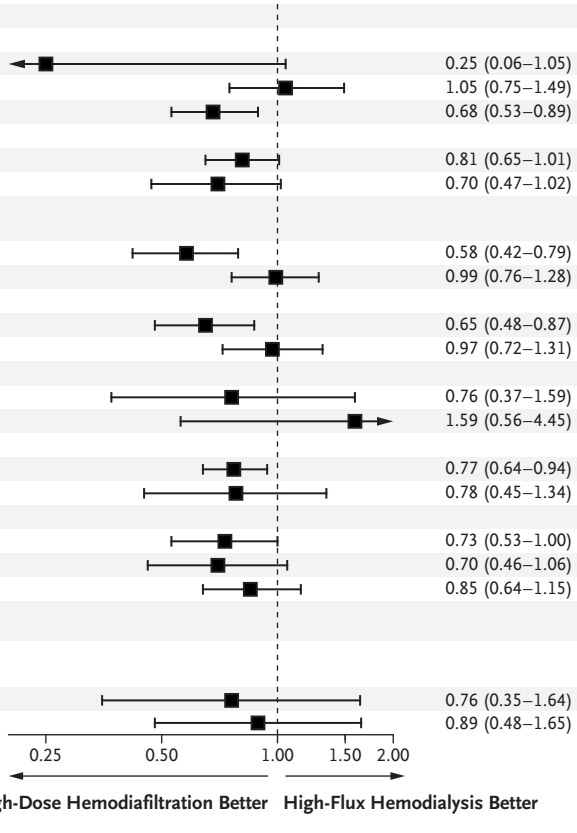


Figure 2 (facing page). Overall Survival and Subgroup Analysis.

Panel A shows Kaplan–Meier curves for overall survival as calculated with the use of data regarding death from any cause (the primary outcome) among the patients who had received either high-dose hemodiafiltration or high-flux hemodialysis. Panel B shows a forest plot with hazard ratios for death from any cause and from cardiovascular causes among prespecified subgroups. No adjustment for multiplicity was made, so the 95% confidence intervals should not be used in place of hypothesis testing.

was stable over the course of the trial (Table S2 and Fig. S1). The Kt/V value (in which K represents the urea clearance by the dialyzer, t represents the treatment time, and V represents the urea distribution volume) was higher in the hemodiafiltration group than in the hemodialysis group and remained so during the course of the trial (Fig. S2).

PRIMARY OUTCOME

Death from any cause occurred in 118 patients (17.3%) in the hemodiafiltration group (7.13 events per 100 patient-years) and in 148 patients (21.9%) in the hemodialysis group (9.19 events per 100 patient-years) (hazard ratio, 0.77; 95% confidence interval [CI], 0.65 to 0.93; P=0.005) (Table 2 and Fig. 2A). Of the 266 total deaths, 68 (25.6%) were attributed to cardiovascular disease, 26 (9.8%) to Covid-19, and 56 (21.1%) to other infections (Table S3).

Treatment effects differed according to whether patients had a history of cardiovascular disease at baseline (Fig. 2B). Among the patients with such a history, the risk of death was similar in the two groups (hazard ratio, 0.99; 95% CI, 0.76 to 1.28). However, among those without such a history, the risk of death was lower in the hemodiafiltration group (hazard ratio, 0.58; 95% CI, 0.42 to 0.79). Treatment effects also differed according to the history of diabetes mellitus, with a lower risk of death in the hemodiafiltration group among those without diabetes mellitus (hazard ratio, 0.65; 95% CI, 0.48 to 0.87) but a similar risk among those with diabetes mellitus (hazard ratio, 0.97; 95% CI, 0.72 to 1.31).

In sensitivity analyses, competing risks of kidney transplantation or treatment switches were included, along with the exclusion of the recruiting site as a random effect. In these analyses, the results were similar to those in the primary analysis (Section S6).

SECONDARY OUTCOMES

The risk of death from cardiovascular causes (hazard ratio, 0.81; 95% CI, 0.49 to 1.33) and the composite outcome of fatal or nonfatal cardiovascular outcomes (hazard ratio, 1.07; 95% CI, 0.86 to 1.33) were similar in the hemodiafiltration group and the hemodialysis group. An apparent reduction in favor of the high-dose hemodiafiltration group with respect to infection-related death, including from Covid-19, was found (hazard ratio, 0.69; 95% CI, 0.49 to 0.96).

The risk of recurrent hospitalization was similar in the two groups, including for nonfatal hospitalization (hazard ratio, 1.11; 95% CI, 0.98 to 1.25) and for infection-related hospitalization that included Covid-19 (hazard ratio, 1.06; 95% CI, 0.86 to 1.30) and that excluded Covid-19 (hazard ratio, 0.97; 95% CI, 0.74 to 1.26) (Table 2).

DISCUSSION

In our trial, we found a lower risk of death from any cause among patients with kidney failure who were receiving high-dose hemodiafiltration than among those receiving conventional high-flux hemodialysis. A previous meta-analysis of 11 studies (involving 3396 patients) that compared various convective dialysis therapies (hemofiltration, hemodiafiltration, and acetate-free biofiltration) with hemodialysis showed a reduction in cardiovascular mortality but no effect on death from any cause, nonfatal cardiovascular events, or hospitalization.[10] An individual-participant data analysis of four randomized, controlled trials involving 2793 patients[3-6] showed a significant reduction in death from any cause and from cardiovascular causes that favored hemodiafiltration, especially among patients receiving high-dose hemodiafiltration.[9] This beneficial effect of hemodiafiltration has been attributed to confounding according to indication (i.e., a high convection volume was predominantly reached in healthier patients with lower event risks).

Our trial differs from previous studies in that we enrolled patients who were likely candidates for high-dose hemodiafiltration nearly all the time. We did not identify an association between failure to achieve the high-dose target and any particular

patient characteristic or vascular access type.[15-20] Thus, our trial results support the evidence that high-dose hemodiafiltration can result in a clinically important survival benefit. Furthermore, since our trial was both randomized and controlled, our finding does not appear to be due to confounding according to indication.

The results of previous pharmacologic intervention studies involving patients with kidney failure have often been neutral. Possibly, such results have to do with the fact that an intervention that is targeted to modify a single mechanism or intervention late in the patient-treatment pathway is not sufficiently powerful or protective to mitigate risk and to change clinical outcome in patients with multiple coexisting illnesses.[21] Hemodiafiltration is a general and nonselective intervention that potentially involves multiple mechanisms, including increased removal of uremic toxins and other physiologic processes.[22]

Analyses of both infection-related and cardiovascular deaths showed a suggestion of benefit for hemodiafiltration, although drawing such conclusions is complicated because Covid-19 as a diagnosis was added during the course of the trial. We cannot make the distinction between death from Covid-19 and death from other causes (e.g., cardiovascular) in a patient with Covid-19. Thus, these subanalyses should be interpreted with some caution.

We increased the likelihood of an unbiased effect estimate through the trial design, which included complete follow-up of mortality, no data censoring after certain key events (e.g., renal transplantation),[23] and competing-risk statistical analyses. However, some limitations exist. Our achieved sample size was lower than we originally calculated because of the Covid-19 pandemic and difficulties in recruitment during lockdowns. Furthermore, we found an overall risk of death that was lower than what has been generally reported and lower than what we used for determining the sample size.[1,2,9,24] The lower mortality can be partly attributed to selection by the treating physician to enroll patients who were likely to reach a convection volume of at least 23 liters during each session, an indication that these patients had relatively good vascular access. Furthermore, patients were expected to complete outcome assessments.[11] An overall lower risk of death among the trial patients as such does not invalidate our findings of an association between hemodiafiltration and a reduction in death from any cause.

For our trial to have an effect on clinical practice, the question of the applicability of the findings to clinical practice is important. Features to support generalizability include a pragmatic trial design without numerous exclusion criteria. However, our inclusion criteria may have resulted in a trial population that was healthier than the general hemodialysis population in Europe[1] and in the United States[24] (Section S8). Also, we did not collect data regarding race or ethnic group among our European patients, so our findings may not be generalizable to non-White patients with kidney failure.

Moreover, among the patients in the hemodiafiltration group, the absolute survival advantage may have varied between individual patients. Previously, we reported the most survival benefit from hemodiafiltration among patients who were younger, did not have diabetes or cardiovascular disease, and had increased serum creatinine and albumin levels.[25] Updating the hemodiafiltration-pooling project with individual-participant data from the present trial and from other trials (e.g., the High-Volume Hemodiafiltration vs. High-Flux Hemodialysis Registry [H4RT] trial[26]) would allow more precise exploration of treatment effects across subgroups.[9] Our trial results, together with those of several other trials and large observational studies,[9,10,27-29] seem to indicate that the safety of hemodiafiltration was acceptable, provided that hygienic and microbiologic rules are fully respected.

In our trial, at a median follow-up of 30 months after randomization, patients with kidney failure who received high-dose hemodiafiltration had a lower risk of death than those who received conventional high-flux hemodialysis.

Supported by the European Commission Research and Innovation, Horizon 2020 (H2020-SC1-2016-2017), under the topic SC1-PM-10-2017: Comparing the effectiveness of existing health care interventions in the adult population (grant no. 754803-2).

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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