The CONVINCE randomized trial found positive effects on quality of life for patients with chronic kidney disease treated with hemodiafiltration

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Matthias Rose[1,2,3], Felix H. Fischer[1,2,3], Gregor Liegl[1,2], Giovanni F.M. Strippoli[4,5], Carina Hockham[6], Robin W.M. Vernooij[7,8], Claudia Barth[9], Bernard Canaud[10], Adrian Covic[11], Krister Cromm[1,2,12], Andrea M. Cucui[13], Andrew Davenport[14], Kathrin I. Fischer[1,2], Jörgen Hegbrant[15], Hanna Jaha[1,2], Anna Schappert[1,2,3], Marietta Török[16], Mark Woodward[5,17], Michiel L. Bots[8] and Peter J. Blankestijn[7]; for the CONVINCE Scientific Committee and CONVINCE Investigators

[1]Department of Psychosomatic Medicine, Center of Internal Medicine and Dermatology, Charité Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany; [2]Center for Patient Centered Outcomes Research, Charité Universitätsmedizin Berlin (CPCOR), Berlin, Germany; [3]German Center for Mental Health (DZPG, Germany; [4]Department of Precision and Regenerative Medicine and Ionian Area (DIMEPRE-J), University of Bari, Bari, Italy; [5]School of Public Health, University of Sydney, Sydney, Australia; [6]The George Institute for Global Health, School of Public Health, Imperial College London, London, UK; [7]Department of Nephrology and Hypertension, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; [8]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, the Netherlands; [9]B. Braun Avitum AG, Medical Scientific Affairs, Melsungen, Germany; [10]Montpellier University, School of Medicine, Montpellier, France; [11]Department of Nephrology, University of Medicine "Grigore T. Popa" Iasi and Fresenius Nephrocare, Romania; [12]Fresenius Medical Care Deutschland GmbH, Global Medical Office, Bad Homburg, Germany; [13]Fresenius Nephrocare Dialysis Center, Bucharest, Romania; [14]UCL Department of Renal Medicine, Royal Free Hospital, Division of Medicine, University College London, London, UK; [15]Division of Nephrology, Department of Clinical Sciences, Lund University, Lund, Sweden; [16]Corporate Medical Office Diaverum, Malmö, Sweden; and [17]The George Institute for Global Health, University of New South Wales, Sydney, Australia

In the CONVINCE trial, the primary analysis demonstrated a survival benefit for patients receiving high-dose hemodiafiltration (HDF) as compared with high-flux hemodialysis (HD). A secondary objective was to evaluate effects on health-related quality of life (HRQoL); assessed in eight domains (physical function, cognitive function, fatigue, sleep disturbance, anxiety, depression, pain interference, social participation) applying instruments from the Patient-Reported Outcome Measurement Information System (PROMIS) before randomization and every three months thereafter. In total 1360 adults with dialysis-dependent chronic kidney disease, eligible to receive high-flux HDF (23 liters or more), were randomized (1:1); 84% response rate to all questionnaires. Both groups reported a continuous deterioration in all HRQoL domains. Overall, raw score changes from baseline were more favorable in the HDF group, resulting in a significant omnibus test after a median observation period of 30 months. Most relevant single raw score differences were reported for cognitive function. Patients receiving HDF reported a decline of -0.95 units (95% confidence interval -2.23 to +0.34) whereas HD treated patients declined by -3.90 units (-5.28 to - 2.52). A joint model, adjusted for mortality differences, utilizing all quarterly assessments, identified a significantly slower HRQoL decline in physical function, cognitive function, pain interference, and social participation for the HDF group. Their physical health summary score declined -0.46 units/year slower compared to the HD group. Thus, the CONVINCE trial showed a beneficial effect of high-dose hemodiafiltration for survival as well as a moderate positive effect on patients' quality of life, most pronounced with respect to their cognitive function.

Registration: NTR7138 on the International Clinical Trials Registry Platform

Kidney International (2024) ■, ■–■; https://doi.org/10.1016/j.kint.2024.07.014

KEYWORDS: health-related quality of life; hemodiafiltration; hemodialysis; patient-reported outcomes; quality of life; randomized controlled trial

Correspondence: *Felix Fischer, Center for Patient-Centered Outcomes Research, Department of Psychosomatic Medicine, Medical Clinic, Center for Internal Medicine and Dermatology, Campus Benjamin Franklin, Mitte und Virchow Klinikum, Charité Universitätsmedizin Berlin, 10097 Berlin, Germany. E-mail: felix.fischer@charite.de*

Received 25 January 2024; revised 18 June 2024; accepted 2 July 2024

Kidney diseases are highly prevalent and associated with increased mortality.[1] The health of patients with kidney failure is affected by specific symptoms, limitations in functional status, and burden of kidney replacement therapy (KRT).[2] Next to mortality and morbidity, physical and psychosocial aspects of perceived health, often also described as

Lay Summary

People with end-stage chronic kidney disease have a life-limiting condition. As the disease progresses further, many of those may require renal replacement therapy. Compared with widely used hemodialysis, hemodiafiltration improves the clearance of specific types of uremic toxins. In the CONVINCE clinical trial, 1360 patients on high-flux hemodialysis were randomly assigned to continue with high-flux hemodialysis or switch to high-volume hemodiafiltration. In this trial, hemodiafiltration prolonged life expectancy compared with hemodialysis. We also investigated which treatment is associated with a better quality of life and collected self-report questionnaires from both groups over the course of the study. By the end of the study, patients treated with hemodiafiltration reported a better quality of life, in particular with respect to their cognitive function, compared with those receiving hemodialysis.

health-related quality of life (HRQoL), are important outcomes for patients with kidney disease.[3,4]

As enhancing the HRQoL of the patients is a primary objective of KRT,[5] a critical inquiry arises as to whether distinct kidney replacement treatment modalities, in particular hemodiafiltration (HDF) versus conventional hemodialysis (HD), differentially affect patient health.[6] Several mechanisms have been discussed that might lead to improved health perceptions and reduced treatment burden, including improved clearance of a broader molecular weight spectrum of uremic toxins, improvements in hemodynamic stability, anti-inflammatory effects, and correcting endothelial dysfunction.[7,8]

Previous study findings on the effects of HDF versus HD on HRQoL have been inconclusive. Some observational studies supported the assumption that HDF is accompanied by better perceived HRQoL.[9,10] A prospective randomized controlled trial (RCT) found positive effects for HDF compared with HD on disease-specific symptoms and other aspects of HRQoL,[11] a finding that is partially supported by other randomized trials.[12,13] However, within the Convective Transport Study (n = 714), comparing effects of HDF with low-flux HD on HRQoL, no meaningful group differences were observed.[14] Several other studies equally did not find considerable differences.[15–18]

A systematic review from 2014, including 6 RCTs evaluating HDF, concluded that the current evidence was too inconsistent to draw conclusions about the effect of HDF versus HD on HRQoL.[19] A meta-analysis from 2018 reported that HDF was associated with significantly increased social activity compared with HD; however, HDF did not improve other HRQoL-related domains.[20]

To date, there is a lack of conclusive evidence stemming from large-scale RCTs comparing the impact of HDF versus HD on perceived HRQoL.[21] To fill this research gap, the CONVINCE trial included a state-of-the-art HRQoL assessment, secondarily to its primary end point, mortality.[22]

METHODS

Study design

CONVINCE was an open-label RCT to assess the benefits and harms of high-dose HDF compared with high-flux HD on all-cause mortality, cardiovascular events, hospitalizations, patient-reported outcomes, including HRQoL, and cost-effectiveness. The CONVINCE protocol has been previously detailed,[22,23] and registered as NTR7138 on the International Clinical Trials Registry Platform. Patients were treated at 61 centers in 8 European countries (Supplementary Table S1), screened and enrolled from November 2018 to April 2021. Participants remained in the trial until the observation period ended in April 2023, after the intended minimal observation period of 24 months had been reached for the final enrolled patient.

CONVINCE was an investigator-initiated trial, designed and overseen by a steering committee comprising academic and dialysis providers, conducted, and analyzed independently of the financial contributors. The study was funded by the European Commission (Horizon 2020 research and innovation program, agreement 754803). The scientific committee (Supplementary Table S2) had final responsibility for the interpretation of the data and the preparation of the manuscript.

CONVINCE was monitored by an academic contract research organization, Julius Clinical (www.juliusclinical.org), following standard operation procedures. Each site that randomized ≥1 patients was visited at least once, and more often when >31 patients had been enrolled. Periodic contacts were undertaken by video call or telephone. All data were reviewed by Julius Clinical for completeness and accuracy.

Study population

Patients aged ≥18 years were included, on HD treatment for ≥3 months, likely to achieve high-dose HDF (≥23 L in postdilution mode), willing to have dialysis sessions with duration of ≥4 hours, 3 times a week. Participants needed to be able to complete the questionnaires without assistance in their local language. Written informed consent was obtained in accordance with the Declaration of Helsinki, laws and regulations, and the General Data Protection Regulation Directive (regulation 2016/679).

Randomization and intervention

Participants who successfully completed the screening procedures were randomly assigned in a 1:1 ratio to receive either high-dose HDF or continuation of high-flux HD. The allocation to the study arm was concealed and performed by a centralized block randomization scheme, stratified by center, using a central interactive web response system managed by Julius Clinical. Because of the nature of the study, it was not possible to blind participants, or site investigators for participants' treatment assignment. The central investigator

team, including the statistics team, remained blinded throughout the duration of the study. The intervention was high-dose HD with online production of substitution fluid and ultrapure bicarbonate-based dialysis fluid. High-dose HDF was defined as a convection volume of ≥23 L per session in postdilution mode. The comparison group received conventional HD using high-flux dialysis membranes and ultrapure bicarbonate-based dialysis fluid as standard of dialysis care.[6,22]

HRQoL outcome

To assess the generic HRQoL, we followed suggestions by the International Consortium for Health Outcomes Measurements,[4] applying the Patient-Reported Outcome Measurement Information System (PROMIS)-29 v2.0 profile, a commonly used instrument of the PROMIS.[24] This instrument includes 4-item short forms for 7 health domains (physical function, fatigue, sleep disturbance, depression, anxiety, pain interference, and ability to participate in social roles and activities) as well as a single item measuring pain intensity.[25] These scales cover core domains also recommended by the Standardized Outcomes in Nephrology initiative.[3] As fatigue was identified as particularly relevant, 2 additional PROMIS items from the fatigue item bank were added. A 4-item PROMIS cognitive function short form[26] was administered to cover another prespecified patient-reported outcome domain by the Standardized Outcomes in Nephrology initiative in all countries except Romania, as translations were not available for this particular domain.

PROMIS-29 v2.0 domains were aggregated to physical and mental health summary scores.[27] The physical health summary score is largely determined by physical function and pain scores, whereas the insidMHS mainly represents affective health (depression, anxiety), fatigue, sleep disturbance, as well as social participation. PROMIS scores are calibrated to a T-score metric with a representative US general population mean of 50 and an SD of 10. Patient-reported outcomes were collected at baseline, and then every 3 months thereafter until the end of the study period, or completion of treatment due to mortality, study withdrawal, renal transplantation, or loss to follow-up.

Further patient-reported assessments used in the study were a symptom list from the KDQoL, collected quarterly over the course of the study, and a health use module collected every 6 months, including the EQ-5D, the SF-12, and the PHQ-9 for the purpose to use in the economic evaluation. Although this article primarily reports the comparative HRQoL outcomes as measured by the PROMIS instruments, we report postintervention data on these scales to ensure comprehensive reporting.

Statistical analyses

We followed recent analysis recommendations from the SISAQOL group,[28] to assess overall HRQoL changes. The difference between HDF and HD in mean change from baseline was assessed after an observation period of 30 respectively 36 months, using an omnibus test for all 8 scales to avoid multiple testing. For this analysis, we used the available data at both time points only and did not impute any missing values. In particular, patients who died or received a kidney transplant during the course of the study have been excluded.

Within the statistical analysis plan published in advance,[6] a linear-mixed model of change from baseline was chosen as the primary analytic method (see Supplementary Methods). This model estimates the trajectory of individual patients, based on all available data at all follow-up time points. To be included, patients had to complete the baseline assessment and at least 1 follow-up. No missing data were imputed because the linear-mixed model deals with missing information appropriately, when data are missing at random.[29] The effect of HDF compared with HD on continuous health domains was modeled as the change from baseline per year. We modeled group allocation and time since randomization (quarterly) as well as their interaction as fixed effects.[30] The respective baseline score was controlled for, and a random intercept was included as well as a random slope for time since randomization for each participant.

Mortality and perceived health are likely to be dependent outcomes, as patients more likely to decease may report a more compromised health state and quality of life beforehand and vice versa.[31,32] Hence, for missing observations of patient-reported outcome data due to death, the statistical assumption of missing at random may be violated. Because the risk of death is different between treatment groups, linear-mixed model results may therefore be biased.[33] To investigate the robustness of the linear-mixed model results against such a violation, we thus additionally applied a joint model,[34] which takes the potential dependency of self-reported health status measures and observed differences on mortality rates into account.[22]

In the joint model, the longitudinal model was specified as described above. Time to event (all-cause mortality) was modeled using a Weibull relative risk model, with value and slope of the health outcome as predictor. Robustness of linearity assumptions were assessed. As measures of efficacy, we report point estimates, the respective 95% confidence intervals, and P values for both the main and interaction effect of group allocation from the longitudinal model.

Sample size calculations were based on the expected effect on mortality and described in the statistical analysis plan.[23] The achieved sample size provides >95% power to identify small group HRQoL single-domain differences (effect sizes >0.2) in all 3 types of analyses. Analyses were performed using R (version 4.1.2) and detailed in the statistical analyses plan.

RESULTS

Participants

Between November 2018 and April 2021, 1407 patients were assessed for eligibility; 47 did not meet the eligibility criteria, or declined their participation. The remaining 1360 patients

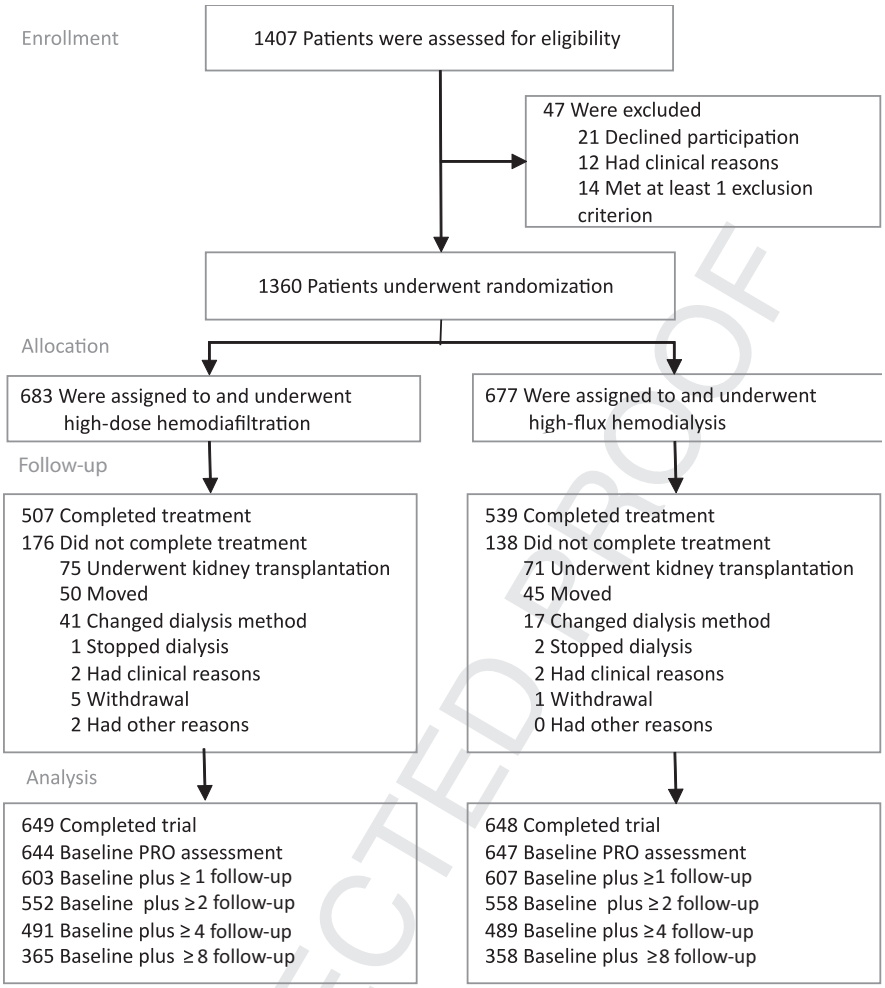

Figure 1 | Consort flowchart. Completed treatment: includes all patients who remained in the allocated treatment for the entire study period or died within the study period. Completed trial: includes all patients who had provided at least 1 patient-reported outcome (PRO) assessment and did not withdraw their participation or were lost to follow-up. Within the linear mixed model and the joint model, all available PRO data have been included. Linear mixed model and joint model estimates are based on 607 patients from the hemodialysis group and 603 patients from the hemodiafiltration group. Q28

were randomized, of whom 683 patients were assigned to HDF and 677 to HD (Figure 1). Patients had been on KRT for >2.5 years on average, with a mean age of 62 years, with a majority of men (63%; Table 1 and Supplementary Table S3).

Baseline characteristics of participants who completed the trial as well as the treatment have been similar to those who did not (Supplementary Tables S4–S7). One of the reasons that the treatment was not completed was a change in treatment modality after randomization. This occurred in 6% of the cases in the HDF group and in 3% within the HD group. The reasons for this change were not assessed systematically. Patient-reported health data were collected from 1291 (95%) participants at baseline, with similar characteristics for both randomized groups. In particular, participants who die or receive a kidney transplantation during the study are comparable in both groups at baseline. Because of mortality, study withdrawal, renal transplantation, or loss to follow-up, 954 participants remained in the study over the minimal observation period of 2 years after the final patient was enrolled. HRQoL questionnaires could be collected from 807 patients (84.6%). After the median observation period of 30 months, 657 remained in the study; of those, 541 answered HRQoL instruments (82.3%) (Figure 2). The average response rate over all 12 quarterly follow-up assessments was 84.0%, with no notable difference between groups. Also, comparisons of baseline characteristics of participants still included in the study at quarterly assessments indicate that at each time point, treatment groups are comparable and no selective dropout in regard to baseline variables occured. Overall, a median observation period of 30 months was achieved (Supplementary Table S8).

HRQoL changes

Baseline scores were comparable to the representative general population for fatigue, sleep disturbance, anxiety, depression, pain interference, and the ability of participate in social roles

Table 1 | Summary characteristics and patient-reported health status at baseline

Variable	Total (n = 1360)	High-flux hemodialysis (n = 677)	High-dose hemodiafiltration (n = 683)
Sociodemographic variables			
Age, yr	62.4 ± 13.5	62.3 ± 13.5	62.5 ± 13.5
Women, n (%)	504 (37.1)	257 (38.0)	247 (36.2)
Biomedical variables			
Cardiovascular disease, n (%)[a]	612 (45.0)	316 (46.7)	296 (43.3)
Diabetes, n (%)	481 (35.4)	251 (37.1)	230 (33.7)
Body mass index, kg/m^2	27.4 ± 5.7	27.5 ± 5.7	27.4 ± 5.6
Body surface area, m^2[b]	1.9 ± 0.2	1.9 ± 0.2	1.9 ± 0.2
Systolic blood pressure/predialysis, mm Hg	141 ± 22	141 ± 22	141 ± 22
Diastolic blood pressure/predialysis, mm Hg	73 ± 15	72 ± 15	73 ± 14
Hemoglobin, g/dl	11.3 ± 1.2	11.3 ± 1.2	11.3 ± 1.2
Serum creatinine, mg/dl[c]	7.4 ± 2.4	7.3 ± 2.3	7.4 ± 2.5
C-reactive protein, median (IQR), mg/l	5 (2–10)	4 (2–10)	5 (2–11)
Blood flow rate, ml/min[d]	368 ± 55	367 ± 56	369 ± 54
Single-pool Kt/V, median (IQR)[e]	1.6 (1.4–1.8)	1.6 (1.4–1.8)	1.6 (1.5–1.8)
Dialysis vintage, median (IQR), mo	33 (15–72)	30 (14–67)	35 (16–78)
Region, n (%)			
Eastern Europe	467 (34.3)	233 (34.4)	234 (34.3)
Southern Europe	452 (33.2)	226 (33.4)	226 (33.1)
Western Europe	441 (32.4)	218 (32.2)	223 (32.7)
Patient-reported outcomes			
Health domains			
Physical function	44.0 ± 9.9	43.8 ± 9.9	44.3 ± 10.0
Cognitive function	51.3 ± 9.3	51.5 ± 8.9	51.1 ± 9.7
Fatigue	50.3 ± 9.3	50.3 ± 9.5	50.2 ± 9.1
Sleep disturbance	49.0 ± 9.3	49.0 ± 9.2	49.1 ± 9.4
Depression	50.3 ± 9.0	50.2 ± 9.1	50.5 ± 9.0
Anxiety	49.4 ± 9.3	49.5 ± 9.3	49.3 ± 9.4
Pain interference	51.9 ± 9.7	51.5 ± 9.7	52.3 ± 9.7
Social participation	51.8 ± 10.5	51.7 ± 10.4	51.9 ± 10.5
Summary scores			
PROMIS physical health	44.8 ± 10.1	44.5 ± 10.1	45.1 ± 10.2
PROMIS mental Health	50.3 ± 8.9	50.2 ± 9.0	50.3 ± 8.8
SF-12 physical component score	42.4 ± 9.2	42.4 ± 9.1	42.5 ± 9.2
SF-12 mental component score	47.9 ± 12.0	48.3 ± 11.8	47.5 ± 12.2
EQ-5D health utility	0.8 ± 0.3	0.8 ± 0.2	0.8 ± 0.2
EQ-5D VAS	68.0 ± 21.0	68.3 ± 20.7	68.2 ± 20.8

EQ-5D, xxx; IQR, interquartile range; PROMIS, Patient-Reported Outcome Measurement Information System; SF-12, xxx; TIA, transient ischemic attack; VAS, xxx.

[a]Cardiovascular disease includes history of any 1 or more of: angina, myocardial infarction, coronary stent or dotter procedure and coronary artery bypass graft, diagnosis of congestive heart failure, atrial fibrillation, TIA, cerebrovascular accident, abdominal aortic aneurysm or intermittent claudication, placement of pacemaker or internal defibrillator, carotid endarterectomy, stent or dotter procedure, bypass surgery or amputation of the arteries of the lower extremities, and stent or dotter procedure of the renal arteries.

[b]Body surface area was calculated using the Du Bois formula.

[c]Geometric mean of predialysis and postdialysis serum measurements.

[d]Blood flow rate through extracorporeal circuit.

[e]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.

Data are given as mean ± SD unless otherwise indicated.

(49.0–51.9; SD, 9.0–10.5). Summary scores for mental health show a mean similar to the general population (PROMIS mental health summary score, 50.3 SD, 8.9; SF-12 mental component score, 52.1 SD, 7.1), and diminished physical health status, scoring half an SD below the representative general population at baseline (PROMIS physical health summary score, 44.8; SD, 10.1; SF-12 physical component score, 44.6; SD, 7.2). Over the course of the study, we observed a small to modest HRQoL deterioration affecting all domains (Figure 2).

For all scales, the observed HRQoL decline was slower in the HDF group. After 30 months, the most prominent score change was reported by patients receiving HD treatments with respect to their physical function (–3.90 [95%

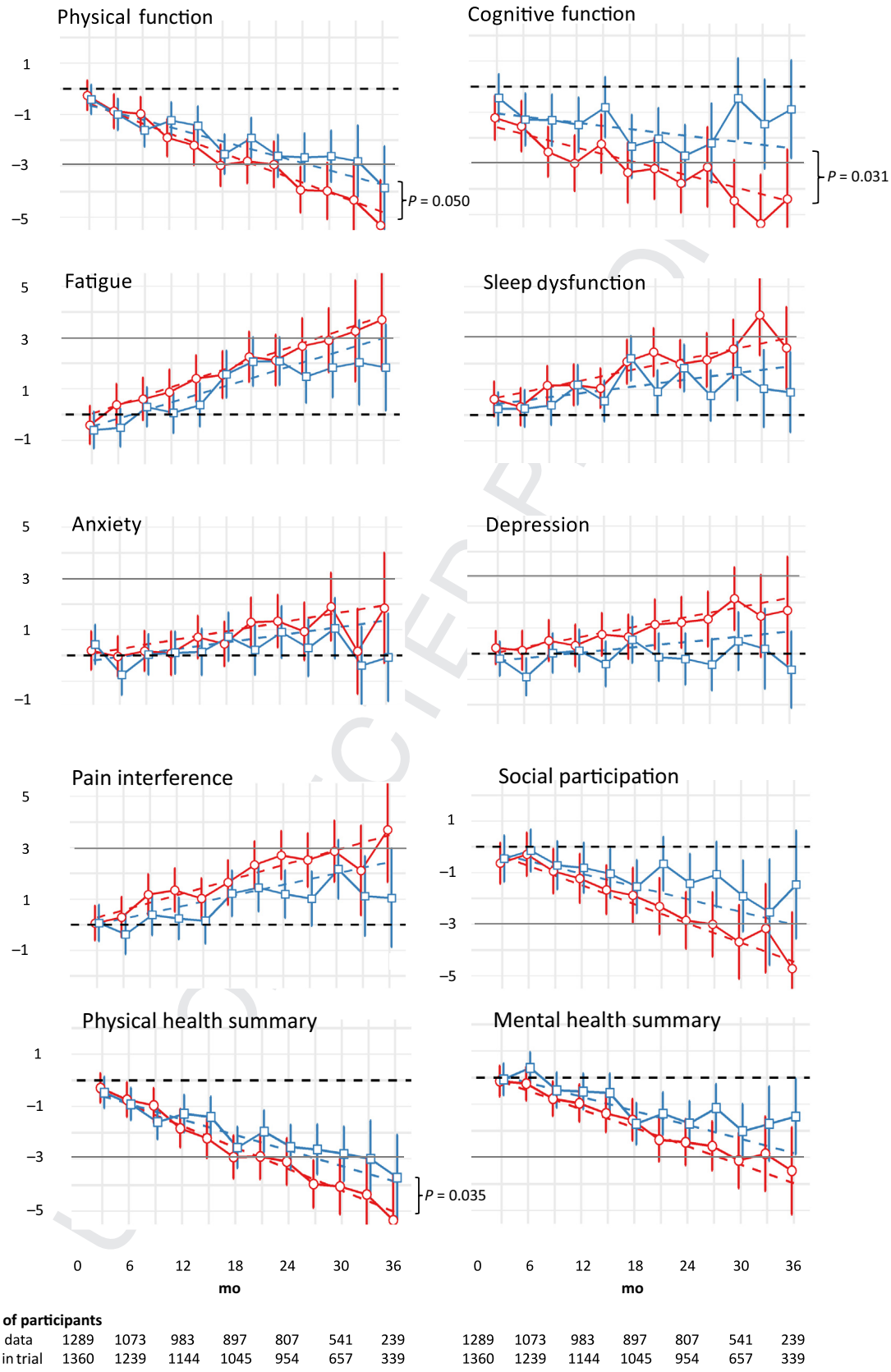

Figure 2 | Patient (Pat.)-reported health status trajectory. Red: hemodialysis group; blue: hemodiafiltration group. Dotted line: estimated health decline based on linear mixed model (LMM); for fatigue, sleep disturbance, anxiety, depression, and pain interference, higher scores mean less favorable health; for all other scales, lower score indicate less favorable health. Error bars are 95% confidence intervals. *P* values refer to group × time interaction effects in the LLM (see Table 2). PRO, patient-reported outcome.

confidence interval {CI}, –4.96 to –2.85]), cognitive function (–3.90 [95% CI, –5.28 to –2.52]), and social participation (–3.62 [95% CI, –4.68 to –2.56]). The overall HRQoL, including all domains, was significantly better for the HDF group after 30 months compared with the HD group ($P = 0.006$). The most relevant score differences between both groups were observed for cognitive function (2.95 [95% CI, 1.06–4.84]), followed by social participation (1.65 [95% CI, 0.17–3.13]), and physical function (1.20 [95% CI, –0.27 to 2.68]) (Table 2). Individual item analyses did not reveal additional insights. Descriptive findings for the symptom list from the KDQoL, EQ-5D, SF-12, and PHQ-9 are reported in Supplementary Figure S1.

Within the linear mixed model, all patients with a baseline score and at least 1 follow-up assessment could be included. No baseline differences between patients with and without any follow-up assessment were observed. The linear mixed model showed a statistically significant interaction effect between time and group allocation for cognitive function and the physical health summary score ($P = 0.030$ and 0.035). The estimated change per year in overall physical health was –1.65 for those receiving HD, whereas for patients treated with HDF, it was –1.19 units. Cognitive function declined twice as fast for the HD group compared with the HDF group (–1.05 vs. –0.49 units/year; Table 2 and Supplementary Table S9).

The joint model gave similar estimates to the linear-mixed model. For 4 of 8 domain scales, the joint model identified a statistically significant slower decline for the HDF group (physical function, cognitive function, pain interference, and social participation). Slopes had been 25% to 50% flatter within the intervention group (i.e., patients undergoing HDF could retain their physical and social health status considerably longer than those patients receiving HD; Table 2 and Supplementary Table S10), with estimated scores falling below a 3-unit mark between 6 and 18 months later for physical function, social participation, and cognition (Figure 2).

DISCUSSION

In this open-label RCT, participants reported a slow, but constant, decline in all aspects of their perceived HRQoL over the study period. A more noticeable deterioration was observed for scales measuring aspects of physical or social health, whereas affective health aspects (i.e., depression and anxiety) remained comparatively more stable.

The perceived HRQoL change was more pronounced for the HD group in all scales. Patients receiving HD treatment reported the most prominent decline in HRQoL with respect to their physical function. After 30 months, the remaining study participants showed a decline in this domain by nearly 4 units; after 3 years, by>5 units (i.e., a decrease from the 27th percentile to the 14th percentile of the general population). Cognitive function, as well as the patients' ability to participate in social roles, declined by >3 units in the HD-treated group (i.e., 30% of the SD of the general population).

HDF treatment sustained HRQoL more effectively. Patients reported a similar trajectory, but their perceived health deterioration was significantly slower for physical function, cognitive function, as well as their ability to participate in social role activities. Observed scores in all domains were more favorable for the HDF group early on, with score differences between groups increasing over time; this was more noticeable in scales with a steeper decline. Overall, we observed a consistent pattern of positive effects for patients receiving HDF treatment, which sums up to a statistically significant difference in their HRQoL after the median observation period of 30 months and beyond.

Previously, there have been several smaller studies, with inconsistent results about potential positive effects of HDF on patient HRQoL.[9–18] Mostly inconsistencies of interventional studies comparing HDF with HD had been discussed with respect to small sample sizes, short follow-up, differences in instruments being used, or the fact that studies failed to achieve the targeted high convective dose. As there is some variable convective clearance with high-flux HD, then, when the threshold convective dose with HDF, which reflects the driving force of the intervention, is not achieved, one cannot expect to observe a positive impact, neither on the patients' perception of health nor on cardiovascular end points.

In addition, some fundamental considerations about the perception of health have rarely been reflected, which also affect the choice of psychometric methods. Our baseline assessments demonstrated that the study population reported a reduced physical health status (physical health summary score, 44.8 ± 10.1; physical component score, 44.6 ± 7.2), but a mental health status similar to those of representative general population values (mental health summary score, 50.3 ± 8.9; mental component score, 52.1 ± 7.1). The latter may seem astounding, given that patients with KRT are experiencing a life-limiting condition. Yet, this observation is in accordance with other large studies. The Convective Transport Study (n = 714 patients) reported a similar observation, with an unimpaired mental health status (mental component score, 50 ± 12), and more diminished physical health status (physical component score, 40 ± 10).[14] Also, in 1 of the largest cohorts studying patients with chronic kidney failure (CRIC Study),[35] it was demonstrated that their overall mental health status was unimpaired (mental component score, 50.4 ± 10.5; physical component score, 41.3 ± 11.5), and independent from disease status or laboratory results. Obviously, patients with kidney failure, or other chronic conditions,[36] can adapt relatively well to their situation. Being able to accept deteriorating health states is a key psychological function to stay subjectively "healthy." This adjustment of expectations is also known as "response shift," and may potentially interfere with and reduce any effects attributable to an intervention.[37,38]

The CONVINCE study demonstrates that depression and anxiety remained largely stable over the study period in both groups, whereas physical health scores declined slowly and steadily. Similar observations were made in the Convective

Table 2 | Change scores and group differences

Variable	Raw change score (baseline to 30 mo), mean (95% CI)			Raw change score (baseline to 36 mo), mean (95% CI)		
	HD	HDF	ΔHDF–HD	HD	HDF	ΔHDF-HD
Domains						
Physical function	**−3.90** (−4.96 to −2.85)	−2.70 (−3.73 to −1.67)	1.20 (−0.27 to 2.68)	**−5.35** (−7.07 to −3.62)	**−3.84** (−5.36 to −2.31)	1.51 (−0.80 to 3.81)
Cognitive function	**−3.90** (−5.28 to −2.52)	−0.95 (−2.23 to 0.34)	2.95 (1.06 to 4.84)	**−3.41** (−5.15 to −1.68)	−1.65 (−3.18 to −0.11)	1.77 (−0.56 to 4.10)
Fatigue	2.92 (1.87 to 3.97)	1.81 (0.78 to 2.85)	−1.10 (−2.58 to 0.37)	**3.45** (1.74 to 5.16)	2.02 (0.50 to 3.55)	−1.43 (−3.72 to 0.86)
Sleep	2.33 (1.27 to 3.39)	1.94 (0.91 to 2.97)	−0.39 (−1.87 to 1.09)	1.81 (0.07 to 3.55)	1.52 (−0.02 to 3.05)	−0.30 (−2.63 to 2.03)
Depression	1.79 (0.73 to 2.85)	0.83 (−0.20 to 1.87)	−0.96 (−2.44 to 0.52)	1.07 (−0.67 to 2.80)	−0.13 (−1.67 to 1.40)	−1.20 (−3.53 to 1.12)
Anxiety	1.73 (0.67 to 2.79)	1.22 (0.19 to 2.26)	−0.50 (−1.99 to 0.98)	1.24 (−0.50 to 2.98)	0.39 (−1.13 to 1.92)	−0.85 (−3.17 to 1.48)
Pain interference	2.76 (1.70 to 3.82	2.26 (1.23 to 3.29)	−0.50 (−1.97 to 0.98)	**3.33** (1.60 to 5.07)	1.32 (−0.21 to 2.85)	−2.01 (−4.33 to 0.31)
Social participation	**−3.62** (−4.68 to −2.56)	−1.97 (−3.00 to −0.93)	1.65 (0.17 to 3.13)	**−4.59** (−6.31 to −2.86)	−1.57 (−3.10 to −0.04)	3.02 (0.71 to 5.33)
Omnibus test		***P* = 0.006** favors HDF			***P* = 0.037** favors HDF	
Summary scores						
Physical health	**−4.02** (−4.99 to −3.05)	−2.84 (−3.79 to −1.89)	1.17 (−0.18 to 2.53)	**−5.46** (−7.06 to −3.86)	**−3.62** (−5.03 to −2.21)	1.84 (−0.29 to 3.97)
Mental health	**3.08** (−4.05 to −2.11)	−2.04 (−3.00 to −1.09)	1.03 (−0.33 to 2.39)	**−3.34** (−4.94 to −1.74)	−1.59 (−3.00 to −0.18)	1.75 (−0.39 to 3.88)

CI, confidence interval; HD, hemodialysis; HDF, hemodiafiltration; LLM, linear-mixed model; NS, not significant group × time effect ($P > 0.05$).
[a]All time effects are statistically significant ($P < 0.05$) (i.e., showing a health deterioration in all domains.
[b]All group effects are not significant ($P > 0.05$) (i.e., showing no average group difference over time).
[c]Exact *P* value for physical function in LLM was $P = 0.0499$; cells are highlighted if mean difference is >3 units.
The table illustrates 3 types of analyses. Change scores describe the difference between the baseline score and the score at 30/36-month follow-up. Group differences between interventions were tested for all scales in 1 omnibus test. CIs have not been adjusted for multiplicity and should not been used for hypothesis testing. The linear mixed and joint model illustrate the estimated score change per year for the HD group (time), the average mean difference between both groups over the entire observation period (group), as well as the interaction effect (time × group) (i.e., the difference between the slopes of the HD and HDF group). HDF slopes can be calculated adding time effect with time × group interaction effect (e.g., physical health in LLM: −1.65 + 0.46 = −1.19: decline of physical health scores in the HDF group is 1.19 units/year). Bold data indicate XXX.

Transport Study study.[14] This picture was consistent across scales capturing different aspects of physical health. The average decline in CONVINCE reached 3 to 5 scoring points after 3 years on a T-score metric (i.e., approximately one-third to one-half of the SD of the representative population for physical and cognitive function domains). A regression model estimated a mortality-adjusted decline for physical function and social participation of 4 to 5 units over 3 years in the HD group.

Given the relative stability of perceived HRQoL domain scores in gradually progressing conditions, such as kidney failure, differential treatment effects are particularly hard to detect. We were able to apply advanced, domain-oriented patient-reported outcome assessments, to frequently collect results within a large sample, to detect potential treatment effects more sensitively than in previous studies. CONVINCE study data show that for all scales that did not change substantially, no group differences were seen. For almost all scales showing a relevant health deterioration in the HD group, a significantly slower deterioration was observed in the HDF group. We believe that the consistent pattern and solid data base allows the conclusion that HDF has a noteworthy positive effect on physical and social aspects of HRQoL, greater than that observed with hemodialysis, which gained importance over time.

However, although the CONVINCE study is 1 of the most comprehensive RCTs in this field, it has some limitations, which need to be taken into account. The investigated sample had an overall risk of death that was lower than that generally reported, potentially limiting generalizability of our results.[23] The effect sizes may have been different if a less healthy population would have been studied, and this is reflected exclusively in the perception of in-center treated patients. To achieve a meaningful sample size, patients who had previously experienced HD were included. As participants could not be blinded with respect to their treatment, we would expect instant anticipation effects for those switching to a different intervention, if there had been a placebo effect. However, this seems most unlikely as these effects gradually increased over time to explain the time-group-interaction effects we observed.

As of now, there is no established threshold for PROMIS measures (i.e., what score differences should be considered as meaningful for individuals or groups of patients with KRT). The absolute group differences observed in this study could well be considered as small effects. Yet, as the perceived HRQoL deterioration under KRT is generally modest, large treatment differences would not be expected. On the other hand, relative slope differences between treatment groups were rather large (i.e., Δ30% for social participation, or Δ49% for cognitive function). For practical purposes, we suggest that a reasonable threshold may be a deterioration of >3 units (i.e., 30% of an SD of the general population) (Figure 2). The same margin has been recommended for longitudinal studies for PROMIS physical function scores previously reported in patients with cancer.[39]

The CONVINCE trial allowed a comprehensive evaluation of HRQoL, as a more frequent assessment of patient-reported health data was performed than in any other previous RCT.[14] In total, 10,681 sets of questionnaires, including answers to >500,000 items, have been analyzed for this report. However, despite efforts to collect as much patient-reported outcome data as possible, not all patients were able or willing to

Table 2 | (Continued)

Linear-mixed model estimates, mean (95% CI)				Joint model estimates, mean (95% CI)			
Time, yr[a]	Group[b]	Time × group	*P*	Time, yr[a]	Group[b]	Time × group	*P*
−1.53 (−1.82 to −1.24)	−0.16 (−0.89 to 0.58)	0.41 (0.00 to 0.82)	0.050[c]	−1.76 (−2.07 to −1.44)	−0.18 (−0.90 to 0.54)	0.42 (0.00 to 0.83)	0.047
−1.05 (−1.41 to −0.68)	0.40 (−0.56 to 1.36)	0.56 (0.05 to 1.06)	0.031	−1.04 (−1.43 to −0.66)	0.46 (−0.50 to 1.42)	0.51 (0.00 to 1.02)	0.049
1.39 (1.08 to 1.69)	−0.47 (−1.30 to 0.37)	−0.13 (−0.56 to 0.30)	NS	1.62 (1.24 to 2.01)	−0.46 (−1.27 to 0.35)	−0.15 (−0.58 to 0.29)	NS
0.85 (0.55 to 1.14)	−0.16 (−0.89 to 0.56)	−0.32 (−0.73 to 0.09)	NS	0.94 (0.63 to 1.26)	−0.14 (−0.87 to 0.59)	−0.36 (−0.77 to 0.06)	NS
0.78 (0.48 to 1.07)	−0.24 (−1.01 to 0.52)	−0.36 (−0.77 to 0.05)	NS	1.09 (0.80–1.39)	−0.28 (−1.01 to 0.45)	−0.34 (−0.75 to 0.06)	NS
0.69 (0.38 to 0.99)	−0.24 (−1.04 to 0.56)	−0.12 (−0.55 to 0.31)	NS	0.84 (0.50 to 1.17)	−0.24 (−1.03 to 0.54)	−0.12 (−0.56 to 0.31)	NS
1.17 (0.87 to 1.48)	−0.18 (−0.98 to 0.61)	−0.29 (−0.72 to 0.14)	NS	1.25 (1.00 to 1.51)	−0.14 (−0.90 to 0.62)	−0.40 (−0.75 to −0.04)	0.027
−1.49 (−1.86 to −1.11)	−0.06 (−1.00 to 0.88)	0.50 (−0.03 to 1.03)	NS	−1.63 (−1.93 to −1.32)	−0.07 (−0.97 to 0.83)	0.49 (0.07 to 0.91)	0.023
−1.65 (−1.95 to −1.34)	−0.20 (−0.95 to 0.54)	0.46 (0.03 to 0.88)	0.035	−1.86 (−2.19 to −1.54)	−0.22 (−0.95 to 0.51)	0.46 (0.03 to 0.89)	0.037
−1.39 (−1.66 to −1.11)	0.14 (−0.56 to 0.84)	0.33 (−0.05 to 0.71)	NS	−1.61 (−1.91 to −1.32)	0.14 (−0.54 to 0.82)	0.34 (−0.05 to 0.73)	NS

respond. Follow-up assessments were obtained from 84.0% of all patients remaining in the study. Overall, our attrition rate is comparable with other larger studies in patients with kidney failure.[14,35] Furthermore, the attrition rate was not different in the 2 treatment groups.

In conclusion, we observed a moderate generic positive effect for consistently administered high-dose HDF on the HRQoL perceived by the patients, most pronounced on their cognitive function. Similar to the observed better survival,[22] the effect became more relevant over time.

DISCLOSURE

MR is codeveloper of the PROMIS instruments. FHF is member of the PROMIS health organization board. GFMS is a former employee of Diaverum. CB is an employee at B.Braun. BC is a former employee of Fresenius Medical. AC, KC, and AMC are employees of Fresenius Medical. AD is coinvestigator of a similar randomized controlled trial in the UK. KIF is a former employee of Roche Products Ltd and a current employee of Boehringer Ingelheim. JH serves on the Board of Directors of NorrDia AB, provides consultancy services to Triomed AB, and is a former employee of Diaverum AB. MT is employee of Diaverum. MW has been a recent consultant to Amgen and Freeline. All the other authors declared no competing interests.

DATA STATEMENT

Q21 Study data can be requested from the CONVINCE consortium. Access will be limited to address scientific questions. Some data contain information that would allow access to proprietary information from the participating companies. Those data will only be shared on an aggregated level after agreement of the participating companies.

ACKNOWLEDGMENTS

Q22 The CONVINCE trial is an investigator-initiated project, funded by a research grant from the European Union. Members from participating companies were part of the study design and participated as members of the scientific committee on the preparation of the manuscript. They have not been involved in the data analysis. We acknowledge the contribution of the participating patients, taking the time and effort to respond to a large amount of questionnaires for several years, as well as all members of the staff working in the participating dialyses centers. Without their support the study would not have been possible.

FUNDING STATEMENT

This study was funded by the European Commission (Horizon 2020 Q29 research and innovation program, agreement 754803).

AUTHOR CONTRIBUTIONS

The first author prepared all drafts and the final manuscript and had unrestricted access to the data. FHF and CH had main responsibility for the data analyses. All drafts and the final manuscript were reviewed and edited by all authors, who agreed to submit the article for publication. They all vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Supplementary material is available online at www.kidney-international.org. Q23

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