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EDITORIAL

CONVINCE in the context of existing evidence on haemodiafiltration

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Haemodiafiltration (HDF) provides a greater removal of larger solutes and protein-bound compounds than conventional high-flux haemodialysis (HD). There are indications that the patients receiving the highest convection volumes of HDF result in improved survival compared with HD. However, the comparative efficacy of HDF versus HD remains unproven. Here we provide a comparative account of the methodology and aims of 'the comparison of high-dose HDF with high-flux HD' (CONVINCE) study in the context of the totality of evidence and how this study will contribute to reaching a higher level of certainty regarding the comparative efficacy of HDF versus HD in people with end-stage kidney disease.

INTRODUCTION

Haemodiafiltration (HDF) combines diffusive and convective transport within the same exchange module, in contrast to haemodialysis (HD), which relies on diffusion. Improved haemodynamic tolerance can be an advantage of HDF and consequently improve clinical outcomes. Cardiovascular disease is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD), for which uraemic toxins and volume overload and management are likely important contributing factors. Although a rapid increase in the acceptance rate of HDF by the nephrology community is noted [1], the uptake of HDF into clinical practice has been variable across different regions and countries (e.g. 52% in Sweden compared with 14% in Australia) [2–4]. Also, the clinical guidelines have not reached a consensus on the treatment benefit of HDF. The UK National Institute for Health and Care Excellence (NICE) recommends to consider HDF rather than HD [5], yet other guidelines state that HDF might be considered or that additional research is needed to understand whether there is a superior clinical benefit of HDF [6, 7]. In this article, we provide a comparative analysis of 'the comparison of high-dose HDF with high-flux HD' (CONVINCE) study in the context of the totality of evidence and what it will add to build on existing knowledge.

EVIDENCE ON HDF

Mixed results regarding the mortality risk of patients treated with HDF have been reported in several large recent observational studies (Table 1) [3, 8–11]. However, confounding by indication and residual confounding cannot be excluded in these observational studies. The treatment decision regarding HDF, and its associated achieved convection volume, is generally based on clinical grounds and not on selection by chance [as in randomized controlled trials (RCTs)]. Focussing on RCTs instead, in a Cochrane review that included 35 studies with 4039 dialysis participants, no significant different effect on all-cause mortality, but a significantly reduced cardiovascular mortality, was found for convective dialysis [haemofiltration (HF), HDF and acetate-free biofiltration compared with HD] [12]. However, in these analyses of the Cochrane review mixed modalities were included, which are currently not used in routine care (e.g. haemofiltration or acetate-free biofiltration) or older studies that did not consider that convective dose might influence clinical outcomes. An individual participant data (IPD) meta-analysis, including four randomized clinical trials comparing HDF with HD, suggested the existence of a

Table 1. Current knowledge on haemodiafiltration (HDF) versus haemodialysis (HD) stratified by study design

Study design	Potential limitations of the study design	Results on HDF versus HD
Individual-patient data meta-analysis	• Not designed to study the effects of dosage of convection volumes • Heterogeneity across studies in HDF techniques	• Online HDF reduced the risk of all-cause mortality by 14% [95% confidence interval (CI): 1%; 25%] and cardiovascular mortality by 23% (95% CI: 3%; 39%). The largest survival benefit was for patients receiving the highest delivered convection volume, with a multivariable-adjusted hazard ratio (HR) of 0.78 (95% CI 0.62–0.98) for all-cause mortality and 0.69 (95% CI 0.47–1.00) for cardiovascular disease mortality [13].
Systematic reviews of randomized controlled trials	• High risk of bias of included studies (e.g. on allocation concealment, blinding, incomplete reporting) • Not designed to study the effects of convection volumes • Heterogeneity across studies in HDF techniques	• Convective dialysis (i.e. HF, HDF and acetate-free biofiltration) had no significant effect on all-cause mortality [relative risk (RR) 0.87, 95% CI 0.72–1.05], but significantly reduced cardiovascular mortality (RR 0.75, 95% CI 0.61–0.92). Sensitivity analyses limited to studies comparing HDF with HD showed very similar results. [12]. • In a meta-analysis of 6 RCTs, HDF treatment was related to a decreased risk of mortality (RR 0.84, 95% CI 0.73–0.96) and cardiovascular death (RR 0.73, 95% CI 0.57–0.92) compared with HD [14].
Observational studies	• Confounding by indication • Residual confounding • Evidence of association, not causation	• Adjusted mortality HR (95% CI) was 1.14 (1.00–1.29) for any HDF versus HD and 1.08 (0.92–1.28) for HDF >20 L replacement fluid volume versus HD [3]. • When compared with HD, HDF treatment was associated with reduced mortality in the multivariate survival analysis (HR 0.58, 95% CI 0.36–0.93) [8]. • A statistically significant survival advantage of HV-HDF (odds ratio 0.501, CI 0.366–0.684) [9]. • HRs for all-cause and cardiovascular mortality associated with HDF use were 0.84 (95% CI 0.77–0.91) and 0.73 (95% CI 0.61–0.88), respectively [10]. • Substitution volume between 21 and 25 L/session was associated with longer 5-year survival [11].

dose–response effect for convection volumes, i.e. the highest delivered convection volume was associated with the lowest risk for all-cause and cardiovascular mortality, with no differential effect across subgroups (e.g. by age, sex, comorbidity, albumin levels, dialysis vintage or vascular access) [13, 15]. Although safety was not a pre-determined defined endpoint in the previous HDF trials, there were no indications that HDF was unsafe.

Drawing a conclusion on the treatment benefit of HDF is complicated given that different HD (low-flux and high-flux) and HDF techniques were used across different studies and RCTs, with differences in vascular access, blood flow and treatment times, as well as achieved convection volumes. Although a higher achieved convection has been associated with lower mortality [13], the actual delivered convection volume in the previous trials on HDF showed a considerable range as a consequence of the daily clinical practice. For example, the mean actual delivered convection volume ranged from 17.2 L/session [16], 20.7 L/session [17], to 22.9 to 23.9 L/session [18]. The RCTs were not designed to study the effects of convection volumes, with no randomized treatment targets and hence the possibility of confounding by indication cannot be excluded (i.e. a high convection volume is more likely to be achievable in patients with the least comorbidities and thus conferring a lower mortality risk). This occurs when the variables that predispose selection in the dosage of the intervention are also related to outcomes. The patient and treatment characteristics that are associated with achieving higher convective volumes (e.g. less comorbidities, vascular access, blood flow) are also independently associated with mortality and may therefore explain the beneficial effects reported for strata of convection volume [13]. Some observational studies state that the patient characteristics associated with worse prognosis (e.g. age, comorbidities, body mass index) affect the likelihood of achieving high convection volumes [11, 19]. However, this has been contradicted by a recent RCT, where a high convection volume (defined as >22 L/treatment) was achieved in 99% patients randomized to HDF, across different vascular access types, comorbidities and baseline biochemical variables [20]. Nevertheless, this study population might not reflect the dialysis population given the low mean age (i.e. 53 years) and little information reported on the selection procedure and participating centres. These discrepancies might be partly explained by differences in achieved blood flows and treatment times across the studies. Consequently, the positive effects of higher convection volumes might not be extrapolated to the overall dialysis population.

Furthermore, mechanisms of a possible beneficial effect for survival using HDF have not been elucidated. HDF removes middle-sized molecules more effectively than high-flux HD, thereby improving the uraemic environment [21]. It is likely that Kt/V during high-volume HDF will be higher than during high-flux HD, indicating that small solute clearance is also increased. It will be unclear whether this is of relevance in explaining a possible beneficial effect of HDF. It has been

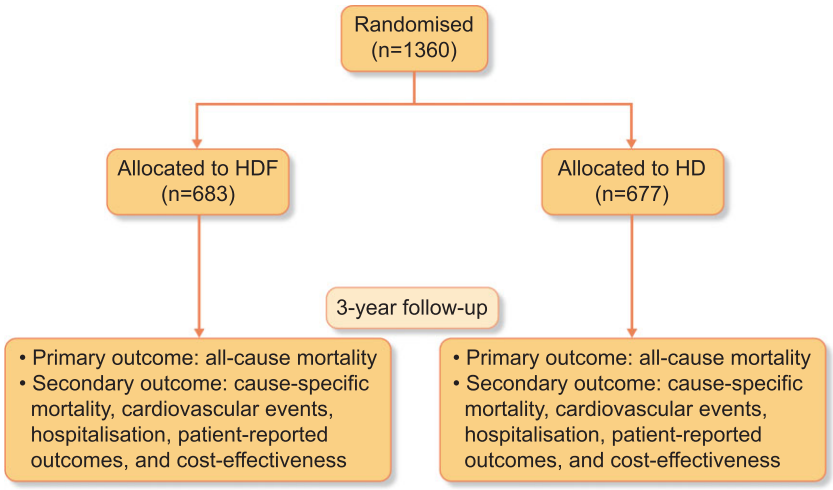

FIGURE 1: Flow chart of the CONVINCE study population, including assessment of the outcomes during follow-up.

suggested that improved haemodynamic stability during HDF could play a role due to the increased thermal losses [22], and less frequent hypotension during dialysis occurs during HDF [23]. Also, a better endothelial function [14, 24], improved cardiac output [25] and less vascular stiffness [24] was found in patients treated with HDF. Better preservation of residual renal function, and a higher proportion of patients with a decline in the left ventricular mass index, has been demonstrated in the HDF patient group compared with patients treated with HD [26]. Yet, no difference in cardiac wall motion abnormalities between patients treated with HDF versus HD was found [27]. Also, no differences in echocardiography with respect to left ventricular mass, ejection fraction or pulse-wave velocity were identified between patients treated with HDF versus low-flux HD [14]. A recent Japanese study on pre-dilution HDF indicated that a beneficial effect was already evident after only a few months of HDF treatment, which might be caused by haemodynamic effects, rather than structural (cardiovascular) changes [28]. A reduction in inflammation, oxidative stress and infection have been suggested, due to the ultrapure dialysate fluids in HDF [29, 30]. At the same time, further efforts are required to explore whether the potential improved patient outcomes of higher convective volumes are caused by its impact on traditional risk factors (blood pressure control, anaemia, cholesterol and glycaemic control) or non-traditional risk factors, such as electrolyte mass balance (e.g. sodium, potassium), but also on potential greater removal of unwanted solute mass (e.g. amino acids, small peptides, nutrients, albumin loss).

OPEN QUESTIONS ABOUT HDF VERSUS HD AND THE RECENT ATTEMPTS TO ADDRESS THEM: THE CONVINCE AND H4RT TRIALS

Since there is no definite proof that online high-volume HDF is superior to high-flux HD, two important initiatives were started recently. Funded by a grant from the European Commission, we initiated the CONVINCE study, which is a collaboration between dialysis departments in academic hospitals, general hospitals and a clinical network of private-for-profit renal care providers of Fresenius, BBraun and Diaverum [31]. CONVINCE has recruited 1360 patients in 61 dialysis centres, both academic and hospital based-dialysis centres, and private dialysis providers, in seven European countries (Figure 1). Patients were selected within the populations of the participating centres. We did not collect the characteristics of the total potentially available study population due to logistical and organizational reasons. However, the patients included in CONVINCE will be compared with registries data to identify important differences. The lack of this information might be considered as a limitation of our study. The trial is designed with a follow-up time for each patient of at least 24 months and will run up to 2023. The other study is the High-volume HDF versus High-flux HD Registry Trial (H4RT) study, which aims to assess the effects of high-volume HDF treatment compared with high-flux HD with 32–50 months of follow-up [32]. This study runs in 31 centres in the UK, for which recruitment started in November 2017 and is estimated to run until March 2022. Both studies are currently prolonged due to the COVID-19 pandemic.

There are some minor differences between H4RT and CONVINCE (Table 2). First, the inclusion criteria. In CONVINCE patients with end-stage kidney disease (ESKD) who have received at least 3 months of HD treatment are recruited [31], compared with ESKD patients who received a minimum of 4 weeks of maintenance HD or HDF in the H4RT trial [32]. There are also differences in the outcomes. For example, in H4RT the primary outcome is a composite of non-cancer mortality or hospital admission for a cardiovascular event or infection, compared with all-cause mortality in CONVINCE [31, 32]. In H4RT, the impact on sustainability/ecology is studied as a secondary outcome, but no such analysis is scheduled in CONVINCE. Subgroup analyses will be important to try to explore which groups of patients may benefit the most from either treatment; that is, to explore treatment heterogeneity [33]. Both studies will contribute to this. In CONVINCE the pre-determined subgroup analyses are based on age, sex, residual kidney function, diabetes, cardiovascular disease, serum albumin, vascular access and dialysis vintage. In H4RT the pre-determined subgroup analyses are based on residual

Table 2. Comparison of the protocols of the CONVINCE and H4RT study

	CONVINCE	H4RT
Intervention	• High-dose HDF with online production of substitution fluid and ultrapure dialysis fluid. Substitution fluid should be infused in post dilution mode. High-dose HDF is defined as a convection volume of ≥ 23 L (range ± 1 L)	• High-volume HDF (aiming for 21+ L of substitution fluid per session adjusted to body surface area
Comparator	• High-flux HD using high-flux dialysis membranes and ultrapure bicarbonate-based dialysis fluid as standard of dialysis care	• High-flux HD aiming for a small solute clearance comparable to the high-volume HDF • (Kt/V = 1.4)
Primary outcome	• All-cause mortality	• A composite of non-cancer mortality or hospital admission with a cardiovascular event or infection within 3 years
Secondary outcomes	• Cardiovascular events • Cause and infection-related hospitalizations • Patient-reported outcomes o Patient-Reported Outcomes Measurement Information System (PROMIS) Fatigue 6-item customized short form o Dialysis-related time to recovery module o Modified Kidney Disease Quality of Life (KDQOL) symptom checklist o Health transition items (2 items of the SF-36) o PROMIS Physical Function 4-item short form (part of the PROMIS Profile-29) o PROMIS Cognitive Abilities 4-item customized short form o PROMIS Pain Interference 4-item short form (part of the PROMIS Profile-29) o PROMIS Pain Intensity one item (part of the PROMIS Profile-29) o PROMIS Anxiety 4-item short form (part of the PROMIS Profile-29) o PROMIS Depression 4-item short form (part of the PROMIS Profile-29) o PROMIS Ability to participate in social roles and activities 4-item short form (part of the PROMIS Profile-29) o PROMIS Sleep disturbance 4-item short form (part of the PROMIS Profile-29) • Cost-effectiveness o EQ-5D-5L	• All-cause mortality • Cardiovascular and infection related morbidity and mortality • Health-related quality of life (HRQoL) a. quality adjusted life years gained (EQ-5D-5L) b. generic quality of life (SF-36) c. disease specific (kidney disease symptoms within KDQOL-36) and time to recover after each dialysis • Cost-effectiveness • Environmental impact
Inclusion criteria	• Signed and dated written Informed Consent Form obtained from the participant or his/her guardian or in accordance with local regulations • Aged ≥18 years • Diagnosed with ESKD • On HD treatment for ≥3 months • Likely to achieve high-dose HDF (≥23 L, in post-dilution mode), according to the protocol • Willing to have a dialysis session with duration of ≥4 h, three times a week • Understands study procedures and is able to comply	• Adult patients receiving in-centre, maintenance HD for ESKD • Dialysing three times a week in a main dialysis or satellite unit • Potential to achieve high-volume HDF • Signed and dated written informed consent form the participant
Exclusion criteria	• Severe participant non-compliance defined as severe non-adherence to the dialysis procedure and accompanying prescriptions, especially frequency and duration of dialysis treatment • Life expectancy <3 months • HDF treatment < 90 days before screening • Anticipated living donor kidney transplantation <6 months after screening • Evidence of any other diseases or medical conditions that may interfere with the planned treatment, affect participant compliance or place the participant at high risk for treatment-related complications • Participation in any other study will be discussed with and decided by the Executive Board • Unavailable ≥3 months during the study conduct for study visits	• Lack of capacity to consent • Clinician predicted prognosis of <3 months • Started maintenance HD or HDF within the preceding 4 weeks • Transition to living kidney donor transplant or home dialysis scheduled within next 3 months • Not suitable for high-volume HDF for other clinical reasons such as dialysis less than thrice weekly or unlikely to achieve sufficient blood flow rates with current vascular access, or prior intolerance of HDF
Pre-determined subgroup analyses	• Age (<50, 50–65, >65 years) • Sex • Residual renal function (<200 mL/day, 200–1000 mL/day, >1000 mL/day) • Diabetes • Cardiovascular disease • Serum albumin (≤40 g/L) • Vascular access • Dialysis vintage (<2 years, 2–5 years, 5 years)	• Residual renal function (urine volume <100 mL/day and 100+ mL/day) • Age (18–64 years and 65 years)
Calculated sample size	• 1800 patients	• 1550 patients
Follow-up	• 3 years follow-up	• A minimum of 32 months and a maximum of 50 months

renal function and age. Apart from the differences between CONVINCE and H4RT, collaboration and harmonization of outcome definition and analyses across trials are envisaged in an IPD meta-analysis, using the crude individual-level data from both trials, taken together with the data from the IPD meta-analysis of Peters *et al.* [13], which will be updated. This might lead to individual patient data on at least 6000 people, almost double that of the previous Cochrane review (40 studies comprising 3483 participants). This will allow the dialysis community to explore, with greater precision, in which patient group the treatment estimates differ. This totality of evidence is expected to provide a conclusive 'end of discussion' in the comparison of HDF and HD.

INNOVATIONS IN PATIENT-REPORTED OUTCOMES

Mortality, or cardiovascular morbidity, should not be the only outcomes that inform treatment decisions. It is increasingly acknowledged that, even more so in the absence of a difference in other endpoints, differences in patient-reported outcomes might be equally important. For example, a change in nutritional status alone might be a reason to prefer one dialysis modality over the other [34]. Previous studies have focussed largely on established clinical outcomes. The effects of HDF on health-related quality of life (HRQoL) and fatigue are important, but have been scarcely investigated [12, 35–37]. Most studies, albeit with limited sample sizes and a short duration of follow-up (<2 years), suggest no differences in HRQoL scores between HDF and HD patients [12, 35, 37–40]. Conversely, others have demonstrated a beneficial effect of HDF on HRQoL, including social, physical and professional domains in association with fewer episodes of hypotension, cramps, itching, fatigue, joint pain and stiffness [26, 36, 39, 41].

However, generic HRQoL questionnaires (SF36 or EQ-5D) are not sufficiently specific or sensitive tools to explore the effects of dialysis on ESKD patients' perception. Likewise, the accuracy and validity of the disease-specific Kidney Disease Quality of Life (KDQOL) survey are questionable [42]. It has recently been shown that more specific questions regarding dialysis had more predictive value for patient outcomes with CKD than the generic HRQoL questionnaires [43–46]. Both CONVINCE and H4RT aim to elucidate the difference between HDF and HD in terms of patient's HRQoL and cost-effectiveness. The number of domains to be addressed in CONVINCE is larger and more comprehensive than H4RT. CONVINCE identifies health domains and symptoms relevant to ESKD patients based on established core outcomes sets (i.e. the Standardised Outcomes in Nephrology initiative, International Consortium for Health Outcomes Measurement [47, 48]) and input from patients and health care professionals. Most of these health domains are assessed by PROMIS® (customized) short forms, complemented by a modified version of the KDQOL symptom checklist and a newly developed module to assess dialysis-related time to recovery (Table 2). In contrast, H4RT is using a conventional approach to assess HRQoL in patients with ESKD, combining generic and disease-specific legacy measures. In CONVINCE, additional psychosocial factors (i.e. stress, self-efficacy and social support) are assessed at baseline that are considered as potential predictors of the disease trajectory that may influence treatment success. Furthermore, performance-based measures to assess the physical performance of patients were included at baseline. Further investigation is required to explore which domains in HRQoL, e.g. fatigue, mental health, social activities, differ between HD versus HDF.

INNOVATION IN METHODOLOGY AND DATA ANALYSIS

The quality of evidence of the studies included in the Cochrane review was considered low to very low due to the high risk of bias (e.g. allocation concealment, blinding, incomplete reporting and mixed modalities) in the included studies (Table 3) [12]. Of the four RCTs included in the IPD meta-analysis [13], the methodological quality was also considered suboptimal. For example, allocation concealment, blinding of outcome assessment and incomplete outcome data were rated poorly in at least half of the RCTs. We expect that both the CONVINCE and H4RT study will provide high-quality evidence. Also, for at least the mortality outcomes, both trials will follow up with the patients who dropped out during the trial to minimize missing data.

When patients switch to the other treatment arm or receive alternative treatment that stops their HDF or HD treatment, estimation of treatment effects might be influenced, notably, if the switching of treatment depends on patient characteristics that are related to the risk of the outcome. Given the importance of considering concomitant kidney transplantation affecting the patient's prognosis, it is important that this is carefully considered before interpreting the treatment estimates [49]. Both CONVINCE and H4RT will take these concurrent treatments into account by accounting for post-randomization events through causal models to arrive at valid estimates of the difference between treatments [31, 32]. In CONVINCE, several reasons for study treatment discontinuation are defined, including: kidney transplant, moved to other dialysis centre, changed dialysis modality or stopped dialysis. Participants who discontinued the study treatment and consented to remain in the study will be followed for mortality and morbidity unless lost to follow-up or withdrawal of consent. The analytical approach is detailed in the CONVINCE statistical analysis plan (online appendix).

CONCLUSION

The comparative efficacy of HDF versus HD remains unproven given clinical and methodological heterogeneity across the available evidence. The two studies presently underway are aimed to provide a more firm statement and conclusion on the potential benefits and harms of high dose HDF versus high-flux HD for clinical and patient-reported outcomes and which group of patients, if any, may benefit the most from HDF treatment.

Table 3. Risk of bias of the four randomized controlled trials included in the individual patient data meta-analysis and the two ongoing trials.

	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
CONTRAST[a]	+	?	−	+	+	+
ESHOL[a]	+	?	−	−	−	+
French study	+	+	−	?	+	+
Turkish HDF 2013[a]	?	?	−	−	−	+
CONVINCE	+ (A block randomization scheme, stratified by centre)	+ (Allocation to high-flux HD and high-dose HDF will be concealed by central randomization)	− (Open label)	+ (Objective outcomes or self-reported outcomes)	+ (If a participant drops out e.g. due to kidney transplantation, switching to another dialysis modality or transferring out of the participating centre, effort will be made to collect information on his/her vital status until the end of the study follow-up)	+ (Netherlands National Trial Register—NTR 7138)
H4RT	+ (Randomization will utilize the existing remote automated computer randomization application)	+ (Randomization will be done using the Bristol Randomised Trials Collaboration Randomization System, which provides a secure service to generate allocations)	− (Open label)	+ (Objective outcomes or self-reported outcomes)	+ (Adherence to the protocol will be monitored through UK Renal Registry treatment modality returns and contact with dialysis units throughout the follow-up. As the UK Renal Registry follows all patients on renal replacement therapy in the UK, patients should not be lost to follow-up unless they move to another country)	+ (A priori developed protocol)

+: low risk of bias, ?: unclear risk of bias, −: high risk of bias, [a]as assessed by Nistor *et al.* (2015).

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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CONFLICT OF INTEREST STATEMENT

None declared. The opinions expressed in this manuscript reflect the view of the individual authors and not the view of the employers of the authors.

APPENDIX

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