Nephrol Dial Transplant, 2023, **0**, 1–3
https://doi.org/10.1093/ndt/gfad136
Advance access publication date: 30 June 2023

Haemodiafiltration for all: are we CONVINCEd?

Rukshana Shroff[1], Carlo Basile[2], Frank van der Sande[3] and Sandip Mitra[4]; on behalf of the EuDial Working Group[†] of the European Renal Association

[1]Renal Unit, UCL Great Ormond Street Hospital and Institute of Child Health, London, UK
[2]Associazione Nefrologica Gabriella Sebastio, Martina Franca, Italy
[3]Department of Internal Medicine, University Hospital Maastricht, Maastricht, The Netherlands
[4]Manchester Academy of Health Sciences Centre, Manchester University Hospitals, University of Manchester, Oxford Road, Manchester, UK
Correspondence to: Rukshana Shroff; E-mail: Rukshana.Shroff@gosh.nhs.uk
[†]Members of the EuDial Working Group are listed in the Acknowledgements.

Nearly 4 million people in the world receive life-sustaining kidney replacement therapy, with haemodialysis (HD) accounting for approximately 69% of all treatments [1]. Despite substantial improvements in dialysis technology the survival of patients on HD is lower than for many types of cancer [1]. Cardiovascular disease is a major cause of morbidity and accounts for almost 50% of deaths in HD patients. Although this high mortality is attributable to many causes, the limited clearance of potentially harmful middle molecules through standard HD may be a contributor. Online haemodiafiltration (HDF) augments the clearance of middle molecular weight uraemic toxins through convective clearance while standard HD treatment is mainly based on diffusion [2]. A number of biologically plausible explanations have been suggested for improved outcomes with HDF including the removal of middle-sized molecules more effectively than high-flux HD, increasing haemodynamic stability due to increased thermal losses during HDF, and reducing inflammation and oxidative stress. Convection volume, a key determinant of outcomes, is the cornerstone of treatment with HDF [2].

Four randomized controlled trials (RCTs) have compared all-cause and cardiovascular mortality between HDF and HD in patients receiving maintenance dialysis [3–6]. Of these, only the Estudio de Supervivencia de Hemodiafiltración Online (ESHOL) Trial, which achieved convection volumes of ≥18 L per session, demonstrated a significant reduction in all-cause mortality with on-line post-dilution HDF compared with high-flux HD [4]. Different HD (low- vs high-flux) and HDF techniques were used across the four RCTs, and patient demographics, access type, treatment time and the targeted versus actual delivered convection volume also differed. Importantly, in two of the RCTs a significant proportion of high-risk patients were removed from the HDF arm after randomization. Given the heterogeneity across these RCTs and methodological shortcomings, the relative efficacy of HDF versus HD remains unproven and current clinical guidelines have not reached a consensus on the treatment benefit of HDF.

THE CONVINCE TRIAL

The recently published CONVINCE (Comparison of high-dose HDF with high-flux HD) trial [7] aimed to address the methodological shortcomings of previous RCTs. Patients who had received at least 3 months of HD treatment were recruited from 61 dialysis centres in eight European countries and were randomized, with 683 in the high-dose HDF and 677 in the high-flux HD arms [7]. A key inclusion criterion was that the patient was likely to achieve a convection volume of ≥23 L/session in post-dilution mode [8]. The primary outcome was all-cause mortality, and key secondary outcome measures included cardiovascular events, hospitalizations, health-related quality of life measures and costs.

Despite block randomization stratified by centre only, at baseline both study arms were well balanced for age, sex, residual kidney function, access type, the number of smokers, and patients with diabetes and underlying cardiovascular disease. Over a median follow-up of 30 months deaths from any cause occurred in 118 (17.3%) in the HDF group and 148 (21.9%) in the HD group, such that there was a 23% higher risk of death in patients receiving high-flux HD compared with those receiving high-dose online HDF (hazard ratio 0.77, 95% confidence interval 0.65 to 0.93) [7]. In pre-determined subgroup analyses, mortality was significantly lower in patients >65 years of age, those with a dialysis vintage of <2 years, those dialysing through an arteriovenous fistula and those without pre-existing cardiovascular disease or diabetes [7]. While detailed exploratory analyses from the authors are awaited, these data suggest that older patients with fewer comorbidities are likely to have better outcomes with high-dose HDF compared with high-flux HD.

Using the time-to-event data, we calculate that one would need to treat 21 patients with high-dose HDF rather than high-flux HD for 3 years in order to prevent one death (from any cause) per year (95% confidence interval 14–68). Individual patient data from CONVINCE will augment the existing pooled individual participant data analysis [9] from previous RCTs [3–6] and may suggest that certain populations do better on HDF.

ARE WE CONVINCEd?

CONVINCE aimed to provide a conclusive 'end of discussion' RCT on the optimal dialysis modality for patients on long-term dial-

Received: June 22, 2023; Editorial decision: June 27, 2023

ysis. While the authors must be congratulated on performing a rigorous, large-scale trial during the COVID-19 pandemic, a major limitation of the study was that patients were selected from within the populations of the participating centres. This limitation was reported in a previous methodology article published by the CONVINCE scientific committee, acknowledging that the characteristics of the total potentially available study population was not collected for logistical and organizational reasons [10]. This preliminary selection of patients explains the very high recruitment rate (96.7% of patients who were approached agreed to participate) and a very low withdrawal or dropout rate (only 4.9% and 4.2% in HDF and HD cohorts, respectively). It also explains the very high percentage (>80%) of arteriovenous fistulas: investigators may have selected somewhat younger patients who were less frail and had fewer comorbidities, so that they could achieve the target convection volume. Thus, the CONVINCE population is not truly representative of the 'usual' population of adults receiving in-centre dialysis in Europe. Nevertheless, this recruitment strategy achieved impressive and consistently high convection volumes of 25.3 L/session throughout the 3-year study period, which has not been possible in any of the previous RCTs.

Several questions remain unanswered, many of which will no doubt be addressed in the *post hoc* analyses of CONVINCE. Meanwhile, a few points are discussed below:

(i) Despite well-matched groups, a significantly lower mortality was only seen in patients dialysing through an arteriovenous fistula and not in those with grafts or catheters, although a small sample size in the latter group may have reduced statistical power. It would be interesting to know the comparative blood flow rates and convection volumes through different access types.

(ii) Patients in both study arms achieved excellent blood flow rates of approximately 370 mL/min, consequently achieving very high clearance of low molecular weight solutes as evidenced by the excellent Kt/V (at least for the single-pool Kt/V analysis which is reported). However, small molecule clearance is unlikely to have improved outcomes, and clearance of middle molecules such as beta-2 microglobulin are more likely to influence outcomes, but have not been reported.

(iii) The CONVINCE investigators must be applauded for achieving a mean absolute convection volume of 25.3 L/session (95% confidence interval 24.8 to 25.7) over the 3-year study period, and consistently above the already high target of 23 L/session at all time points. However, when outcomes are stratified by convection volume it may become apparent that somewhat lower convection volumes may also achieve beneficial effects, or that there may be a ceiling effect beyond which no further benefit is seen. Perhaps, based on the clearance kinetics of different molecules, different outcomes may be seen at different convection volumes. Finally, to challenge the 'one-size-fits-all' concept, it is important to analyse outcomes after standardizing convection volumes for body size.

(iv) Although counterintuitive, patients with a low dialysis vintage of <2 years seem to have better survival on HDF. Early after dialysis start there is still residual diuresis and one would not expect a large survival benefit from HDF. Similarly, older patients achieved better survival on HDF, perhaps because there were too few deaths in the younger patients to show significant differences, or that these older adults without diabetes or cardiovascular disease were a selected group of survivors. These findings in subgroups may be biased by hidden confounders and require further analysis.

(v) A crucial piece of missing information is on the residual urine output, with data available in only 11%. With a median dialysis vintage around 33 months in CONVINCE, residual output is expected to be very limited, and the 'missing data' might in fact be due to a very low urine output that patients thought was too little to report. The very limited information on residual output will significantly complicate some *post hoc* analyses.

(vi) Performing any large-scale trial in the COVID-19 era was fraught with complexities, and in the case of the CONVINCE trial this may have affected outcomes as well. Among patients with COVID-19 infection there were significantly more events in the HD compared with the HDF group, with a mortality risk of 3.6 vs 2.3 per 100 patient years (hazard ratio 0.69, 95% confidence interval 0.49 to 0.96). It was not possible to distinguish between deaths due to COVID-19 versus deaths in patients with COVID (response from lead author at ERA Congress). Surprisingly, cardiovascular mortality was not significantly different between groups, but infection-related deaths accounted for the higher all-cause mortality in the HD group. Interestingly, not only were the COVID-19-related deaths lower in the HDF group (15 vs 21), but so were deaths from sepsis (7 vs 14), respiratory infection (2 vs 5) and cardiac infection (0 vs 2). The ESHOL trial also reported that deaths from infectious causes were significantly reduced in their HDF cohort [4]. Although there were significantly more catheter-related infections and hospitalizations in the HD cohort in ESHOL, this was not seen in CONVINCE. HDF may have a beneficial effect on immunological function by removing cytokines and inflammatory mediators which are middle molecular weight substances, and greater haemodynamic stability in HDF may also help by reducing gut ischaemia and bacterial translocation.

SO, DO WE NEED ANOTHER HDF TRIAL?

The nephrology community has witnessed the power of cumulative evidence from multiple RCTs to accelerate adoption of novel interventions in chronic kidney disease. The High-volume HDF versus High-flux HD Registry Trial (H4RT) is an ongoing RCT that aims to assess the effects of high-volume HDF compared with high-flux HD [11] with a composite primary outcome of non-cancer mortality or hospital admission with a cardiovascular event or infection. The trial has completed recruitment of 1550 patients and should report in late 2025. Importantly, it differs from CONVINCE in including people regardless of their ability to achieve high-volume HDF as the intervention is 'aiming for high-volume HDF' and will therefore provide evidence on HDF and its application universally in all dialysis patients. Also, H4RT will have significant pre-COVID-19, COVID-19 and post-COVID-19 follow-up periods, which will help untangle the effects of the pandemic.

IMPLICATIONS FOR PATIENTS, CLINICIANS AND POLICYMAKERS

Currently, the uptake of HDF in clinical practice is highly variable and HDF is not available even in many high-income countries. Optimal dialysis requires the best vascular access, and given the overwhelming pre-selection of patients with arteriovenous fistulas in CONVINCE, this suggests that higher convection volumes are more likely to be achieved via fistulas compared with catheters or grafts. The CONVINCE protocol involves further exploratory analyses to identify the modifiable risk factors that influence achievement of target convection volumes, and together with these data we encourage the investigators to share their experience in implementing high-quality HDF.

In addition to monetary costs, the sustainability and environmental burden of dialysis therapy is already substantial. The widespread adoption of online HDF would require considerable improvements to infrastructure in some settings, in particular the provision of 'ultrapure' water. The production of such ultrapure water has an important climate impact: the production of an extra 23 L of ultrapure water per dialysis session (required for some HDF machines) would require 66 L of water per session or an extra 10 300 L of water per patient per year (a 17% increase). Better understanding and personalization of dialysis treatment based on the benefits of HDF shown in select subgroups in CONVINCE would offer a compromise between improving survival and reducing the climate impact of dialysis. Important secondary outcomes of the CONVINCE trial on formal assessments of health-related quality of life measures, health economic analyses and cost-utility analyses expressing costs per quality-adjusted life year are eagerly awaited. The Standardised Outcomes in Nephrology (SONG-HD) trial has shown that patients value quality of life and lifestyle choices on a par with survival alone, and these data may likely influence an individual's choice of dialysis therapy.

In summary, CONVINCE is a milestone in dialysis research. It provides the first convincing evidence that patients receiving high-dose HDF have improved survival compared with those receiving high-flux HD. Although it might not convince us to see HDF as the cure-all, it leaves an important mark. It tells us that with a good study design, sufficient power and strict adherence to the study protocol, it is possible to demonstrate significantly reduced overall mortality in a subgroup of patients with end-stage kidney failure. Meanwhile, dialysis remains a suboptimal life-support, placing an enormous burden on patients and their families. Innovations are required to substantially improve their health and quality of life outcomes, and we hope that this study and this outcome will strengthen the case for future landmark studies in patients on maintenance dialysis.

ACKNOWLEDGEMENTS

The EuDial Working Group is an official body of the European Renal Association.

EuDial Working Group members: Christian Combe; Centre Hospitalier Universitaire de Bordeaux, Bordeaux, France. Gaetano Alfano; University Hospital of Modena, Modena, Italy. Adrian Covic; University of Medecine, Grigore T Popa, Iasi, Romania. Casper Franssen; University Medical Center Groningen, University of Groningen, The Netherlands. Vassilios Liakopoulos; AHEPA Univ Hospital and Aristotle Univ of Thessaloniki, Thessaloniki, Greece. Valerie A. Luyckx; Department of Public and Global Health, Epidemiology, Biostatistics and Prevention Institute, University of Zurich, Zurich, Switzerland. Björn Meijers; Nephrology and Kidney Transplantation, UZ Leuven, Leuven, Belgium.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Bello AK, Okpechi IG, Osman MA. *et al.* Epidemiology of haemodialysis outcomes. *Nat Rev Nephrol* 2022;**18**:378–95. https://doi.org/10.1038/s41581-022-00542-7
2. Tattersall JE, Ward RA; EUDIAL Group. Online haemodiafiltration: definition, dose quantification and safety revisited. *Nephrol Dial Transplant* 2013;**28**:542–50. https://doi.org/10.1093/ndt/gfs530
3. Grooteman MP, van den Dorpel MA, Bots ML. *et al.* Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *J Am Soc Nephrol* 2012;**23**:1087–96. https://doi.org/10.1681/ASN.2011121140
4. Maduell F, Moreso F, Pons M. *et al.* High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol* 2013;**24**:487–97. https://doi.org/10.1681/ASN.2012080875
5. Ok E, Asci G, Toz H *et al.* Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. *Nephrol Dial Transplant* 2013;**28**:192–202. https://doi.org/10.1093/ndt/gfs407
6. Morena M, Jaussent A, Chalabi L. *et al.* Treatment tolerance and patient-reported outcomes favor online hemodiafiltration compared to high-flux hemodialysis in the elderly. *Kidney Int* 2017;**91**:1495–509. https://doi.org/10.1016/j.kint.2017.01.013
7. Blankestijn PJ, Vernooij RWM, Hockham C. *et al.* Effect of hemodiafiltration or hemodialysis on mortality in kidney failure. *N Engl J Med* 2023; Online ahead of print. https://doi.org/10.1056/NEJMoa2304820
8. Blankestijn PJ, Fischer KI, Barth C. *et al.* Benefits and harms of high-dose haemodiafiltration versus high-flux haemodialysis: the comparison of high-dose haemodiafiltration with high-flux haemodialysis (CONVINCE) trial protocol. *BMJ Open* 2020;**10**:e033228. https://doi.org/10.1136/bmjopen-2019-033228
9. Peters SA, Bots ML, Canaud B. *et al.* Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. *Nephrol Dial Transplant* 2016;**31**:978–84. https://doi.org/10.1093/ndt/gfv349
10. Vernooij RWM, Bots ML, Strippoli GFM. *et al.* CONVINCE in the context of existing evidence on haemodiafiltration. *Nephrol Dial Transplant* 2022;**37**:1006–13. https://doi.org/10.1093/ndt/gfac019
11. Caskey FJ, Procter S, MacNeill SJ *et al.* The high-volume haemodiafiltration vs high-flux haemodialysis registry trial (H4RT): a multi-centre, unblinded, randomised, parallel-group, superiority study to compare the effectiveness and cost-effectiveness of high-volume haemodiafiltration and high-flux haemodialysis in people with kidney failure on maintenance dialysis using linkage to routine healthcare databases for outcomes. *Trials* 2022;**23**:532.

Received: June 22, 2023; Editorial decision: June 27, 2023