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Editorial Comment

EDITORIAL COMMENT

Unmasking the CONVINCE trial: is hemodiafiltration ready to steal the spotlight in real-world practice?

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INTRODUCTION

Hemodialysis (HD) is the main form of kidney replacement therapy (KRT) for the approximately 4 million people receiving chronic KRT worldwide, and there is an average annual growth rate of 7% on a global scale which underlines its social and economic burden [1]. Since the advent of HD, considering the unsatisfactory survival and quality of life provided by this renal replacement modality, there have been persistent endeavors to improve the technique, with the ultimate goal of prolonging the survival and the quality of life of patients with end-stage kidney disease (ESKD) [2]. However, we must agree that the priorities for many countries are not so much trying to improve the performance of HD as ensuring full replacement treatment of kidney function and even more, improving the general healthcare of the patients, including having clean water.

The technique of hemodiafiltration (HDF) broadens the spectrum of solute removal by employing both convective and diffusion mechanisms to enhance the overall elimination of solutes, particularly medium and larger molecular weight uremic toxins [3]. Therefore, from a theoretical perspective, there is a strong rationale to support the advantages of convective solute removal over diffusion-dominated dialysis.

WHAT DO WE KNOW SO FAR? RESULTS OF OBSERVATIONAL STUDIES AND RCTs

The majority of observational studies suggest that OL-HDF may provide a survival benefit compared with diffusion-based dialysis modalities [4]. A Cochrane Database systematic review of 20 randomized controlled trials (RCTs) comparing convective dialysis modalities [haemofiltration (HF), HDF] and acetate-free biofiltration with another convective therapy or diffusive therapy (HD) for the treatment of ESKD, involving 667 participants, found insufficient evidence of treatment effects on major clinical outcomes to draw clinically robust conclusions. However, it was concluded that convective dialysis may reduce cardiovascular but not all-cause mortality [5]. Several RCTs have also evaluated the impact of OL-HDF on mortality rates across various nations (Table 1A) [6–10]. Major trials include the Dutch Convective Transport Study (CONTRAST) [7], the Comparison of Post-dilution Online Hemodiafiltration and Hemodialysis (Turkish OL-HDF) Study [8], the Estudio de Supervivencia de Hemodiafiltración Online (ESHOL) study [9] and the French Convective versus Hemodialysis in the Elderly (FRENCHIE) study [10]. Nevertheless, the outcomes of these investigations are indeterminate, as only one out of the four studies exhibited a beneficial impact on mortality. The observed inconsistencies among these RCTs may be attributed to several factors, such as variations in study designs, selection of control groups, presence of selection bias and confounding variables such as the utilization of low-flux HD membranes, differences in targeted substitution volume and variations in the delivery of convective volume. In the ESHOL study, the cohort of patients was comparatively younger, had fewer cases of diabetes, demonstrated less severe comorbidities (as evidenced by lower Charlson Comorbidity Index scores) and had a smaller proportion of individuals undergoing dialysis with central venous catheters and some imbalances in the randomization. A *post hoc* analysis of the CONTRAST study indicated that convective volumes >21.95 L/treatment were associated

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Table 1: The features of (A) the five major randomized control trials on HDF and (B) the CONVINCE trial.

	Study	Number of patients	Comparator arms	Convective volume	All-cause mortality	Cardiovascular mortality	limitations	*Post hoc* analysis
A	Locatelli *et al.* (2010) [6]	146	HDF (predilution) vs low-flux HD		No difference	HDF slightly better in reducing intradialytic symptomatic hypotension	Comparator arm was low-flux HD; overall mortality was not the primary aim primary outcome	
	Grooteman *et al.* (2012), CONTRAST Study [7]	714	OL-HDF (postdilution) vs low-flux HD	20.7 L per session	No difference	No difference	Comparator arm was low-flux HD; most patients did not receive pre-defined target CV, and possibility of center-effect bias	Lower mortality in HDF patients treated with the highest CV (>21.95 L)
	Ok *et al.* (2013), Turkish Online HDF Study [8]	782	OL-HDF (postdilution) vs high-flux HD	19.6 L per session	No difference	No difference	High dropout rates; inclusion of a relatively "healthy" dialysis population as indicated by very low incidence of hypertension, diabetes, hypoalbuminaemia and hyperphosphataemia)	Patients treated with a median CV >17.4 L per session had better cardiovascular and overall survival compared with the high-flux HD group
	Maduell *et al.* (2013), ESHOL study [9]	906	OL-HDF (postdilution) vs high-flux HD	22.9–23.9 L per session	Lower in HDF arm	Lower in HDF arm	Patients were slightly younger, fewer diabetic, had low median CCI and fewer with CVC in HDF arm; high dropout rates	
	FRENCHIE (2017) [10]	381	OL-HDF (post-dilution) vs high-flux HD	21 L per session	No difference	No difference; low occurrence of intradialytic hypotension in HDF arm	Possibility of ascertainment bias, underpowered	
B	COVINCE trial (2023) [13]	1360	OL-HDF (post-dilution) vs high-flux HD	23.5 L per session	Lower mortality from any cause	No difference	Selection of the patients able to reach a CV >23 L; included healthier population; non-generalizable to non-white patients	

CV: convective volume; CVC: central venous catheter; CCI: Charlson Comorbidity Index scores.

with lower all-cause mortality. The Turkish trial also indicated that substitution volumes >17.4 L per session were associated with lower all-cause mortality; however, this study lacked sufficient statistical power to assess differences in mortality between the two dialysis modalities. It is important to note that in the ESHOL trial, the amount of convective volume was the highest among these RCTs (median quarterly convective volume was 22.9–23.9 L/session). The findings from the pooled individual participant analysis showed that OL-HDF is associated with a lower risk of all-cause mortality by 14% and cardiovascular mortality by 23% when compared with conventional HD [11]. Additionally, the patients who received the highest delivered convection volume, >23 L per 1.73 m^2 body surface area per session, experienced the largest survival benefit.

A meta-analysis suggested that OL-HDF does not yield significant enhancements in quality of life for HD patients when compared with conventional HD [12].

Thus, RCTs had yet to definitively establish a reduced mortality rate using OL-HDF in comparison with conventional HD. Moreover, there have been multiple iterations of discourse pertaining to the minimal convection volume necessary to achieve enhanced survival outcomes.

THE CONVINCE TRIAL

Blankestijn *et al.* [13] in the latest issue of the *New England Journal of Medicine* attempted to solve the question of whether OL-HDF provides a survival benefit compared with high-flux HD in their pragmatic, multinational, RCT Comparison of high-dose HDF with high-flux HD (CONVINCE). A cohort of 1360 individuals was subjected to randomization, with 683 assigned to the high-dose (at least 23 L per session) OL-HDF group and 677 assigned to the high-flux HD group (Table 1B). Over a median follow-up period of 30 months, the authors reported that the incidence of the primary outcome, which was death from any cause, was 17.3% among patients receiving high-dose HDF and 21.9% among those receiving HD (hazard ratio 0.77; 95% confidence interval 0.65–0.93 and 7.13 events per 100 patient-years in the OL-HDF group and 9.19 events per 100 patient-years in the HD group). Surprisingly, no significant difference was observed in the risk of cardiovascular mortality between the two cohorts, given that the composite endpoint of fatal or nonfatal cardiovascular outcomes was similar. The lack of difference in cardiovascular survival is particularly concerning as this was postulated to be the main pathway of action for OL-HDF, so either cardiovascular disease is overrated in HD patients or OL-HDF fails to prove its superiority, or CONVINCE contains some unrecognized bias.

It is also striking that the mortality from infection was higher than the mortality from cardiovascular diseases in both the group's cohorts. Furthermore, it is worth noting that significantly lower mortality related to infections was observed in the high-dose OL-HDF group. This finding conflicts with the results of the pooled analysis of individual participants which showed no significant difference in the risk of mortality from infections between the treatment arms [11]. The risk of recurrent hospitalization, including non-fatal and infection-related hospitalizations, was similar in both groups. Given the difference in mortality attributed to coronavirus disease 2019 (COVID-19), it would be interesting to know, apart from the possible effect related to the very large amount of convection, the different capacities of the membranes used with the two techniques to absorb inflammatory cytokines produced by the virus. In addition, it is also important to emphasize that during the COVID-19 pandemic, there may have been instances of erroneous adjudication. The authors themselves have acknowledged the challenge of distinguishing between deaths caused by COVID-19 and deaths resulting from other factors, such as cardiovascular reasons, in individuals diagnosed with COVID-19.

In subgroup analyses, the findings of OL-HDF demonstrated more favorable outcomes in patients who were aged <50 and >65 years old, and who did not have pre-existing cardiovascular disease or diabetes. Thus, the significant positive results of the trial in terms of survival are largely due to the healthier population. This suggests that high-dose OL-HDF achieves its best results in a healthier population. However, the subgroup analysis does not appear to be powered enough to derive any conclusive statement.

WHAT FACTORS CONTRIBUTED TO THE DIVERGENT RESULTS OBSERVED IN THE CONVINCE STUDY COMPARED WITH THE MAJORITY OF PRIOR RCTs?

The primary distinction between the CONVINCE trial and previous RCTs appears to lie in the inclusion criteria. CONVINCE selected only patients able to attain convection volumes of at least 23 L per session. Moreover, the author deserves commendation for effectively attaining a convective volume of at least 23 L per session, which was reached in 92% of the patients, and for maintaining a low dropout rate in both groups within a substantial cohort. Prior studies have presented varying findings regarding the minimum and maximum convective volume thresholds associated with enhanced survival, with reported values ranging from 15 L to 23.1 L. Thus, existing research findings suggest that in order to achieve improved survival rates with post-dilution OL-HDF, a minimum convection volume of at least 23 L per 4-h session is necessary. This seems to be the reason why the CONVINCE trial has adopted the selection criterion of recruiting only patients able to obtain and maintain a convective volume >23 L per session. The baseline characteristics of the CONVINCE population exhibit a relatively healthier profile, which is typically not observed in routine clinical practice. Specifically, in the OL-HDF group the mean age was 62.5 ± 13.5 years, over 80% of the population had arteriovenous fistula, less than 40% were diabetic, the mean body mass index was 27.4 kg/m^2, <25% had coronary artery disease and patients had already undergone high-flux HD for a minimum of 3 months. This raises some concerns about the general applicability of these results, also considering that the general population from which the patients were selected is unknown, but the selection should have been very strict since the enrolled population's mortality was approximately half that of the general population on dialysis. Thus, an important limiting factor for the general applicability of the results of the CONVINCE study could be the difficulties of achieving these levels of convective volume in the general HD population, although some studies have shown that this is possible [14, 15] but likely only in selected centres with very highly motivated physicians and nurses.

While the author presents an analysis of single-pool Kt/V, data on the clearance of middle molecules, such as beta-2-microglobulin, which are known to have a greater impact on outcomes, are unfortunately not yet available in this primary presentation. Of note, data on residual urine output was missing in 89% of patients. The utilization of an open-label trial design was deemed essential due to the inherent characteristics of the intervention, which posed challenges in implementing blinding procedures. Nevertheless, the events were documented by

treating physicians who were aware of the treatment allocation, and there was no presence of an impartial committee responsible for unbiased event assessment. Furthermore, despite experiencing lower enrollment and event rates than initially anticipated (likely due to COVID-19 pandemic), resulting in reduced statistical power, a noteworthy positive impact was observed.

In clinical practice, the convective volume in post-dilution OL-HDF is influenced by determinants related to both the patient and the treatment. It is also crucial to comprehend that the convective volume depends on the product of substitution flow rate (Qs) and time. The performance of Qs is influenced by various factors such as blood flow rates, membrane fiber diameter, blood viscosity, fiber length and membrane clotting. Hence, it is essential to contemplate that those patients with improved access, which may confer a survival benefit, are more likely to exhibit elevated convection volume. Patients possessing accesses that can endure a considerably elevated blood flow rate are expected to receive greater convection volume doses, provided that the session duration remains constant.

IS HDF POISED TO MAKE ITS TRIUMPHANT ENTRANCE INTO THE REAL WORLD?

According to the Dialysis Outcomes and Practice Patterns Study data obtained from the Middle East, it has been observed that around 20% of patients are being treated with OL-HDF [16]. However, there is significant variation in the usage of this technique based on the country and gender of the patients. The acceptance of OL-HDF in developing and low- and middle-income countries (LMICs) remains a subject of exploration. The scarcity of national kidney registries in developing countries has resulted in a dearth of information regarding the prevalence of HDF treatments. The utilization of HDF is constrained as a result of the financial burden associated with dialysis treatments, limited accessibility of OL-HF machines and prevailing reimbursement policies. Thus, the most referenced apprehensions pertain to intricacy, cost and extensibility of incongruous patient results. Although a probabilistic sensitivity analysis by Ramponi *et al*. [17] showed the cost-effectiveness of OL-HDF compared with HF-HD with a probability of ∼81% at a threshold of €40 000/quality-adjusted life years, cost-effectiveness and feasibility of HDF in LMICs is yet to be elucidated. The unavailability of OL-HDF in the USA is attributed to regulatory limitations. It can be speculated that this particular HD technique may only be accessible to patients dialyzed in infrastructures that possess adequate resources and capacity to facilitate such approaches.

The present dialysis machines hold the ability to produce substitution fluid online, thereby eliminating a significant portion of the intricacy and supplementary expenses associated with relying on pre-packaged bagged solutions. In addition to the online generation of substitution fluid, the acquisition of clinical proficiency in the technique, as well as the provision of reimbursement by governmental entities, are crucial factors in fostering widespread acceptance of OL-HDF on a global scale. Another concern pertains to the substantial amount of water required for OL-HDF. Considering a mean reinfusion of at least 20 L each HDF session, extra consumption of >2000 L/year per patient is a matter of concern. This raises questions about the extent to which the application of this technique aligns with the principles of green nephrology. Moreover, the need for ultrapure water is another potential limitation to its penetration, although nowadays ultrapure water is considered mandatory for standard dialysis as well.

Trials comparing the long-term effects including survival and quality of life of extended HD versus OL-HDF are of paramount importance. This, also considering the regulatory limitations for OL-HDF in the USA, is primarily attributed to concerns related to the online production of substantial quantities of sterile, nonpyrogenic substitution fluid. However, the positive outcomes and the safety reported in the CONVINCE trial are reassuring.

The different reimbursement policies in countries could also be a limitation to the penetration of this dialysis modality. This topic of discussion is explored in the Haemodiafiltration versus High-flux Haemodialysis Registry Trial (H4RT) [18]. The primary outcome measure of the trial is mortality, while patient-reported outcomes and economic evaluation have also been integrated into their trial design.

It is important to underline that the CONVINCE trial provides a rich dataset and intends to fill important knowledge gaps that should drive further evidence generation and the feasibility of OL-HDF being employed worldwide. One of the notable virtues of the study is the presence of comparable distributions in various demographic factors, including age, gender, residual kidney function, type of access and smokers, and the inclusion of patients with diabetes and underlying cardiovascular disease in both groups. Assuming hygienic and microbiological requirements are adhered to, the study lends credence to HDF's safety profile. This study incites the implementation of patient-centered outcomes and the assessment of the economic and practical viability of HDF in global contexts, particularly in LMICs. It is imperative to consider additional outcomes beyond mortality and cardiovascular morbidity when making treatment decisions. Therefore, the results of the CONVINCE trial comparing OL-HDF and HD in terms of patient health-related quality of life and cost-effectiveness is a valuable endeavor, and are awaited with much interest.

CONCLUSION

The CONVINCE trial should be considered a milestone in the history of OL-HDF. Future research should expand the number of participants to include patients from diverse regions and ethnic backgrounds. It would be appropriate to stratify future studies based on residual kidney function and the presence or susceptibility of hemodynamic instability during dialysis, as well as the presence of comorbidities such as diabetes, amyloidosis, and heart and liver diseases. Thus, the utilization of OL-HDF may provide an additional benefit for these specific demographics. Nevertheless, it is important to recognize the considerable challenges associated with conducting such trials, given that the CONVINCE trial required a tremendous amount of effort, and the authors should be commended for their accomplishment. The integration of OL-HDF alongside escalated treatment frequency, as a strategy for ameliorating the hazards linked with extended interdialytic intervals, has the potential to foster enhanced survival rates among HD patients. Thus, the results of this trial should be confirmed in real-world practice in a true general population. Delving into the logistics of equipment, infrastructure and the expertise of healthcare professionals will illuminate the viability of OL-HDF as a real-world treatment option. Furthermore, the issues of the sustainability/ecology of OL-HDF which were not studied in the CONVINCE trial should be further clarified.

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CONFLICT OF INTEREST STATEMENT

P.M. and F.L. have nothing to disclose.

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