Has the CONVINCE trial convinced the nephrology and dialysis community?

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Introduction

The CONVINCE trial, conducted during the summer of 2023, represents a pivotal moment in nephrology, addressing the longstanding question of whether high-volume hemodiafiltration (HVHDF) can significantly reduce mortality in patients with kidney failure (KF). This pragmatic, multinational, randomized controlled trial (RCT) involved 1,360 patients who had been undergoing high-flux hemodialysis (HFH) for at least three months (1). Participants were randomly assigned to either continue with conventional HFH or switch to HVHDF, with a convective volume target of at least 23 liters per session, exclusively in post-dilution mode.

The primary outcome of interest was mortality from any cause, assessed over median follow-up period of 30 months. Throughout the trial, the HVHDF group achieved a mean convection volume of 25.3 liters per session in post-dilution mode. The results indicated a mortality rate of 17.3% in the HVHDF group compared to 21.9% in the HFH group, with a hazard ratio of 0.77 [95% confidence interval (CI): 0.65 to 0.93] (1). Additionally, the target convective volume of at least 23±1 liters per session was met in 92% of the HVHDF sessions delivered (1).

Aim and rationale behind the CONVINCE trial: evaluating high-dose hemodiafiltration: what trigger the authors to design the CONVINCE trial?

The primary aim of the CONVINCE trial was to assess whether HVHDF could reduce overall mortality in patients with KF who had been undergoing HFH for at least three months (1). The goal was to achieve a high convective dose of 7.75 liters per hour for 4 hours in post-dilution to eliminate uremic toxins, cytokines, and other physiological waste products (2,3).

Previous research, including a pilot RCT by Honore *et al.* in 2000, suggested potential benefits of high convective doses in improving hemodynamic stability and reducing mortality, particularly in acute settings. This study aimed to investigate the potential improvement of hemodynamic

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status in patients with refractory septic shock through the removal of cytokines (though not measured) (4). It used pulse high-volume hemofiltration (P-HVHF) with a convection dose of 9 liters per hour over four hours in post-dilution, showing acute hemodynamic improvement in 20 patients with septic shock (4). However, due to its small sample size and varied methodologies, the results were inconclusive results.

The ESHOL trial conducted by Maduell *et al.* in 2013 provided the first robust evidence that high convective doses could improve all-cause mortality compared to standard HFH (5). This trial demonstrated that patients receiving intermediate tertile convection volumes (23.1–25.4 L) and upper tertile convection volumes (>25.4 L) experienced lower mortality rates than those undergoing hemodialysis. Thus, the ESHOL trial was the first to show that achieving a convective volume of more than 18 liters per session with HVHDF is associated with a reduction in all-cause mortality (5). Despite this, subsequent RCTs on continuous HVHF, including an important meta-analysis, reported negative results in terms of mortality, likely because they did not achieve such high convection volumes exclusively in post-dilution (4,6,7).

Motivated by these findings, the CONVINCE trial aimed to definitively evaluate the benefits of HVHDF by achieving a convection volume of over 23 liters per session. The trial found that patients receiving HVHDF had a 22% relative risk reduction for all cardiac events and a 31% reduced risk for fatal cardiac events compared to those on conventional HFH, indicating a clear minimal target dose for high convective treatment to be beneficial (8).

Despite these significant findings, the CONVINCE trial faced issues regarding selection bias and generalizability. The patient population had lower rates of diabetes mellitus (33.7%), coronary diseases (19%), and catheter usage (13.2%), and higher rates of arteriovenous fistulas (81.7%) compared to real-world populations. These figures were at least as favorable as those in the ESHOL trial, if not more so (5,9).

The authors of the CONVINCE trial acknowledged that their patient selection was more favorable compared to previous studies, aiming to ensure participants were likely candidates for high-dose HVHDF. This distinction from real-life scenarios, where only about 60% of patients might achieve the minimal target dose during hemodiafiltration, highlights the need for further research to confirm these results in broader, more representative populations.

Potential mechanistic hypotheses behind HVHDF

Hypothesis 1: removal of uremic toxins and cytokines

HVHDF is designed to achieve high convective volumes, which enhances the removal of a broad range of uremic toxins and cytokines from the blood (3,10,11). By maintaining a convection volume greater than 23 liters per session, HVHDF effectively eliminates these waste products, which can lead to significant clinical benefits. This high convective dose has been associated with a substantial reduction in the relative risk of all cardiac events and fatal cardiac events, highlighting the importance of adequate toxin and cytokine removal in improving patient outcomes.

Hypothesis 2: reduction of inflammatory mediators and oxidative stress

Another key hypothesis is that HVHDF helps in the removal of inflammatory mediators and oxidative stress components, leading to improved endothelial function. Another key hypothesis is that HVHDF helps in the removal of inflammatory mediators and oxidative stress components, leading to improved endothelial function (12). Studies, such as the CONTRAST study, have shown that patients undergoing HFH experience higher inflammatory responses, with elevated levels of C-reactive protein and interleukin-6, compared to those treated with HVHDF (13). Additionally, dialysis patients typically have higher levels of endothelial-derived extracellular vesicles, which are associated with increased expression of the proatherogenic miR-223 (14). After nine months, the study showed that theses extracellular vesicles contributed to decreased angiogenesis, and increased apoptosis and vascular smooth muscle cell calcification. HVHDF mitigated these detrimental effects, thereby potentially reducing the inflammatory and oxidative stress burden on patients.

Hypothesis 3: HVHDF improves hemodynamic tolerance and reduces the incidence of intradialytic hypotension compared to HFH

The third hypothesis posits that HVHDF improves hemodynamic tolerance and reduces the incidence of intradialytic hypotension compared to HFH. Intradialytic hypotension episodes, which can significantly decrease

cardiac blood flow, lead to cardiac ischemia and changes in contractility, thereby increasing the risk of arrhythmias and sudden cardiac death (15). A recent RCT indicated that while intradialytic hypotension episodes increased with HFH (from 7.1% to 7.9%), they decreased with HVHDF (from 10.6% to 5.2%) (16). This suggests that HVHDF is more effective at maintaining stable blood pressure during dialysis sessions. Given that more than 25% of annual deaths among hemodialysis patients are attributed to arrhythmias and sudden cardiac death, the potential of HVHDF to reduce these risks is significant (17). Preliminary observations also suggest that HVHDF may be associated with fewer pro-arrhythmogenic ECG changes, though further studies using implantable loop recorder devices are needed to thoroughly assess this impact (18).

Three hypotheses have been proposed to explain the observed effects of HVHDF. One hypothesis is that HVHDF effectively removes uremic toxins, cytokines, and other physiological by-products, including beta-2-microglobulin, which can accumulate during KF (19). Another hypothesis suggests that HVHDF reduces inflammatory mediators and oxidative stress components, thereby providing better protection for endothelial function. Endothelial dysfunction is a significant factor in the progression of vascular diseases in patients undergoing dialysis (12). The final hypothesis focuses on the improved hemodynamic tolerance and reduced incidence of intradialytic hypotension with HVHDF compared to HFH. Intradialytic hypotension can decrease cardiac blood flow, leading to cardiac ischemia, altered contractility, arrhythmias, and sudden cardiac death (14). By focusing on these three hypotheses, HVHDF aims to provide a more comprehensive and effective dialysis treatment, addressing not only the removal of small and medium-sized toxins but also improving inflammatory status, oxidative stress, and hemodynamic stability.

Issues to be resolved

Nuanced conclusions required

Critics argue that the patient cohort selected for the CONVINCE trial may not accurately represent the broader population on individuals attending dialysis clinics, thereby raising concerns about the generalizability of the findings despite the study's pragmatic design. This has led to speculation that the investigators might have inadvertently overstated the survival benefits, extending them to a broader category of "patients with KF resulting in kidney-replacement therapy" than is appropriate (20). The trial, conducted during the pandemic, reported a lower incidence of infection-related death, including from coronavirus disease 2019 (COVID-19), with HVHDF compared to conventional HFH. Additionally, the two groups exhibited a similar risk of death from cardiovascular causes (20). However, the reported advantages were more pronounced in younger and healthier patients, indicating that the conclusions drawn may lack sufficient nuance (20).

Contradictory results regarding cause of death

High-dose hemodiafiltration is not systematically available and is even prohibited in out-of-hospital settings in some countries, such as France (18). Among patients with no history of cardiovascular disease or diabetes mellitus at baseline, the risk of death was lower in the HVHDF group compared to the HFH group. However, no significant difference in the risk of death was observed between the groups for patients with histories of these diseases (21). Contradictory findings regarding the cause of death necessitate further investigation.

Feasibility in selected centers

Existing research suggests that a minimum convection volume of 23 liters per 4-hour session is essential to achieve improved survival rates with HVHDF in post-dilution (22). Consequently, the CONVINCE trial adopted a selection criterion that included only patients who are capable of obtaining and maintaining a convective volume greater than 23 liters per session. The baseline characteristics of the CONVINCE trial population demonstrated a healthier profile, not typically observed in routine clinical practice. For instance, the mean age in the HVHDF group was 62.5±13.5 years, over 80% had arteriovenous fistulae, and fewer than 40% were diabetic. The mean body mass index was 27.4 kg/m^2, and less than 25% had coronary artery disease, with all patients having undergone HFH for a minimum of 3 months.

These criteria suggest a potentially stringent selection process, as evidenced by the mortality rate of the enrolled population being approximately half that of the general dialysis population (23). Although some studies have indicated that achieving these levels of convective volume is possible in selected centers with highly motivated healthcare professionals, the limiting factors for the general

applicability of the CONVINCE trial results to the broader HVHDF population must be considered (23).

Can the CONVINCE trial be generalized in current practice?

The generalizability of the CONVINCE trial's findings to current clinical practice faces several challenges. Notably, inconsistencies were identified regarding the potential benefits of HVHDF in reducing coronary disease incidence and sudden cardiac death. The study exclusively included patients who could tolerate HVHDF at a volume greater than 23 liters per session, resulting in a younger and healthier cohort. Consequently, the observed benefits of HVHDF were confined to patients without a baseline history of diabetes mellitus or cardiovascular diseases. The underlying reasons for these selective benefits remain unclear.

Improving infection-related mortality by reducing infection rates aligns with the initial theory derived from studies on acute septic shock patients in the ICU, who achieved a convection volume of 36 liters over 4 hours through full post-dilution (4). The challenge remains in demonstrating this effect conclusively.

Another major consideration is cost. The widespread implementation of HVHDF is constrained by the financial burden associated with dialysis treatments, the limited availability of on-line hemodiafiltration (OL-HF) machines, and prevailing reimbursement policies (23). Regulatory restrictions further hinder the generalization of the CONVINCE trial results, particularly in the USA and France. Although hemodiafiltration is permitted in French hospital dialysis centers, it is reimbursed at the same rate as conventional hemodialysis, similar to most EU countries. Only Italy and Japan offer higher, specific reimbursement for hemodiafiltration.

Additionally, the logistical requirements for post-dilution hemodiafiltration, such as the need for ultrapure dialysate, pose significant challenges in middle- and low-income countries. The process demands substantial water usage, raising environmental concerns if adopted on a large scale. Therefore, HVHDF should be reserved for subsets of patients who are likely to derive the highest potential benefit.

What about the use of this technique in low income countries and in real-world scenario?

A recent study by Brazilian researchers evaluated the outcomes of HFH and HVHDF using real-world data. The study analyzed a cohort of patients undergoing HVHDF at a single center and compared their results with those of patients receiving HFH therapy within the Brazilian Public Health System (SUS). The primary outcome measured was all-cause mortality.

The study compared 85 HVHDF patients with 149,372 HFH patients from the SUS, utilizing a 2:1 propensity score to match 170 HFH patients with the HVHDF group. The Kaplan-Meier analysis revealed a one-year survival rate of 92.1% for HVHDF patients versus 79.9% for HFH patients ($P<0.001$). These findings suggest that HVHDF may offer survival advantages over HFH in real-world settings (24).

However, the study has limitations, including being underpowered to reliably evaluate mortality outcomes. Additionally, the mortality rate from infections was higher than that from cardiovascular diseases in both groups, with the HVHDF group exhibiting significantly lower infection-related mortality. This finding contradicts pooled analyses of individual participants, which showed no significant difference in infection-related mortality risk between HVHDF and HFH (25).

Furthermore, a 2018 meta-analysis comparing HVHDF and HFH in RCTs found no significant differences in quality of life between the two modalities (26). This discrepancy highlights the need for further research to confirm the potential benefits of HVHDF in broader and more diverse populations, particularly in low-income countries where the accessibility and cost of advanced dialysis treatments pose significant challenges.

Conclusions

The potential benefits of HVHDF in improving patient outcomes, including survival rates, need further validation in broader, more representative patient populations. The findings from the CONVINCE trial and other studies are promising, but their generalizability is limited by selection biases and specific clinical settings. Addressing scientific uncertainties and practical constraints—such as equipment availability, infrastructure, costs, and the expertise of healthcare professionals—is crucial for determining the feasibility of HVHDF as a standard treatment option. Future studies should aim to confirm these results in real-world practice with diverse populations and sufficient power to robustly assess mortality and other critical endpoints. This will ensure that the adoption of HVHDF is based on comprehensive evidence, making it a viable option for the wider dialysis patient community.

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Footnote

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