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Online hemodiafiltration and mortality risk in end-stage renal disease patients: A critical appraisal of current evidence

Helmut Schiffl

Department of Internal Medicine IV, Medical Center of the University of Munich, Munich, Germany

The life expectancy of end-stage renal disease patients undergoing regular hemodialysis (HD) remains significantly lower than in the general population. Reducing excess mortality by improving renal replacement options is an unmet medical need. Online post-dilution hemodiafiltration (HDF) has been promoted as the gold standard, offering improved clinical outcomes, based on numerous observational studies that suggest a reduced mortality risk and lower morbidity with HDF compared with standard HD. However, most randomized controlled trials (RCTs) have failed to demonstrate a significant beneficial effect of HDF on all-cause mortality. The effects on secondary outcomes were often negligible or absent. Unfortunately, these RCTs were characterized by a moderate to high risk of bias. In *post-hoc* analyses of the largest RCTs and meta-analysis of individual participant data from four RCTs, HDF patients receiving the highest convection volume consistently and dose-dependently saw superior outcomes. However, as these studies were not designed a priori to clarify this issue, and there are no indisputable mechanisms underlying reduced mortality risks, we cannot exclude the possibility that the health status of patients (with vascular access as a proxy) may affect outcomes more than the convective technique itself. There is currently insufficient evidence to support the contention that high-volume HDF confers relevant benefits to patients over standard HD. The conflicting data of published RCTs reduce confidence in the superiority of high-volume convective therapy. Hopefully, ongoing large RCTs (for example, CONVINCE) may supply an indisputable answer to the crucial question of high-volume HDF.

Keywords: Chronic kidney failure, Hemodiafiltration, Mortality

Introduction

Maintenance hemodialysis (HD) prevents immediate death from uremia, but survival remains an important issue. The 2017 Annual US Data Report showed a 27% decline in the adjusted death rate for prevalent HD patients from 2001 to 2015, suggesting that advances in HD performance (access, dose, membranes, and water purification) and advances in medical care are providing beneficial results. However, the current patient population continues to experience substantially higher overall five-year mortality, and fewer expected remaining life years, compared with the general population or patient populations with cancer, diabetes, or cardiovascular disease. The largest category of known cause-specific mortality

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Correspondence: Helmut Schiffl
Department of Internal Medicine IV, Medical Center of the University of Munich, Ziemssenstr. 1, D-80336 München, Germany. E-mail: h-schiffl@t-online.de

for HD patients is death due to cardiovascular disease [1].

In-center HD, performed three times weekly with a single-pool Kt/V urea of at least 1.20 per session, is the worldwide standard renal replacement therapy (RRT) for patients with end-stage renal disease (ESRD). Standard HD clears uremic toxins primarily through diffusion driven by the thermal energy of the uremic toxin molecules. Clearance is inversely proportional to the radius of the toxin molecule. As a result, conventional HD clears large or protein-bound toxins less effectively than small ones and fails to completely correct the uremic milieu. Attempts to improve removal of uremic toxins include initiation of dialysis at higher glomerular filtration rates, increases in dialysis frequency and/or duration, use of high-flux membranes, or alternative hemofiltration. However, higher clearance of low-molecular-weight toxins or high-flux membranes had no impact on patient mortality [2]. The poor survival of HD patients reflects, at least in part, the persistence of a residual uremic syndrome, incomplete correction of inorganic ion disturbance, intradialytic hypotension (IDH)-induced myocardial stress, and repeated injury of the compromised cardiovascular system by aggravation of systemic low-grade inflammation associated with ESRD using bioincompatible dialysis compounds (membrane chemistry, microbiological purity of dialysis fluid) [3]. Interventions that can improve outcomes in maintenance HD patients are urgently needed.

Principles, practice, and uptake of hemodiafiltration

The European Dialysis Working Group defined hemodiafiltration (HDF) as a single RRT that combines diffusive and convective solute removal by ultrafiltration of 20% or more of the blood volume processed through a high-flux dialyzer and maintenance of fluid balance by sterile, nonpyrogenic replacement-fluid infusion directly into the patient's blood. In online HDF, large volumes of sterile replacement fluid are obtained by online filtration of standard dialysate though a series of bacteria- and endotoxin-retaining filters. HDF provides greater removal of middle-molecular-weight and protein-bound uremic retention solutes than does conventional low-or high-flux HD [4].

Current HDF systems are based on conventional dialysis machines with added features to safely prepare and infuse sterile replacement fluid and closely control fluid balance. Various modes of HDF, differing by the site of replacement-fluid infusion, are in clinical use: post-dilution HDF, pre-dilution HDF, mid-dilution HDF, mixed dilution HDF, and push-pull HDF. Post-dilution HDF is the most efficient method of HDF in terms of solute removal. One potential disadvantage is that hemoconcentration at high ultrafiltration rates can result in deposition of plasma proteins on the membrane surface, clogging of membrane pores, and occlusion of dialyzer blood channels. The sum of these effects reduces clearances and may result in clotting of the extracorporeal circuit [4].

Adequacy and safety of online HDF rely on a) correct prescription of HDF; b) staff education on performing a high convection volume; and c) decent vascular access. High-volume HDF (a substitution fluid volume greater than 21 L/session or a target convection volume greater than 23 L corrected for body surface area) is feasible three or more times per week (4 to 5 hours) in clinical practice, providing blood-flow rates greater than 350 to 400 mL/min, dialysate flow rates higher than 500 mL/min, and filtration fractions of 25% to 30%. With respect to the safety of HDF, an online-produced substitution should be sterile and non-pyrogenic [5]. There seems to be no clinically relevant protein loss in ESRD patients on HDF [6]. Reassuringly, there have been no published studies or case reports on adverse patient outcomes of HDF.

HDF was used routinely to treat more than 160,000 patients worldwide in 2014 [7]. The percentage of HDF patients on extracorporeal RRT was 7%. At the international level, there are different rates of HDF therapy. HDF is used mainly in Europe, Pacific Asia (Japan), and the Middle East, and rarely in Latin America (less than 1%). HDF is available in the US, but less than 1% use it. Within Europe, there are enormous differences among countries, regions, cities, and centers [8].

There are several practical problems for setting up HDF [9]. First, there is a lack of conclusive evidence of a clinical benefit of HDF compared with standard HD. Second, HDF techniques remain expensive (machine upgrades, ultra-filters, additional costs for substitution fluid, and microbiological tests), which can be an insurmountable issue for widespread utility in many countries. Third, large amounts of substitution fluids of microbiological quality [10] and the unintended removal of nutrients and other compounds, including medication and activation

Table 1. Disadvantages of post-dilutional hemodiafiltration (HDF)

Theoretical risks
1. Transmission of infections or induction of inflammatory reactions related to the sterility of large amounts of substitution fluids directly infused into the patient
2. Loss of serum albumin, amino acids, or other hydrosoluble nutrients
3. Endothelial cell and blood cell activation during treatment
Clinical practice
1. There is no published literature showing any undesirable effect of post-dilution HDF or superiority of standard high-flux hemodialysis over post-dilution online HDF.

Table 2. Advantages (observed benefits) of post-dilution hemodiafiltration

Morbidity
1. Fewer episodes of intradialytic hypotension
2. Fewer/delayed clinical manifestations of AB amyloidosis
3. Improved nutritional status
4. Better correction of renal anemia
5. Improved quality of life
6. Growth of pediatric end-stage renal disease patients
Mortality
1. Reduced all-cause mortality
2. Reduced cause-specific mortality (cardiac death)

of blood cells, pose potential safety concerns (Table 1). Fourth, post-dilution HDF is not appropriate for all personalized medicine approaches (insufficient vascular access, non-adherence to longer session duration, and patients with high comorbidity), and there is no consensus about specific indications for HDF [11].

Online HDF and clinical expectations

Clinical expectations of post-dilution online HDF originate primarily with innumerable observational (mostly retrospective) studies that have suggested, albeit inconsistently [12], which multiple clinical benefits in prevalent HD patients are allocated to HDF instead of low- or high-flux HD.

The expected advantages of HDF (Table 2) encompass: a) less all-cause mortality by reducing both fatal cardiovascular events and lethal infections; b) fewer hospitalizations as a result of lower cardiovascular morbidity and fewer infections; c) better intradialytic hemodynamic stability; d) less inflammation-induced malnutrition, atherosclerosism and erythropoietin resistance due to superior biocompatibility; e) fewer cases of dialysis-related amyloidosis and uremic polyneuropathy; f) improved derangement of calcium-phosphate homeostasis and less vascular calcification by better removal of phosphate, parathyroid hormones, and fibroblast growth factor 23; g) better preservation of residual renal function; h) improved quality of life; and i) better growth of children with ESRD [13,14].

However, one downside of randomized controlled trials (RCTs) may be a lack of applicability to routine clinical practice. Patients participating in clinical trials typically do not represent the entire spectrum of ESRD patients. Data analyses of the French Renal Epidemiology and Information Network registry reported by Mercadal et al [15] may bridge the gap between practice-based and evidence-based medicine. This study is representative of current ESRD patients commencing RRT as well as current clinical and routine practice. Its sample size is large enough for analyses of patient subgroups. Between January 2008 and December 2011, 5,526 of 28,047 ESRD patients used post-dilution HDF for a median of 1.2 years. Both all-cause mortality and cardiovascular mortality associated with HDF use fell significantly. In patients treated exclusively with HDF (n = 2,254) the reduction of mortality risk (adjusted hazards ratios [HR]) was more pronounced (HR 0.77 and 0.66, respectively). The survival benefit of HDF patients appeared to be independent of age and gender. This benefit was observed in well-defined subgroups of HDF patients with diabetes mellitus obesity or cardiovascular or chronic respiratory diseases. This study showed that post-dilution online HDF has beneficial associations with ESRD patients' survival and can be performed without obvious safety concerns in a cost-acceptable manner.

RCTs and mortality risk of online post-dilution HDF patients

To be considered superior and qualify for inclusion in clinical guidelines or national reimbursement regulations, evidence-based medicines require results from RCTs that show significant beneficial effects on prespecified outcomes of a well-defined intervention for this mode of RRT.

In recent years (2010–2017), five prospective RCTs were conducted in different European countries, including Italy [16], Netherlands [17], Turkey [18], Spain [19], and France [20], to compare survival (primary outcome) and secondary outcomes in prevalent HD patients randomized to conventional HD and online-post-dilution HDF: a) the Italian Trial (146 patients, including 70 low-flux HD, 40 HDF, and 36 hemofiltration), b) the Turkish Trial (782 patients, including 391 high-flux HD and 391 HDF), c) the CONTRAST Trial (Netherlands, Norway, and Canada) (714 patients, including 356 low-flux HD and 358 HDF), d) the ESHOL Trial (906 patients, including 450 high-flux HD and 456 HDF), and e) the FRENCHIE Trial (381 patients, including 191 high-flux HD and 190 HDF).

None of these five RCTs gave a definitive answer to the critical question of whether ESRD patients receiving online post-dilution HDF demonstrated superior survival compared with conventional HD. A primary analysis of four RCTs showed that the incidence of all-cause mortality was not affected by treatment. The ESHOL Trial was the first (and up to now the only) randomized study to show a significant reduction in all-cause mortality (30%), a non-significant reduction in cardiovascular mortality of 33% and a significant reduction in infection-related mortality (55%) by online post-dilution HDF [19]. However, all had serious limitations and were at mid to high risk for major sources of bias.

In the control HD group of the Italian [16] and CONTRAST ("Dutch") Trial [17], low-flux membranes were used, while the HD patient group in the other three studies was treated with high-flux or both membranes. Not all patients were treated three times per week, and approximately 10% of all treatments of low-flux HDF patients were delivered with high-flux membranes. All studies included prevalent HD patients who were either anuric or had minimal residual kidney function. The mean time on HD (prior to randomization) was 2.9 ± 2.8 years in the CONTRAST Trial, 57.9 ± 44.6 months in the Turkish Trial, and 28.0 (12.0 to 59.9) months in the ESHOL Study. The difference in time already on dialysis at the point of randomization may have contributed to lead time bias. The mean follow-up time was 3.04 (0.4 to 6.6) years in the CONTRAST Trial, 22.5 ± 10.9 months in the Turkish Study, and 1.9 ± 1.1 years in the ESHOL Study. Thus, most of the patients participating in these three large trials had spent a considerably long time on dialysis and relatively short time on HDF. The mortality rate was likely affected by survival bias. In the ESHOL Study, HDF patients received renal transplants more often than did HD patients. In the Turkish Study, 40 patients were excluded from the HDF group during follow-up due to vascular access problems, but none were excluded in the HD group.

The rates of patients dropping out from these clinical trials were high: 38% in the CONTRAST Trial, 57% in the Turkish Trial, and 61% in the ESHOL Study. For assigned HDF patients participating in the ESHOL Study, a minimum of 18 L of replacement fluid was requested per session. HDF patients not receiving the performance characteristics of the allocated treatment modality for more than two consecutive months were withdrawn from the study. Forty-one percent of the participants of the Turkish Trial left the study for reasons other than death, including 11% of the patients allocated to HDF, who withdrew due to vascular access problems. These trials were at high risk of incomplete follow-up, i.e., drop-outs were censored at a non-fatal event, mostly kidney transplantation or transfer to another dialysis facility, and not followed up for primary outcome.

Convection strategies, it should be emphasized, were highly heterogeneous, and most studies did not randomize the participants to specific targeted convection volumes. The actual delivered convective volumes obtained by the three largest RCTs showed a considerable range of means: 20.7 L/session (CONTRAST Trial), 17.2 L/session (Turkish Trial), and 22.9 to 23.9 L/session (ESHOL Study). A serious limitation of the CONTRAST Trial was that the pre-defined target convection of 6 L/session was not reached in most patients, and one third received 18 L or less, mainly due to inadequate vascular access. Different practices in various regions of the CONTRAST Trial may have also led to a center-effect bias.

Davenport and colleagues [21] showed that higher standardized delivered-body-surface convection volumes (more than 23 L/1.73 m^2 per session) with online post-dilution HDF may be the key parameter for the superior survival of HDF. *Post-hoc* analyses of all three large studies showed significantly lower mortality in the HDF patients treated with the highest convection volume (greater than 21.95 L in the CONTRAST Study, 17.4 L in the Turkish Study, and 23–25 L/session or 25 L/session in the ESHOL Study). However, it can be inferred that survival rates were good when a high blood-flow rate could be

obtained in "healthier" patients with well-functioning vascular access.

The three trials were at high risk of other sources of bias, including commercial sponsoring. Finally, another potential risk of bias was the unavailability of information on blinding for the assessment and outcome.

Meta-analyses on convective therapies and mortality risk

Meta-analyses on convective therapies (hemofiltration, modes of HDF vs. standard HD) were published in 2013 and 2014, but they showed discordant outcomes [22–25]. Three meta-analyses found no impact of convective therapies on all-cause mortality. The meta-analysis of Mostovaya and colleagues [22] reported that HDF was associated with a decreased risk for all-cause and cardiovascular mortality. However, treatment effects of convective therapies are unreliable due to limitations in trial methods and reporting. These analyses differed in the number of studies and patient populations included, the definitions of comparator and intervention therapy, and the types of studies (small observational studies vs. large RCTs). In the meta-analysis by Susantitaphong et al [24], low-flux HD was the reference therapy, while both low-flux and high-flux HD were reference therapies in the other three studies. Considering the intervention arm, inclusion covered hemofiltration, acetate-free biofiltration (AFB), and various HDF modalities using different types of membranes. Nistor et al [23] compared HD with HDF or AFB, while Wang et al [25] compared convective modalities (HDF and hemofiltration [HF]) against standard HD. Mostovaya et al [22] considered only RCTs in which HDF (post-dilution, predilution, and mid-dilution HDF) was compared with HD.

However, neither AFB nor off-line HDF can be considered high-volume convective therapies, as volumes of 10 to 12 L/session are completely different from high-volume, high-efficiency online post-dilution HDF (more than 23 L/session). Generally, the studies included were predominantly of suboptimal quality and underpowered, with imbalances in some prognostic variables at baseline. Intention-to-treat analysis was not always used. All four meta-analyses were limited to aggregate datasets of published articles.

Taken together, the published RCTs contain potential risks of bias, leading to either an over- or underestimation of the true effect.

An individual participant data (IPD) meta-analysis approach, which can improve the quality of both data and analysis and thus the reliability of the results, is considered the gold standard.

Peters et al [26] conducted IPD meta-analysis from four randomized trials (CONTRAST, Turkish, ESHOL, and the FRENCHIE Study [unpublished at the time of this IPD meta-analysis]). The analysis was intentionally restricted to these four online post-dilution HDF trials to ensure higher quality of event adjudication, reasonable power, and lower risk of bias. The study was an analysis of individual participant data but also established the outcome in those patients who had been censored in the original trials. Mortality was prespecified as a secondary outcome variable in the FRENCHIE Study and as a primary outcome in the other three trials. This IPD meta-analysis indicated that online post-dilution HDF reduced the risk of all-cause mortality by 14% and cardiovascular mortality by 23%. The largest survival benefit was for patients receiving the highest delivered convection volume (more than 23 L/1.73 m^2 body surface area per session). A major limitation of this IPD analysis was that the included trials were not designed to assess the impact of delivered convection volume with online-HDF and mortality risk. Moreover, RCTs often lack applicability to routine clinical practice because RCT participants typically do not represent the whole distribution of ESRD patients, and results of RCTs or meta-analyses incorporating RCTs may therefore not be generalizable.

In contrast with the core results of the IPD meta-analysis reported by Peters et al [26], the recently published analyses of current "real time" HDF practices do not support the notion that online post-dilution HDF is a superior RRT in comparison with standard HD, even focusing on HDF with the highest convection volumes. Locatelli and colleagues [27] analyzed 8,567 prevalent patients on extracorporeal RRT (6,555 HD and 2,012 HDF patients) from seven European countries of the dialysis outcomes and practice patterns study (DOPPS) phases 4 and 5 (2009–2015). The median follow-up was 1.5 years (0.7 to 2.5 years). Replacement fluid was 4 to 15 L for 314 patients (16.5%), 15 to 19 L for 538 patients (27%), and more than 20 L for 1,010 patients (50%), including 279 with more than 30 L (14%). The authors found no evidence for

reduced cardiovascular, infection-related, or all-cause mortality, even in patients on high-volume online post-dilution HDF. However, a number of methodological limitations (questionnaire-based study, restriction to phases 4 and 5 of DOPPS) and reporting bias (missing data) cast doubts on the interpretation of the study results and its applicability to clinical practice. Because the performance of HDF (i.e., substitution volume and ultrafiltration volume) was based on prescription data and not on achieved treatment data, the effective convective dose of HDF delivered remains speculative. The items of the questionnaire specified neither the mode of HDF (post-, mixed-, or pre-dilution) nor the exact convective treatment modality (HDF, HF, or AFB). Moreover, the substitution volume was estimated at study baseline and never re-assessed at regular intervals to document that the initial prescription remained largely unchanged over the entire observation period. When the large variations of actual HDF performance at the patient level or in other studies (effective treatment time, ultrafiltration volume) are considered, it is difficult to accept the reliability of the study results for daily clinical practice.

Reduction of mortality of ESRD patients by high-volume HDF: critical questions

Conflicting clinical data on high-volume HDF with respect to reduction of mortality risk of ESRD patients and discrepancies among studies have left the nephrological community with little upon which to agree. A jumble of positive, negative, and meaningless findings, and hypotheses have been developed to answer critical questions regarding the mixed results.

First, selection bias may lead to confounding, which occurs when the variables that predispose selection into the intervention are also related to outcomes. Indeed, higher blood-flow rates are only achievable in healthier patients with well-functioning vascular access and a low all-cause mortality risk. Residual confounding may always remain in-spite of multiple adjustments. There is no doubt that patients selected for RCTs are healthier than patients excluded from investigations [28]. Compared with the real-world DOPPS HDF population, the HDF patients participating in the three large trials more often had well-functioning vascular access. Moreover, Turkish or Spanish Study patients assigned to HDF and with non-optimal fistula function were excluded from further investigation when blood-flow rates were inadequate.

Second, the use of high-volume online-post-dilution HDF may be associated with a true survival benefit, and reduction of all-cause mortality in HDF patients reflects reductions in fatal cardiac events (acute myocardial infarction, arrhythmia, and congestive heart failure). However, this subclassification of fatal cardiac events is too simple. Non-cardiac causes of death, i.e., electrolyte disorders, chronic fluid overload, or hypertension, should not be confused with cardiac death. Cardiac events may occur simultaneously. For example, a non-fatal acute myocardial infarction may eventually lead to arrythmia or heart failure resulting in death [29].

The precise mechanisms of an expected effect on the risk of cardiac mortality remain unclear (Fig. 1). First, the retrospective analysis of the entire Romanian maintenance dialysis population did not show a relationship between convective volume (median convective volume 22.2 L/session) and mortality risk. These observations

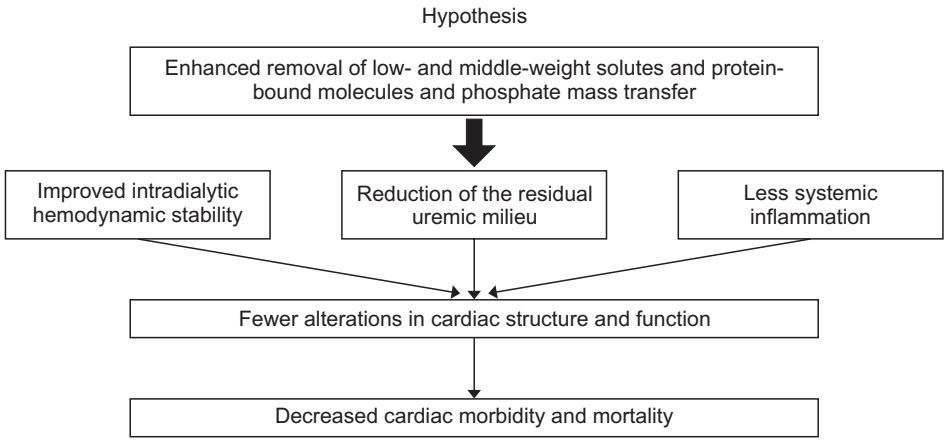

Figure 1. Reduction of cardiovascular mortality of end-stage renal disease patients on post-dilution online hemodiafiltration.

at least partly contradict the initial hypothesis that better correction of the uremic milieu by high-volume HDF results in less cardiac organ damage and improved cardiac outcomes. This study suggested that HDF treatment could reduce all-cause mortality both in incident and prevalent patients [30].

Second, there is no compelling evidence to date that high-volume HDF reduces mortality by improving traditional (blood pressure control, cholesterol levels, anemia, and glycemic control) or non-traditional risk factors (removal of small or middle-sized molecules, i.e., Kt/V or beta-2- microglobulin, systemic inflammation [high sensitivity C-reactive protein], oxidative stress, or disturbed calcium-phosphate metabolism).

Third, whether hemodynamic stability, as measured by IDH, is better preserved during high-volume post-dilution HDF than during standard dialysis utilizing non-cooled dialysate remains unclear. In the ESHOL Study, IDH was monitored, and there were significantly more episodes of IHD with standard HD. However, none of the three large trials comparing HDF with standard HD reported dialysate temperature. By contrast, Smith et al [31] conducted a random crossover study of post-dilution HDF (convection volumes greater than 20 L per session) and high-flux HD involving 100 patients and a blinded method. There was no difference in recovery time after dialysis, and there were significantly more intra-treatment hypotension episodes reported by HDF. The fact that the superiority of HDF was denied in a strict crossover study is an objection to the prevention of IHD by high-volume HDF [31]. Moreover, a recent small study (n = 12 stable patients) using magnetic resonance imaging observed profound deleterious effects on various cardiac variables. However, there was no difference between HDF and HD patients [32]. Interestingly, an echocardiographic study reported that neither changes in blood pressure nor variations in ultrafiltration rate were related to HD-induced regional left ventricular systolic dysfunction [33]. Finally, the low-temperature effect of the substitution fluid volume cannot rely on pre-dilution HDF. Hence, treatment-related hemodynamic stability may not contribute to treatment-induced perfusion defects in vital organs such as the heart, brain and gut).

Fourth, whether prevention of alterations in cardiovascular structure contributes to the expected effect on the risk of cardiac mortality has not been fully elucidated. The reported data are scarce and conflicting. An echocardiographic analysis of a subset of patients participating in the CONTRAST Study revealed no significant differences in left ventricular mass, ejection fraction, or pulse-wave velocity among HDF and low-flux HD patients [34]. A small RCTs (22 patients) compared atherosclerotic markers (brachial-ankle pulse-wave velocity, intima-media-thickness of the carotid artery) and cardiac function in online HDF patients and conventional HD patients for one year. Online HDF showed protective effects compared with patients on standard HD, i.e., significant regression in the left ventricular mass index and prevention of a significant worsening of brachial pulse-wave velocity and left ventricular capacity [35]. Our group conducted a two-year prospective comparison of two cohorts of ESRD patients initiating RRT (high-efficiency post-dilution online HDF in 58 patients and conventional HD in 60 patients). Our data indicate better preservation of residual renal function and a more pronounced decline in augmented left ventricular mass index in the HDF patient group compared with the HD patient group [36]. However, it is difficult to imagine that a switch from standard HD to high-volume HDF would alter cardiovascular structure in prevalent patients participating in the three large RCTs in such a way that outcomes improved in a relatively short period of follow-up.

Fifth, high-volume HDF may have a favorable effect on cardiovascular function rather than cardiovascular structure. An RCT reported that high-volume HDF (more than 22 L per session) prevented the endothelial dysfunction and stiffening in conduit arteries that was noted in HD patients [37].

The clinical benefits of pre-dilution online HDF

Various modes of online HDF, differing by the site of replacement-fluid infusion, are used. Post-dilution HDF is the reference method for convective therapies in Europe, the Middle East, and Africa. Pre-dilution HDF is performed largely in the Asia Pacific region (Japan and Korea). In Japan, more than 95% of all online HDF patients are treated with chronic intermittent pre-dilution HDF. The main reason for the wide use of pre-dilution HDF is the average blood-flow rate in Asian ESRD patients. Because of low blood-flow rates (200–250 mL/min), pre-dilution HDF allows for adequately high volumes of sub-

stitution fluids (more than 40 L/session in nearly all patients). Compared with post-dilution HDF, pre-dilution HDF removes more low-molecular-weight proteins and protein-bound toxins and is associated with less bio-incompatibility (shear stress or membrane-cell or cell-cell activation) [38]. Small and retrospective studies suggest that pre-dilution HDF may improve patient symptoms such as shoulder pain, loss of appetite, itching, and insomnia. The Japanese Renal Data Registry compared the one-year prognosis of patients receiving pre-dilution HDF and standard HD using a propensity score-matched method. Predilution HDF with a higher convective volume (more than 40 L/session) decreased all-cause mortality and cardiovascular mortality compared with standard HD or predilution HDF with small convective volumes. Analyses of this nation-wide database indicated that survival curves began to diverge within months of the switch [39,40]. A head-to-head comparison of various modes of HDF on clinically relevant outcomes has never been done.

Conclusions

Online HDF is currently the most innovative, technologically advanced, and promising alternative to conventional high-flux HD. Provided that best clinical practices and hygienic standards are applied, and optimal convection volumes are achieved, online HDF offers a reliable, efficient, and cost-effective extracorporeal RRT for daily care of ESRD patients.

Clinical benefits from enhanced removal of uremic toxins and positive clinical experience with post-dilution HDF appear to be biologically plausible. However, there is no conclusive evidence supporting the superiority of HDF over standard HD. Currently, the number, size, and quality of reported RCTs are too low to draw reliable conclusions. The situation has not been helped by seemingly contradictory reviews of studies that compared convective with diffusive modalities. There is a need for further patient- or cluster-randomized clinical trials that adhere to high standards of trial conduct and reporting and avoid selection and ascertainment bias that affects much of the current body of literature.

New RCTs targeting different convection volumes, both in online post-dilution as well as pre-dilution HDF, are urgently needed to determine the dose-response effects of high-volume HDF, both in incident and prevalent ESRD patients receiving extracorporeal treatment.

The lack of robust evidence from RCTs for mortality reduction should not deter reasonable clinical application and distribution of this modern RRT modality.

Hopefully, the ongoing CONVINCE study (multicenter multinational RCT) and other planned trials will deliver definitive proofs of the superiority of high-volume HDF over standard HD.

Conflicts of interest

The author has no conflicts of interest to declare.

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