Chapter 12

# Principles and Practices of Haemodiafiltration

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## 1. Introduction

Options for renal replacement therapy (RRT) for patients with end-stage kidney disease (ESKD) include haemodialysis, peritoneal dialysis and renal transplantation. Although renal transplantation offers the best outcomes in terms of quality and quantity of life, most patients with ESKD will be treated with dialysis, either because they are ineligible for transplantation due to their burden of comorbid medical conditions, or because they commonly have to wait several years on dialysis before they are able to receive a kidney transplant. Survival of patients on dialysis remains poor, with reported annual mortality rates ranging from 12.7% in Australia and 14.6% for New Zealand [1] to 17.9% in Europe [2] to 25% in the United States of America [3]. Alternative ways of delivering dialysis that will materially improve patient outcomes are therefore required.

Emerging data suggest that haemodiafiltration (HDF), a form of haemodialysis that combines both diffusive and convective solute removal, may offer clinical benefits when compared to standard high-flux haemodialysis (HD). Despite these findings, the global uptake of haemodiafiltration is variable and generally low, ranging from minimal use in the United States, 3.1% in the United Kingdom to 6% in Australia and 28.8% in Belgium [2]. This chapter will provide an overview of the principles and technical aspects of haemodiafiltration, as well as review the clinical evidence comparing HDF outcomes with those of HD.

## 2. Diffusive versus convective therapy

Physical removal of solutes across a dialysis membrane occurs via diffusion (passive movement down a concentration gradient) and/or convection (obligatory "dragging" of solutes by

fluid removal across the dialysis membrane, i.e. solvent drag) [4]. Some solutes, especially proteins, may also be removed to a limited extent by adsorption to the dialysis membrane.

In conventional low-flux haemodialysis, solute clearance predominantly occurs via diffusion across the dialysis membrane in a counter-current set up whereby blood flows in one direction and the dialysate flows in the other (Figure 1). Solutes move across the semi-permeable dialysis membrane down a concentration gradient. The factors that lead to a higher rate of diffusive exchange are 1) larger concentration gradient; 2) larger membrane pore size; 3) smaller solute molecular size; 4) larger exchange surface area; 5) higher blood flow rate; and, 6) higher dialysate flow rate. Diffusion represents the main mechanism for removal of low molecular weight molecules (<500 Daltons), such as urea (60 Da) and creatinine (113 Da), but is relatively inefficient at removing middle molecules (500 – 60,000 Daltons) [5], such as β2-microglobulin (11,500 Da), and does not appreciably remove large molecules (>60,000 Da), such as albumin (66,500 Da). This limitation can be overcome to a certain extent by the use of high-flux dialysis membranes with a larger pore size. High-flux dialysers permit increased blood water transfer across the membrane at the proximal end of the dialyser, compensated by the phenomenon of backfiltration, in which dialysate flows across the membrane at the distal end of the dialyser under a hydrostatic pressure gradient. Concentration of plasma proteins in the blood compartment will also exert osmotic pull, further contributing to backfiltration [6]. This process results in "internal" convection of up to 5-10L per dialysis treatment, and improves clearance of middle molecules compared to low-flux dialysis.

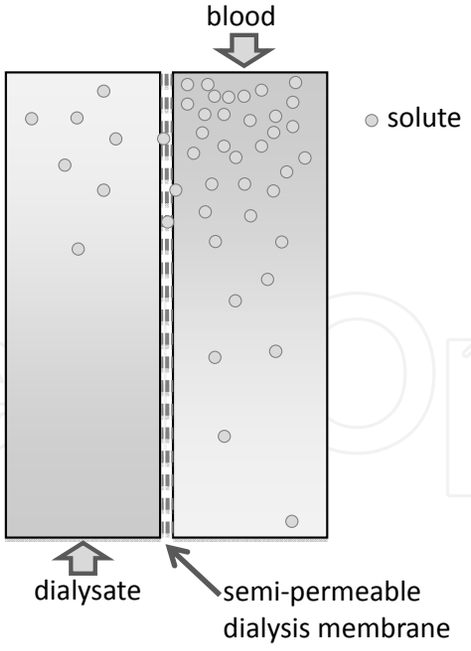


**Figure 1.** Conventional haemodialysis. A solute, shown dissolved in blood, moves across the semi-permeable dialysis membrane by diffusion, into the dialysate, with blood and dialysate flowing in opposite directions (countercurrent). The rate of diffusion is dependent on the initial concentration in the blood, the blood flow rate, the permeability of the membrane for the solute, and the dialysate flow rate. Removal of water (ultrafiltration) is determined largely but the pressure across the membrane.

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In contrast to haemodialysis, haemofiltration clears solutes primarily via convection, allowing water and solutes up to 20 kDa to cross the membrane and achieving more efficient removal of middle and large molecular weight solutes (Figure 2). The factors that lead to a higher rate of convective removal of solute are 1) volume of ultrafiltration, 2) a higher sieving coefficient (solute concentration in the ultrafiltrate divided by plasma concentration) and 3) a higher transmembrane pressure (which leads to a higher ultrafiltration rate) [7]. Given that haemofiltration is dependent upon large volume ultrafiltration, replacement fluid needs to be infused back into the patient to prevent excessive fluid removal. However, although haemofiltration provides efficient clearance of middle and large molecular weight molecules, it is less efficient at removing small molecular weight solutes than conventional haemodialysis.

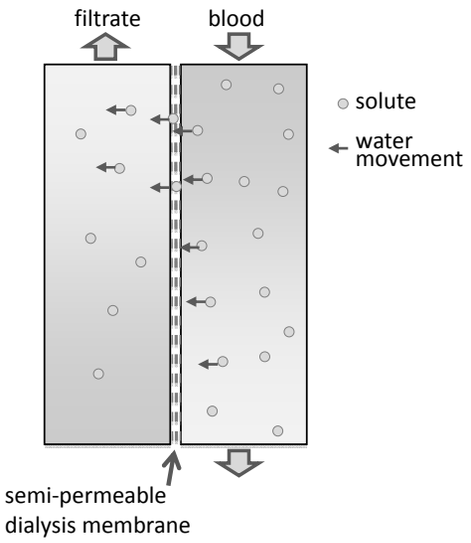


**Figure 2.** Haemofiltration (convection). Movement of water across the more water-permeable membrane 'drags' solute across, and leads to production of a filtrate which contains the solute. Solute removal is largely dependent on the ultrafiltration rate, but is limited by haemoconcentration and so 'pure' haemofiltration is not practical without replacement of fluid.

The distinct and separate advantages of haemofiltration (efficient middle and large molecule clearance) and haemodialysis (efficient small solute clearance) are combined by the technique of HDF, which provides both diffusive and convective clearances (Figure 3). This theoretically offers better overall clearance of small, middle and large molecular weight substances. HDF can produce convective volumes of greater than 20L per session, and this can be achieved by several different means:

1. "Internal" HDF: Achieved through the process of backfiltration in high flux haemodialysis. As mentioned above, this results in smaller convective volumes compared to dedicated HDF modality.

2. Classical HDF: Characterised by the use of an external substitution fluid in the form of sterile solution stored in plastic bags. Logistic and cost issues limit the use of this modality.

3. Online HDF: A form of HDF whereby substitution fluid is produced by the dialysis machine, creating ultrapure dialysate that is sterile, non-pyrogenic, continuous and unlimited while the machine is in operation [4].

As discussed later in the chapter, convective volume, and therefore enhanced removal of larger uraemic toxins, has emerged as an important parameter in outcomes relating to convective therapies. Convective dose is defined as the total ultrafiltered volume, which equates to the sum of volume gained/lost and substitution fluid given [7]. Convective dose has been proposed as the key quantifier of online-HDF by the European Dialysis (EUDIAL) group [8].

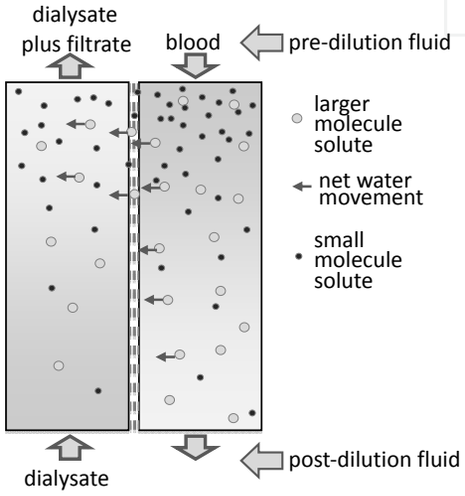


**Figure 3.** Haemodiafiltration (HDF). HDF combines dialysis and filtration across a semi-permeable membrane but uses much larger volumes of dialysate. Extra ultrapure water can be added either pre-dilution or post-dilution to replace the filtrate. Small solutes are removed largely by diffusion whereas larger solutes (middle molecules) are removed by convection. Water removal (ultrafiltration) is regulated by varying the volume of replacement fluid.

## 3. Important considerations for haemodiafiltration

### 3.1. Membrane

Haemodialysis and haemodiafiltration utilise filter membranes composed of cellulose, substituted cellulose or synthetic material. The ideal membrane will provide both solute removal capability as well as biocompatibility [9]. Contact of blood with dialysis membranes elicits inflammatory response, including activation of complement system, polymorphonuclear cells and mononuclear cells [10]. A biocompatible membrane is one that elicits the least amount of inflammatory response in patients exposed to it [11]. Membranes can be described in terms of their efficiency (rate of removal of small solutes) and flux (rate of removal of middle molecules).

High-flux membranes can remove molecules as large as 20kDa, which is better than a traditional low-flux membrane, but still inferior to glomeruli, which can clear molecules up to

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65kDa [12]. 'Super high-flux' or 'high cut-off' membranes have been developed to remove larger molecules of up to 50-60kDa, in an attempt to remove larger uraemic toxins and inflammatory mediators [12, 13]. Early data using these membranes have indicated enhanced clearance of free light chains and myoglobin, in patients with myeloma and rhabdomyolysis respectively, although larger clinical trials are required to demonstrate their impact on important clinical outcomes. Loss of important serum proteins such as albumin is significant, and represents a potential disadvantage of using 'high cut-off' membranes, because of the risk of protein malnutrition [12].

### 3.2. Ultrapure dialysate

Convective therapies result in infusion of substantial quantities of dialysate and substitution fluid, and a major challenge in HDF is the generation of ultrapure dialysate that is sterile and non-pyrogenic. This is because dialysate contaminants can enter the blood via convection or by direct infusion as substitution fluid [14]. The European Best Practice Guidelines (ERPG), American National Standards Institute / Association for Advancement of Medical Instrumentation (ANSI/AAMI) and International Organization for Standardisation (ISO) all mandate that ultrapure fluid contains no more bacteria than 0.1 colony forming units (CFU)/mL, and endotoxins no more than 0.03 endotoxin unit (EU)/mL [14]. Previous studies indicate that ultrapure dialysate improves inflammation-related parameters such as C-reactive protein [14], albumin and haemoglobin [14-17], although endpoints such as mortality and cardiovascular events have not been adequately demonstrated in high quality trials to date.

### 3.3. Site of fluid replacement

In HDF, ultrafiltration for convective solute clearance necessitates that replacement fluid is administered to maintain appropriate fluid balance. The site at which the replacement fluid is infused has an important impact on several dialysis variables.

In post-dilution mode, replacement fluid is added to the venous side of the circuit, distal to the filter. The convective clearance is the same as the volume of filtrate. This is the most efficient form of HDF, with respect to solute clearance, however this modality is complicated by the effects of haemoconcentration. At high ultrafiltration rates the haematocrit rises within the dialyser, increasing the risk of the filter clotting as well as membrane pore occlusion caused by adherence of plasma proteins [8]. Haemoconcentration is proportional to the filtration fraction, typically defined as the ratio of ultrafiltration rate to blood flow rate, which is usually limited to <25% in post-dilution HDF, and necessitates a high blood flow rate [6].

In pre-dilution mode, replacement fluid is given to the arterial side of the circuit, diluting blood before it is filtered. This mitigates the effect of ultrafiltration on haemoconcentration, but at the cost of reducing the efficiency of both diffusive and convective solute clearance. As a result, to achieve equivalent clearances, the ultrafiltration rate is typically set two-fold higher when performing pre-dilution HDF compared to post-dilution HDF. While many centres use post-dilution HDF, dialysis centres in Japan have more experience employing pre-dilution HDF [18,

19]. From their experience, pre-dilution has comparable effects on removal of uraemic toxins, reduces shear stress and results in stable blood pressures during treatment [18].

Recently, mid-dilution HDF has been made possible with the development of specialised dialysis circuits that permit infusion of replacement fluid between an initial post-dilution and subsequent pre-dilution stage. The advantage of this design is the ability to allow higher reinfusion rates, and early studies show better clearance of urea, β2-microglobulin and phosphate compared with high-flux HD [20, 21].

Finally, mixed dilution combining pre-and post-dilution has been developed with the aim of providing the most safe and efficient clearance of solutes. A small study of ten patients suggested that mixed dilution may provide superior clearances compared to mid-dilution, citing high transmembrane pressures in the mid-dilution dialyser potentially compromising membrane permeability and therefore infusion rate [22]. While different modes of fluid replacement in HDF have demonstrated advantages and disadvantages in small pilot studies, more data from larger studies are required to convincingly demonstrate the relative efficacy and safety of each method. For now, regional availability and experience tend to dictate the method utilised.

### 3.4. Cost effectiveness

One important consideration when deciding whether to adopt HDF is that of cost and cost-effectiveness. One French centre estimated that for each session, additional consumables (-€2.55 to+€3.35), microbiological analysis (€1.10) and water consumption (€0.15 to €0.23, based on 50.8 to 74.8 L), resulted in a cost of €-1.29 to €+4.58 per session for HDF over conventional HD [23]. Another cost analysis conducted in the United Kingdom over a 12 month period comparing HDF and high-flux HD found variable consumables costs (-£0.78 to+£1.16, depending on type of line used), similar erythropoiesis stimulating usage and less phosphate binder use (£3.8 and £5.0 weekly) in the HDF group [24].

A cost analysis of HDF versus haemodialysis was performed based on data from the CONTRAST study (mentioned later in the chapter) comparing low-flux HD and HDF. It was found that the annual costs for HDF and HD were €88,722 ± 19,272 and €86,086 ± 15,945, respectively, in 2009 in Europe [25]. However, when cost-utility analysis was applied to assess difference in quality of life, the incremental cost per quality-adjusted year (QALY) of HDF over HD was €287,769. Based on this analysis, the authors concluded that HDF was not cost effective, as concurred by McBrien, et al [26].

### 3.5. Potential role in home haemodialysis

To date, little data has been published regarding HDF utlisation in the home setting. This is not surprising, given that it is yet to be established as the predominant method of haemodialysis. If applied in the home setting, an extra filter used to produce ultrapure dialysate may provide benefits relating to inflammatory parameters, as mentioned above.

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## 4. Clinical benefits of HDF compared with HD

### 4.1. Mortality

The first large randomised trial performed to compare different doses and flux of dialyser was published in 2002. The Effect of Dialysis Dose and Membrane Flux in Maintenance Hemodialysis (HEMO) study [27] was a two-by-two factorial design randomised controlled trial which enrolled 1846 patients between 1995 and 2000, and assigned them to receive standard dose (Kt/V urea of 1.05) or high dose (Kt/V urea of 1.45) dialysis, and to a low-flux or high-flux dialyser. Flux was estimated based on β2-microglobulin clearance, with the low-flux group achieving 3±7mL/min and the high-flux group achieving 34±11mL/min. The primary outcome measured was death from any cause, with mean follow up of 2.84 years. The study found 0.166 deaths per patient-year, and that the rate of mortality did not vary significantly across the groups [27].

However, potential survival benefit from convective therapy was suggested by subsequent clinical data, such as the Dialysis Outcomes and Practice Pattern Study (DOPPS) – Mortality risk for patients receiving haemodiafiltration versus haemodialysis: European results from the DOPPS [28]. In this prospective cohort study involving 2165 patients recruited between 1998 and 2001, patients were stratified into four groups: low-or high-flux HD, low-or high-efficiency HDF. The usage of HDF varied greatly between countries, with 1.8% in Spain and up to 20.1% in Italy [28]. Adjusted mortality rate showed high-efficiency HDF patients had a 35% lower mortality risk than those receiving low-flux HD ($p=0.01$) [28], suggesting that high convective clearance lowers risk of death, independent of dialysis dose. However, this needs to be considered in the context of the observational nature of the study and possible selection bias with residual confounding.

In a Cochrane review in 2009, published evidence on HDF, HF and HD were compared, including 20 randomised trials. There was no significant difference in mortality or hospitalisations [29] between the 3 treatment modalities. However, given the relatively small number of patients in the studies and their heterogeneous nature, the conclusion of this review suggested that larger studies would be needed to prove the benefit of convective therapies.

Recently, three large, randomised controlled trials have compared haemodiafiltration with haemodialysis. While their designs were slightly different, they all measured important patient-level outcomes such as mortality, cardiovascular events, and hospitalisations, amongst others. These three trials were, respectively, the Convective Transport Study (CONTRAST) [30], Comparison of Post-dilution Online Haemodiafiltration and Haemodialysis (Turkish OL-HDF study) [31] and Online Haemodiafiltration Survival Study (ESHOL: *Estudio de Supervivencia de Haemodiafiltracion*) [32]. These three trials will be described in further detail.

In the CONTRAST study, 714 patients across the Netherlands, Canada and Norway, recruited between 2004 and 2009, were enrolled and randomised to post-dilution online HDF (n=358) or low-flux HD (n=356) [30]. One of the remarkable feats of this study was the achievement of 100% follow up. The mean follow up was 3.04 years. No significant difference was observed between the treatment groups with respect to the primary outcome measure of all-cause

mortality (HR 0.95, 95% CI 0.75-1.20), even after adjustment for potential confounders. However, a subsequent *post hoc* analysis, indicated that patients who achieved a higher convective volume (>21.95 L per session), experienced a 38% risk reduction for mortality compared to the low-flux HD group (p=0.012). A potential limitation is that the pre-defined target convection of 6 L per hour (based on modelling calculations) was not reached: the mean convection volume was 20.7 L, and one third of patients received 18 L or less, mainly caused by inadequate vascular access [33].

In the Turkish OL-HDF study, 782 ESKD patients recruited between 2007 and 2008 were randomised to receive high-flux HD (n=391) or post-dilution online HDF (n=391) over a mean follow-up period of 22.7 months [31]. The primary outcome was a composite of all-cause mortality and non-fatal cardiovascular events. The investigators did not find a significant difference in event free survival (HD group 74.8% versus OL-HDF 77.6%, p=0.28). However, on *post hoc* analysis, it was again demonstrated that OL-HDF patients who received higher convective volumes (> 17.4 L per session) experienced a 46% lower risk of mortality (p=0.02) after adjustment for other potential risk factors [31]. Patients recruited in this study had spent considerably longer time on dialysis (average 57.9 months), and therefore mortality rate was likely affected by survival selection bias. The average age of patients selected was also far younger at 56.5 years.

The ESHOL study was an open-label, randomised controlled trial conducted in Catalonia, Spain [32]. 906 patients recruited between 2007 and 2008 who were already on haemodialysis were randomised to receive high-flux haemodialysis (n=450) or post-dilution online HDF (n=456). Unlike CONTRAST and the Turkish OL-HDF study, the ESHOL study specifically targeted high convective volumes in the HDF group. The median follow up was 2.08 years and the primary outcome measured was all-cause mortality. At 3 years, the detected mortality rate was 27.1% in the HD group compared to 18.6% in OL-HDF group (30% risk reduction, hazard ratio 0.53-0.92, p=0.01), in contrast with the two above studies. They also detected a lower risk of stroke (HR 0.39, p=0.03) and lower rate of hospitalisations (HR 0.78, p=0.001)

It is interesting that the three trials, conducted at similar times, produced different outcome results for all-cause mortality. Based on the *post-hoc* analyses of CONTRAST and the Turkish OL-HDF suggesting a mortality benefit in patients achieving higher convective volumes, a possible explanation for the difference is the higher convective volume achieved in the ESHOL trial (mean of 22.9 – 23.9 L per session, compared with 20.7L per session in CONTRAST and 17.2L per session in the Turkish OL-HDF). Furthermore, there was a difference in time already on dialysis at the point of randomisation, which may have contributed to lead-time bias. Different practices in various regions may also have led to centre-effect bias.

A meta-analysis undertaken in early 2014 (Wang A, et al) analysed 16 randomised controlled trials published thus far comparing HD and HF/HDF in terms of cardiovascular outcomes and mortality [34]. Of these, 11 included HDF, 4 incorporated HF, and one included either modality. The three recently published randomised trials contribute to the majority of the data analysis, due to their large patient numbers. The authors did not find significant reduction associated with convective therapies in terms of cardiovascular events (RR 0.85, 95% CI 0.66 – 1.10) or all-cause mortality (RR 0.83, 95% CI 0.65 – 1.05). There was reduction in symptomatic

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hypotension (RR 0.49, 95% CI 0.30 – 0.81) and improved β2-microglobulin levels (-5.95mg/L, 95% CI-10.27 to – 1.64mg/L) [34].

| | CONTRAST [30] | Turkish OL-HDF [31] | ESHOL [32] |
|---|---|---|---|
| **Total patient number** | 714 | 782 | 906 |
| **Control group** | Low-flux HD (n = 356) | High-flux HD (n = 391) | High-flux HD (n = 450) |
| **HDF group** | Post-dilution HDF (n = 358) | Post-dilution HDF (n = 391) | Post-dilution HDF (n = 456) |
| **Average patient age** | 64.1 years | 56.5 ± 13.9 years | 65.4 ± 14.4 years |
| **Prior time on dialysis** | 34.8 ± 33.6 months | 57.9 ± 44.6 months | 28.0 (12 – 59) months |
| **Mean follow up** | 3.04 yrs, range 0.4-6.6 | 22.7 ± 10.9 months | 1.91 ± 1.10 years |
| **Primary outcomes measured** | All-cause mortality | All-cause mortality<br>Non-fatal CV events | All-cause mortality |
| **Secondary outcomes measured** | Fatal & non-fatal CV events | CV mortality<br>Intradialytic complications<br>Hospitalisation rate<br>Laboratory parameters | CV mortality<br>Hospitalisation<br>Treatment tolerability<br>Laboratory parameters |
| **Ultrapure dialysate used for both groups** | Yes | Not specified | Yes |
| **Convective volume on HDF** | 20.7 L / session | 17.2 ± 1.3 L / session | 22.9 – 23.9 L / session |
| **β2 microglobulin reduction** | HDF: 4.3 mg/L<br>HD: -3.1 mg/L (p < 0.001) | HDF: 0.67 ± 9.57 mg/L<br>HD: -0.59 ± 9.02 mg/L | Not specified |
| **Primary outcome result** | Incidence HDF 121 vs HD 127 per 1000 person-yrs (95% CI 0.75-1.20)<br>*_Post hoc_: HDF with convective volume > 21.95L/ session 38% RR for mortality, p = 0.012 | Event free survival HDF 77.6%, HD 74.8%, p = 0.28<br>*_Post hoc_: HDF with convective volume > 17.4L/ session 46% RR for mortality, p = 0.02 | 3 year mortality rate HDF 18.6% vs HD 27.1% ( p = 0.01) |

*HD=haemodialysis, *HDF=haemodiafiltration, *CV=cardiovascular, *CI=confidence interval

**Table 1.** Comparison of recent randomised controlled trials

Another review performed by Mostovoya, et al. focused on six published randomised controlled trials only, namely The Italian Cooperative Dialysis Study Group [35], Hemofiltration and haemodiafiltration reduce intradialytic hypotension in ESRF [36], Efficacy of haemodiafiltration [37], alongside CONTRAST, Turkish OL-HDF and ESHOL. In this meta-analysis, HDF was found to have a decreased risk of mortality (RR 0.84, 95% CI 0.73-0.96) and cardiovascular death (RR 0.73, 95% 0.57-0.92) [38]. Data interpretation needs to be taken with caution given the heterogeneous mix of pre-, mid-and post-dilution modes used, as well as different convective volumes achieved.

While these two systematic reviews drew different conclusions based on different trials included in their analyses, there did appear to be a signal suggesting possibly reduced mortality and cardiovascular events when higher convective volumes were achieved. Indeed,

in the CONTRAST study [30], convective volumes exceeding 21.95L were associated with a 38% risk reduction. Similarly, in the Turkish OL-HDF trial [31], convective volumes exceeding 17.4 L per session were associated with a 46% risk reduction in mortality. The ESHOL trial showed a difference in mortality, but it achieved higher convective volumes (22.9 – 23.9 L per session) [32] than the CONTRAST and Turkish OL-HDF trials.

### 4.2. Intradialytic hypotension

In meta-analyses, symptomatic hypotension was reduced by HDF compared to HD, with RR of 0.49 [34]. The ESHOL trial reported significant difference in occurrence, with 769.2 episodes per 100 patient-years in the HDF group compared with 937.7 episodes ($P<0.001$) [32].

### 4.3. Blood pressure and fluid control

Post-dialysis systolic blood pressure was not significantly affected by treatment modality [34]. The CONTRAST study reported insignificantly different pre-dialysis systolic blood pressure of 146 mmHg for HDF compared to 145 with low-flux HD, and intradialytic weight gain of 1.9 vs 1.85kg [30]. There was also no significant difference in systolic blood pressure in the Turkish study, however a difference in interdialytic weight gain was detected: 3.19% of body mass in the HD group, 3.87% in the low-efficiency HDF group and 3.29% in the high-efficiency group [31]. The ESHOL trial reported no difference in blood pressure levels [32].

### 4.4. Left ventricular mass

Higher left ventricular mass (LVM) has been associated with cardiovascular and overall mortality in patients on dialysis [39, 40]. A subset of 327 patients from the CONTRAST study was assessed in terms of their LVM at baseline with echocardiography [41]. These patients were stratified into tertiles, and those in the highest tertile (LVM > 260grams) had the highest risk of mortality, cardiovascular death and sudden death. So far one small trial involving 22 patients utilising HDF has demonstrated improvement in left ventricular mass index (131.9 to 116.5 $g/m^2$) at 1 year [42]. This surrogate marker will need to be more extensively studied to convincingly demonstrate potential long term clinical effect.

### 4.5. Dialysis related β2-microglobulin amyloidosis

Dialysis related amyloidosis is a syndrome of pain and loss of function due to deposition of amyloid composed of β2-microglobulin in the musculoskeletal system. While β2-microglobulin can be removed on dialysis, pre-dialysis levels often remain elevated [43]. The CONTRAST study demonstrated lower β2-microglobulin level in the HDF group (26.4 mg/L) compared to the HD group (35.4 mg/L), as well as a greater reduction in its level post treatment (4.3 mg/L) [30]. On the other hand, patients in the Turkish study had very similar levels, and achieved a much smaller reduction of 0.67 mg/L [31]. While advancements in renal replacement therapy have allowed manipulation in β2-microglobulin levels, enhanced clearance has not yet translated to clinical difference in dialysis related amyloidosis, particularly given the long periods required for the syndrome to manifest.

### 4.6. Inflammatory markers

Inflammation in chronic kidney disease has been associated with a range of negative outcomes, including cardiovascular mortality [44], atherosclerosis, protein energy wasting, hypo-responsiveness to erythropoiesis stimulating agents (ESAs), platelet dysfunction and endocrine dysfunction [45]. Chronic inflammation is caused by both cytokine dysregulation in chronic kidney disease [46], and the dialysis process itself [47]. A subset of patients from the CONTRAST study was screened for markers of inflammation, including C-reactive protein (CRP) and interleukin-6 (IL-6) [48]. 201 patients from the HDF arm and 204 patients from the HD arm were selected for this study. Baseline CRP levels were 3.0 mg/L in the HD group and 4.1 mg/L in the HDF group. After 3 years, there was a significant steady rise in CRP level in the HD group (~20% per year) whereas it remained stable in the HDF group. Similarly, IL-6 levels increased in the HD group but not for HDF patients. Both of these figures were adjusted for confounders including age, sex and residual renal function, and still remained significant [48]. Given that ultrapure dialysate were used for both groups, the different measurements appear to have arisen from different modalities of dialysis.

### 4.7. ESA hypo-responsiveness

Another clinical outcome examined by the CONTRAST investigators was whether use of HD or HDF resulted in a difference in resistance to erythropoiesis stimulating agents. This was done given the proposed concept that better clearance of middle molecular weight uraemic toxins would reduce inflammation, and therefore improve responsiveness to ESAs [49]. Starting at statistically similar haemoglobin levels (11.9 g/dL in HDF, 11.8 g/dL in HD), with iron replete, they measured ESA index (weekly weight adjusted ESA dose divided by haematocrit) as a measure of ESA resistance. After 12 months, there was no significant difference found [50]. This finding is in keeping with an earlier randomised controlled study involving 146 patients where allocation to low flux HD or HF/HDF did not improve haemoglobin levels or ESA resistance [51].

### 4.8. Quality of life measurement

Assessment quality of life is difficult, due to the subjective nature of outcomes as well as different assessment of tools used. One study reported lower physical wellbeing scores while on HD[52], however meta-analyses have shown inconsistent and insignificant differences in quality of life, particularly when measured with Kidney Disease Quality of Life Questionnaire [34, 53].

## 5. Further trials

As of September 2014, there are several proposed trials currently underway to further elucidate potential clinical benefits of haemodiafiltration, as registered on *ClinicalTrials.gov* [54]:

- Mid-dilution Hemodiafiltration International Randomised Prospective on Incident Patients Focused on Outcome (MILESTONE) [55]
  - Trial identifier: NCT01693354
  - Purpose: "to determine whether mid-dilution haemodiafiltration is effective in the reduction of the crude mortality risk in patients who have been undergoing renal replacement treatment for less than 1 year. Patients will be randomized since the beginning of the study in two groups: standard HF dialysis and mid-dilution HDF"
  - Study type: interventional
  - Estimated enrolment: 800
  - Arms: HF dialysis vs. mid-dilution HDF
  - Primary outcome: crude, all-cause mortality at 5 years
- Tolerance of "On Line" Hemodiafiltration and Impact on Mortality and Cardiovascular Risk Factor in Chronic Renal Failure Patients [56]
  - Trial identifier: NCT01327391
  - Purpose: "to appreciate the tolerance of "on line" hemodiafiltration and its impact on morbidity and cardiovascular risk factors in chronic renal failure patient."
  - Study type: interventional
  - Estimated enrolment: 600
  - Arms: on line hemodiafiltration vs high flux hemodialysis
  - Primary outcome: tolerance of online HDF in terms of adverse events occurring during dialysis sessions
- Randomised Study of High-flux Haemodialysis and Haemodiafiltration [57]
  - Trial identifier: NCT01862679
  - Purpose: to answer the following three main questions in regards to HDF and high-flux HF
    - Does HDF make patients feel better?
    - Is blood pressure more stable on HDF in comparison with HF-HD?
    - Are Phosphate levels and other blood parameters better controlled with HDF than HF-HD?
  - Study type: interventional
  - Estimated enrolment: 100
  - Arms: HF-HF and HDF, crossover at 8 weeks

- Primary outcome: change in the average time taken to fully recover post dialysis

- The Effects of Haemodiafiltration vs Conventional Haemodialysis on Growth and Cardiovascular Markers in Children – 3H (HDF, Hearts and Height) Study [58]
  - Trial identifier: NCT02063776
  - Purpose: to monitor growth, heart and blood vessel scans, blood markers and quality of life in children
  - Study type: Observational case control
  - Estimated enrolment: 150
  - Arms: children on HDF, children on conventional HD
  - Primary outcome: change in carotid intimate thickness standard deviation score, change in height standard deviation score

## 6. Conclusion

Haemodiafiltration, utilising convection via high-flux dialysers and ultrapure dialysate, has been shown to exhibit certain advantages over conventional haemodialysis, such as a reduction of intradialytic hypotension, reduction of left ventricular mass and lower β2-microglobulin levels. However, when it comes to important patient-level outcomes such as mortality and cardiovascular events, HDF has not been shown conclusively to be of benefit, although studies to date have been limited by inadequate statistical power and suboptimal methodological quality. It may be that a minimum amount of convective volume needs to be achieved to demonstrate mortality benefits, and that this volume may be in the order between 17.4 and 23.9L per session, given the heterogeneous cut-offs in trials that have suggested a difference in mortality. A large, well-designed, multi-centre, multi-national randomised controlled trial examining this issue is indicated given the suggestive findings of a potential benefit with high volume HDF to date.

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