



## ORIGINAL ARTICLE

# Achieving high convection volumes in postdilution online hemodiafiltration: a prospective multicenter study

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## Abstract

**Background.** Available evidence suggests a reduced mortality risk for patients treated with high-volume postdilution hemodiafiltration (HDF) when compared with hemodialysis (HD) patients. As the magnitude of the convection volume depends on treatment-related factors rather than patient-related characteristics, we prospectively investigated whether a high convection volume (defined as  $\geq 22$  L/session) is feasible in the majority of patients ( $>75\%$ ).

**Methods.** A multicenter study was performed in adult prevalent dialysis patients. Nonparticipating eligible patients formed the control group. Using a stepwise protocol, treatment time (up to 4 hours), blood flow rate (up to 400 mL/min) and filtration fraction (up to 33%) were optimized as much as possible. The convection volume was determined at the end of this optimization phase and at 4 and 8 weeks thereafter.

**Results.** Baseline characteristics were comparable in participants ( $n = 86$ ) and controls ( $n = 58$ ). At the end of the optimization and 8 weeks thereafter, 71/86 (83%) and 66/83 (80%) of the patients achieved high-volume HDF (mean  $25.5 \pm 3.6$  and  $26.0 \pm 3.4$  L/session, respectively). While treatment time remained unaltered, mean blood flow rate increased by 27% and filtration fraction increased by 23%. Patients with  $<22$  L/session had a higher percentage of central venous catheters (CVCs), a shorter treatment time and lower blood flow rate when compared with patients with  $\geq 22$  L/session.

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**Conclusions.** High-volume HDF is feasible in a clear majority of dialysis patients. Since none of the patients agreed to increase treatment time, these findings indicate that high-volume HDF is feasible just by increasing blood flow rate and filtration fraction.

**Key words:** convection volume, end-stage kidney disease, feasibility, hemodiafiltration, optimization

## Introduction

Although dialysis is a lifesaving treatment in patients with end-stage kidney disease (ESKD), mortality remains unacceptably high [1]. Despite the introduction of high permeability (high-flux) dialyzers, which are capable of removing middle molecular weight substances, large randomized controlled trials (RCTs) have failed to show survival differences between hemodialysis (HD) with pure diffusive transport (low-flux HD) and diffusion in combination with a small amount of convective transport (high-flux HD) [2, 3].

In hemodiafiltration (HDF), diffusion is combined with a surplus of convection by extracting an excess of plasma water in addition to the net ultrafiltration (UF) needed to correct for the interdialytic weight gain. The infusion of replacement fluid after the dialyzer (postdilution online HDF) has been shown to be most efficient [4], and this is currently the preferred modality in clinical practice.

In recent years, three large RCTs have been published comparing postdilution online HDF with HD. Despite a contradictory outcome [5–7], the results of a pooled analysis of individual patient data from the three trials and a fourth, not yet published study, showed a significant all-cause and cardiovascular survival benefit of HDF over HD [8]. Moreover, and in agreement with previous reports, an inverse association was demonstrated between the magnitude of the convection volume and the mortality risk [5–12]. Hence, it seems justified to consider the magnitude of the convection volume as the dose of HDF [13]. In this respect, it is interesting to note that the highest convection volumes ( $\geq 23.4$  L/session) were the result of a stringent and intensive training program for the nursing staff to optimize its magnitude [7].

Previously it was shown that treatment time, blood flow rate and filtration fraction determine the magnitude of the convection volume rather than individual patient characteristics, such as hematocrit or serum albumin [14–16]. Because these factors are modifiable, but may still depend on patient preference and medical condition, in the present study we prospectively investigated whether high-volume HDF (here defined as  $\geq 22$  L convection volume/session) [5] is lastingly feasible in everyday clinical practice ( $>75\%$  of participants), irrespective of preexisting patient profiles.

## Materials and methods

### Participating patients and centers

This prospective trial (NCT01877499) included patients from six dialysis facilities (three university hospitals, two community-based hospitals and one private dialysis clinic) across The Netherlands. It was conducted between 28 May 2013 and 6 March 2015. It should be noted that it was feasible to ask all eligible patients to participate in only three of the six participating centers. Adult patients ( $\geq 18$  years of age) were eligible if they were being treated with low- or high-flux HD or HDF three times per week for at least 6 weeks. Furthermore, participants had to be able to understand the study procedures and provide informed consent. Exclusion criteria were severe noncompliance

with dialysis prescription or a life expectancy  $<3$  months due to nonrenal disease. This study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and approved by the central medical ethics review board of VU University Medical Center, Amsterdam, The Netherlands.

### Characteristics of participants, controls and reference groups

Various demographic, biochemical and clinical data were collected at baseline. Biochemical parameters were assessed prior to dialysis. To ensure that the investigation included a representative sample of the dialysis population, participants were compared with various dialysis cohorts. First, aggregated data on eligible patients not participating in the present study were collected as a control group. Second, participating patients were compared with baseline data from the complete CONTRAST cohort [5]. Lastly, the study population was compared with aggregated cross-sectional data from the Dutch national dialysis registry RENINE on HD patients (reference date: 1 January 2015).

### Dialysis treatment and stepwise protocol

In a stepwise fashion, treatment time, blood flow rate and filtration fraction were optimized as much as possible in all patients who agreed to participate in this study (Figure 1). Both set and actual blood flow rates were noted during the study sessions. Filtration fraction was defined as UF rate/blood flow rate, since blood flow rate is readily obtainable at the bedside. Dialysate flow rate and temperature remained unaltered during the study. During the first dialysis session, treatment time and blood flow rate remained similar to the previous prescription, as did the filtration fraction of participants previously treated with HDF ( $n = 23$ ). For participants not previously treated with HDF ( $n = 63$ ), the filtration fraction was set at 25%. Before the second session, participants with a treatment time  $<4$  h were advised to increase the duration to 4 h. Thereafter, blood flow rate was increased by 50 mL/min/session to a maximum of 400 mL/min or as high as possible within safety limits (Figure 1). Next, the filtration fraction was increased by 2%/session up to a maximum of 33% or as high as possible within safety limits. Suggestions were provided to optimize blood flow rate and filtration fraction when the maximum values were not initially reached (Figure 1). To ensure a uniform approach during the study, a stepwise approach was developed in close contact with a research/dialysis nurse from every participating center. Furthermore, all participating centers were visited multiple times by one of the investigators, who gave clinical lessons to all nurses and explained the stepwise approach to achieving high-volume HDF, as shown in Figure 1. Finally, during the study, all participating centers were provided with a phone contact for answers to practical questions. It is important to realize that the abovementioned treatment-related adjustments were encouraged but not mandatory in order to reflect everyday

**FLOW CHART FOR OPTIMIZING CONVECTIVE VOLUME**

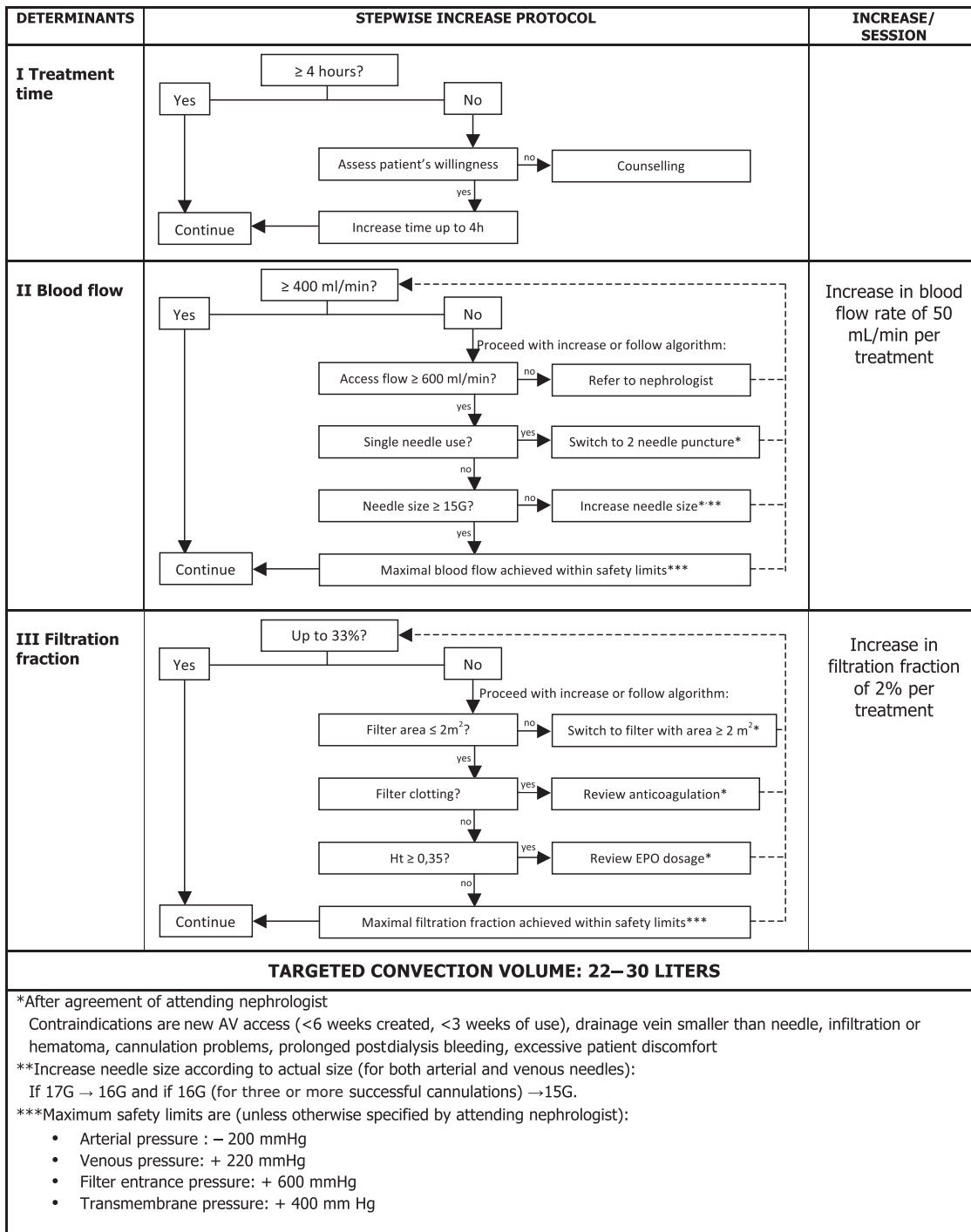


Fig. 1. Flow chart for optimizing the convection volume. In the study, the three important modifiable treatment-related determinants of convection volume were optimized in a stepwise fashion, i.e. at first treatment time up to 4 h, thereafter blood flow rate up to 400 mL/min and finally filtration fraction up to 33%.

clinical practice as much as possible. All decisions were made by the dialysis staff in close consultation with the participant.

**Dialysis equipment**

Different types of dialysis machines, dialyzers and anticoagulation were used across the centers (Table 1). While treatment time and blood flow rate could easily be adjusted in all

machines, no machine provided the option of setting a convection volume goal (substitution volume + net UF) or filtration fraction. Instead, every machine used a different filtration fraction-related parameter. To ensure a comparable study approach in all participating facilities, filtration fraction was used as the parameter in the stepwise protocol. Therefore, an algorithm was built in which treatment time (h, min), blood flow rate (mL/min), filtration fraction (%) and net UF (mL/session)

Table 1. HDF equipment of participating dialysis centers

	Center 1	Center 2	Center 3	Center 4	Center 5	Center 6
Dialysis machine(s)	Fresenius 5008	Nikkiso DBB-05	Nikkiso DBB-07	Gambro AK 200 Gambro Artis	Nikkiso DBB-07	Fresenius 5008
Dialyzer(s)	Polyflux 210H KUF <sup>a</sup> : 85 Surface <sup>b</sup> : 2.1	Xenium XPH 210 KUF: 82 Surface: 2.1 Xenium Ultra 22H KUF: 89 Surface: 2.2	FxCordiax 1000 KUF: 76 Surface: 2.3	Polyflux 210H KUF: 85 Surface: 2.1	FxCordiax 1000 KUF: 76 Surface: 2.3 Elisio 210H KUF: 82 Surface: 2.1	FxCordiax 1000 KUF: 76 Surface: 2.3
Anticoagulation	Dalteparin	Dalteparin	Dalteparin	Nadroparin	Dalteparin	Nadroparin

KUF = dialyzer UF coefficient.

<sup>a</sup>KUF values in mL/(h×mmHg).

<sup>b</sup>Surface areas in m<sup>2</sup>.

could be entered. After selecting a machine type, the algorithm calculated the appropriate filtration fraction-related parameter [i.e. either substitution ratio (%), substitution rate (mL/min) or substitution volume (L/treatment)], as shown in [Supplementary Figure S1](#).

### Follow-up

Since the primary aim of the study was to investigate whether high-volume HDF ( $\geq 22$  L convection volume/session) can be achieved in the majority of dialysis patients (>75% of participants) and the secondary goal was to establish whether this could be lastingly maintained (until 8 weeks thereafter), the study was divided into two phases. In phase one ('optimization phase'), the aforementioned protocol was executed and patients were monitored at every dialysis session. After optimization, treatment time, blood flow rate and filtration fraction were set and the second phase started. In this maintenance phase, data were collected after 4 (W4) and 8 (W8) weeks to investigate the robustness of the findings. Various data were collected before each study session (anticoagulation type and dose, blood flow rate and filtration fraction), during the session (arterial, venous, transmembrane and filter entrance pressures) and after the session (reached UF, substitution volume and treatment time).

### Recirculation

Recirculation occurs when blood from the venous needle does not enter the systemic circulation but reenters the extracorporeal circuit through the arterial needle. This results in a high blood flow rate and thus a high convection volume, which, however, does not contribute to the clearance of toxins. Therefore, monitoring to assess whether the magnitude of the convection volume is 'real' or not is indicated. In our study, recirculation was measured with an ultrasound dilution technique in three centers to determine the scope of this potential problem. Measurements were performed with maximal blood flow rate. When recirculation was  $\geq 10\%$ , it was also measured at lower blood flow rates until it dropped below 10%. Then the blood flow rate was set and used in the study until the problem was solved (e.g. by angioplasty of the vascular access).

### Statistical analysis

At the end of the optimization phase and at W4 and W8, the proportion of patients reaching  $\geq 22$  L of convection volume/session was calculated, as was the mean convection volume per patient per session and the mean pressure values during

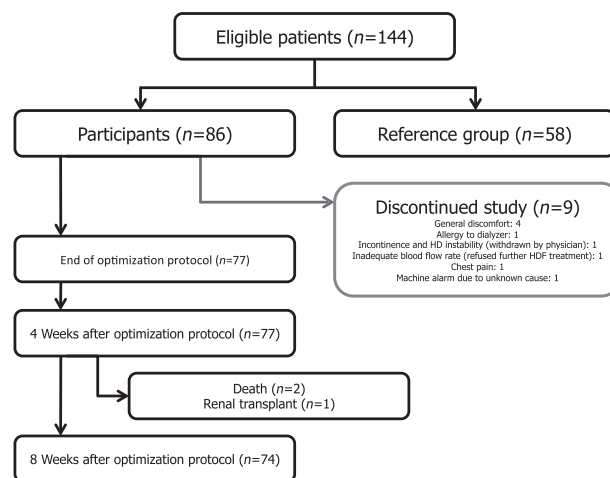


Fig. 2. Flow chart. In total, 144 eligible patients were identified, of which 86 agreed to participate and 58 formed a reference group. During the intensive phase (optimization of modifiable determinants of convection volume), nine quit the study. As the data were analyzed by an 'intention to treat' approach, these patients were taken into account in the results. Between 4 and 8 weeks after end of the stepwise protocol, two patients died and one received a renal transplant. Thus, at the end of the study, 83 patients were analyzed.

dialysis. Data are shown as 'intention to treat'. The relative change between baseline (first session in the study) and the end of the optimization phase was calculated. Differences in patient characteristics between patients  $< \text{or} \geq 22$  L/treatment were calculated with independent t-tests, Mann-Whitney U-tests or chi-square tests, when appropriate. Potential differences among the centers in mean reached convection volume were analyzed with analysis of variance (ANOVA) with Tukey's honest significant difference (HSD) post hoc test to correct for multiple comparisons. All statistical analyses were performed with IBM SPSS Statistics 20.0 (SPSS, Chicago, IL, USA).

## Results

### Clinical data

#### Participants and reference groups

Overall, 144 patients were considered eligible for this study (Figure 2). Of these, 58 individuals served as the control group. Out of a total of 86 participants, 9 discontinued the study

Table 2. Baseline characteristics of participants and reference groups

Determinant	Participants (n = 86)	Controls (n = 58)	CONTRAST (n = 714)	RENINE (n = 5345)
Demographic characteristics				
• Age (years)	60 (18)	57 (22)	64 (14)	68
• Male gender (%)	53 (61.6)	34 (58.6)	445 (62.3)	3130 (58.6)
• BMI (kg/m <sup>2</sup> )	26.4 (5.7)	26.0 (5.9)	25.4 (4.8)	
• Caucasian ethnicity (%)	57 (66.3)	43 (74.1)	600 (84.0)	
Clinical data				
• Diabetes (%)	29 (33.7)	26 (44.8)	170 (23.8)	
• Hypertension (%)	61 (70.9)	42 (72.4)		
• Coronary heart disease (%)	24 (27.9)	8 (13.8)		
• Pre-dialysis SBP (mmHg)	139 (22)	142 (20)	148 (22)	
• RKF (%) <sup>a</sup>	41 (47.7)	30 (51.7)	376 (52.7)	
• CCI (points)	3.0 (2.0–5.0)	4.0 (2.0–5.0)		
• Dialysis vintage (years)	2.0 (1.0–4.3)	2.0 (1.0–5.0)	2.0 (1.0–4.0)	
Laboratory values				
• Hematocrit (L/L)	0.35 (0.04)	0.34 (0.05)	0.36 (0.04)	
• Phosphate (mmol/L)	1.52 (0.45)	1.61 (0.58)	1.65 (0.48)	
• Albumin (g/L)	39.6 (4.8)	38.8 (3.8)	40.4 (3.8)	
• Cholesterol (mmol/L)	4.14 (1.06)	4.06 (1.06)	3.67 (0.96)	
• Urea (mmol/L)	21.0 (7.6)	20.6 (9.0)		
Medication				
• Beta-blocker (%)	53 (61.6)	32 (55.2)	381 (53.4)	
• Calcium antagonist (%)	24 (27.9)	11 (19.0)	230 (32.2)	
• RAS inhibitor (%) <sup>c</sup>	29 (33.7)	16 (27.6)	351 (49.2)	
• Statin (%)	28 (32.6)	16 (27.6)	369 (51.7)	
• Platelet inhibitor (%)	38 (44.2)	22 (37.9)	240 (33.6)	
• ESA (%)	80 (93.0)	53 (91.4)	633 (88.7)	
Treatment characteristics				
• Treatment time (min)	236 (14)	234 (21)	226 (23)	241
• Set blood flow (mL/min)	314 (36)	311 (40)	301 (40)	
• Vascular access				
• AV fistula (%)	68 (79.0)	46 (79.3)	567 (79.4)	1563 (72.8)
• Graft (%)	6 (7.0)	4 (6.9)	97 (13.6)	119 (5.5)
• Access flow (mL/min) <sup>c</sup>	1242 (844–1798)	1128 (871–1580)		
• CVC (%)	12 (14.0)	8 (13.8)	46 (6.4)	296 (13.8)
• spKt/V <sub>urea</sub>	1.42 (0.30)	1.43 (0.30)	1.40 (0.22)	1.44
• UF (mL)	2069 (1527–2683)	2223 (1398–2725)	1900 (1267–2492)	

Data are shown as mean (standard deviation), median (interquartile range) or number (percentage).

Conversion factors for units: haematocrit in L/L to %, × 100; phosphate in mmol/L to mg/dL, /0.3229; albumin in g/L to g/dL, /10; cholesterol in mmol/L to mg/dL, /0.02586; urea in mmol/L to mg/dL, /0.357.

SBP, systolic blood pressure; RKF, residual kidney function; CCI, Charlson Comorbidity Index; RAS, renin-angiotensin system; ESA, erythropoietin-stimulating agent; AV, arteriovenous; ACE, angiotensin-converting enzyme; ATII, angiotensin type II; CONTRAST, CONvective TRANsport Study; RENINE, Registratie Nierfunctieovergang Nederland (Registration Renal Replacement Netherlands); BMI, body mass index.

<sup>a</sup>Defined as >100 mL/24 h.

<sup>c</sup>Use of either an ACE inhibitor or an ATII antagonist.

<sup>d</sup>For either AV fistula or graft; if available (n = 72 for participants, n = 50 for nonparticipants).

protocol: 4 patients discontinued the study due to discomfort, 1 due to a dialyzer allergy, 1 due to hemodynamic instability (although it is unclear if this effect was HDF related), 1 had an inadequate blood flow and refused further HDF treatment, 1 reported chest pain after the start of the dialysis and 1 discontinued the study due to a machine alarm with an unknown cause. Ultimately, 77 participants completed the optimization phase and reached W4. Since 2 patients subsequently died and 1 received a renal transplant, 74 patients completed the study (W8). In general, HDF was well tolerated.

As mentioned before, CONTRAST participants and HD patient data from the national registry database RENINE were used as reference groups as well (Table 2). Although some minor differences existed (e.g. more diabetes among controls, but less cardiovascular disease), in general the groups were comparable. The mean age was higher in RENINE.

### Convection volume

Results are shown in Table 3 and Figure 3. After the optimization phase, 71/86 participants (83%) reached a convection volume of ≥22 L/session (mean 25.5 ± 3.6). At W4, 64/86 participants (74%) reached a convection volume of ≥22 L/session and 66/83 (80%) at W8 with mean convection volumes of 26.2 ± 3.6 and 26.0 ± 3.4 L/session, respectively. Of note, none of the patients agreed to increase their treatment time. An ANOVA analyzing differences among the centers in mean convection volume was significant (P = 0.02); however, it disappeared after the application of Tukey's HSD test for multiple testing.

Patient characteristics were largely comparable between patients with < or ≥22 L/session (Table 4). Interestingly, and counterintuitively the mean predialysis systolic blood pressure was highest in patients with <22 L/session (154 versus 136 mmHg; P = 0.002). In this group of patients, however, the percentage



Table 3. Results

	Baseline <sup>a</sup>	End of stepwise protocol	Relative change between baseline and end protocol (%)	4 weeks after optimization	8 weeks after optimization
Number of patients	86	86	NA	86	83 <sup>b</sup>
Number of patients treated with HDF <sup>c</sup>	86	84	NA	77	74
Patients $\geq 22$ L/session (%) <sup>d</sup>	NA <sup>e</sup>	71 (82.6)	NA	64 (74.4)	66 (79.5)
Convection volume (L/session) <sup>f</sup>	19.2 (3.1)	25.5 (3.6)	+33	26.2 (3.6)	26.0 (3.4)
UF (L/session) <sup>f</sup>	2.1 (1.4–2.7)	2.2 (1.8–2.7)	5	2.1 (1.6–2.7)	2.0 (1.6–2.6)
Actual treatment time (min) <sup>f</sup>	236 (15)	235 (16)	0	238 (13)	238 (14)
Set blood flow rate (mL/min) <sup>f</sup>	300 (300–350)	380 (350–400)	+27	380 (350–400)	380 (350–400)
Blood volume processed (L/session) <sup>f, g</sup>	72.0 (10.7)	81.8 (9.7)	+13	82.8 (10.1)	83.0 (10.5)
Set filtration fraction (%) <sup>f</sup>	26 (2)	32 (2)	+23	32 (2)	32 (2)
Prescribed dose extracorporeal anticoagulation (IU/session) <sup>h</sup>	4482 (1344)	4922 (1703)	+10	4959 (1700)	4989 (1680)
Size arterial needle (G) <sup>i</sup>	16 (15–16)	15 (15–16)	–6	15 (15–16)	15 (15–16)
Size venous needle (G) <sup>i</sup>	15 (15–16)	15 (15–16)	0	15 (15–16)	15 (15–16)

Data are shown as mean (standard deviation), median (interquartile range) or number (percentage).

NA = not applicable; IU = international units.

<sup>a</sup>Defined as the first dialysis session in the study.

<sup>b</sup>Between W4 and W8, two patients died and one received a renal transplant.

<sup>c</sup>Number of patients who continued with the study at the given time point.

<sup>d</sup>Percentage is calculated out of the total number of patients.

<sup>e</sup>Not applicable, as most patients ( $n = 63$ ) were not previously treated with HDF.

<sup>f</sup>Mean values for patients treated with HDF at a specific time point.

<sup>g</sup>Calculated as the mean actual blood flow rate (determined at three time points each session)  $\times$  treatment time.

<sup>h</sup>In the present study, only low molecular weight heparin (dalteparin/nadroparin) was used as extracorporeal anticoagulation.

<sup>i</sup>Corrected for the needle type using the formula: steel lumen = plastic lumen – 1G.

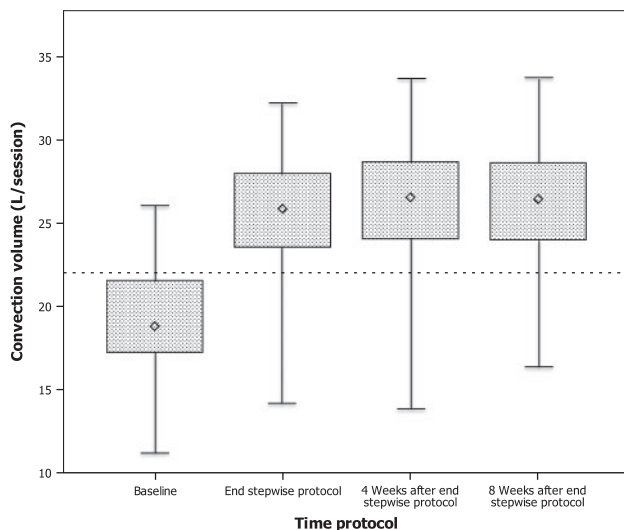


Fig. 3. Convection volumes in the optimization and maintenance phases. The reference line is at 22 L/session, which is generally considered as the threshold between low- and high-volume HDF. Boxes show the 25th and 75th percentiles, diamonds show the median, whiskers are maximum and minimum values. The baseline bar represents the convection volume achieved at the first session of the study (i.e. for all 86 patients using their usual prescribed treatment time and blood flow rate).

with a central venous catheter (CVC) was three times higher (29.4 versus 9.1%). Furthermore, at the end of the optimization phase, patients with  $<22$  L/session were on average receiving treatments that were 20 mins shorter, with an average 60 mL/min lower blood flow rate (Supplementary Table S1).

### Technical and practical issues

#### Treatment time, blood flow rate, needle size and filtration fraction

The mean treatment time, blood flow rate, needle size and filtration fraction at various time points are shown in Table 3.

Treatment time did not change between baseline and the end of the optimization phase, whereas blood flow rate and filtration fraction increased by 27% and 23%, respectively. The median arterial needle size decreased by 1 G between the start and end of the optimization protocol, to 15 G, whereas the venous needle size remained unaltered. Importantly, no needle larger than 15 G was required to achieve high-volume HDF.

#### Recirculation

Recirculation was measured in 39 participants (45.3%) after the maximal blood flow rate was reached; it was present in 2 (5.1%). One patient had a recirculation percentage of 6%, which was accepted and remained stable. The other reached a blood flow rate of 400 mL/min during the optimization phase, although the access flow was only 233 mL/min, due to recirculation of 40%. After angioplasty, access flow increased to 580 mL/min and no recirculation occurred with a blood flow rate of 400 mL/min.

#### Arterial, venous, transmembrane and filter entrance pressure measurements

Arterial pressure became 17% more negative between baseline and the end of the optimization phase, while venous pressure increased by 14% (Supplementary Table S2). Filter entrance pressure, however, increased on average by 21%, and transmembrane pressure increased up to  $>60\%$  (Figure 4) 2 h after starting treatment.

### Discussion

The present study prospectively investigated the feasibility of achieving and maintaining high convection volumes with on-line postdilution online HDF (high-volume HDF, defined as  $\geq 22$  L convection volume/session) in everyday clinical practice. Since important baseline characteristics, such as age and comorbidities of the participating patients, were similar to those of the group of screened patients who did not participate

Table 4. Patient characteristics with < and  $\geq$ 22 L convection volume/session

Determinant	Participants $\geq$ 22 L (n = 66)	Participants <22 L (n = 17)	P for difference
Demographic characteristics			
• Age (years)	58.4 (18.6)	64.5 (13.1)	0.12
• Male gender (%)	41 (62.1)	9 (52.9)	0.49
• BMI (kg/m <sup>2</sup> )	26.5 (5.4)	25.3 (7.3)	0.51
• Caucasian ethnicity (%)	45 (68.2)	9 (52.9)	0.56
Clinical data			
• Diabetes (%)	21 (31.8)	7 (41.2)	0.47
• Hypertension (%)	46 (69.7)	4 (23.5)	0.58
• Coronary heart disease (%)	19 (28.8)	5 (29.4)	0.96
• Mean pre-dialysis SBP (mmHg)	136 (21)	154 (19)	0.002
• RKF (%) <sup>a</sup>	30 (45.5)	10 (58.8)	0.22
• CCI (points)	3.5 (2.0–5.0)	3.0 (2.0–5.0)	0.88
• Dialysis vintage (years)	2.0 (1.0–4.0)	2.0 (1.0–6.5)	0.51
Laboratory values			
• Hematocrit (%)	35 (3)	33 (5)	0.08
• Phosphate (mg/dL)	4.6 (1.2)	4.9 (2.0)	0.55
• Albumin (g/L)	3.83 (0.44)	3.65 (0.56)	0.21
• Cholesterol (mg/dL)	158 (41)	168 (38)	0.38
Medication			
• Beta-blocker (%)	40 (60.6)	11 (64.7)	0.76
• Calcium antagonist (%)	20 (30.3)	4 (23.5)	0.58
• RAS inhibitor (%) <sup>b</sup>	22 (33.3)	6 (35.3)	0.88
• Statin (%)	22 (33.3)	5 (29.4)	0.76
• Platelet aggregation inhibitor (%)	27 (40.9)	10 (58.8)	0.19
• ESA (%)	60 (90.9)	17 (100.0)	0.20
Treatment characteristics			
• Treatment time (min)	240 (7)	222 (26)	0.07
• Blood flow (mL/min)	318 (37)	302 (33)	0.10
• Vascular access			0.52
• AV fistula (%)	56 (84.8)	11 (64.7)	
• Graft (%)	4 (6.1)	1 (5.9)	
• Access flow (mL/min) <sup>c</sup>	1262 (859–1820)	1162 (683–1591)	
• CVC (%)	6 (9.1)	5 (29.4)	
• spKt/V <sub>urea</sub>	1.45 (0.31)	1.33 (0.28)	0.19
• Net UF (L)	2.2 (1.5–2.7)	1.7 (1.3–2.5)	0.36

Data are shown as mean (standard deviation), median (interquartile range) or number (percentage).

Conversion factors for units: haematocrit in % to L/L, /100; phosphate in mg/dL to mmol/L,  $\times 0.3229$ ; albumin in g/dL to d/L,  $\times 10$ ; cholesterol in mg/dL to mmol/L,  $\times 0.02586$ .

BMI, body mass index; SBP, systolic blood pressure; RAS, renin-angiotensin system; ESA, erythropoietin-stimulating agent; AV, arteriovenous; CCI, Charlson Comorbidity Index; RKF, residual kidney function.

<sup>a</sup>Defined as diuresis >100 mL/24 h.

<sup>b</sup>Use of either an ACE inhibitor or an ATII antagonist.

<sup>c</sup>For either an AV fistula or a graft.

in the present study (control group), as well as the baseline characteristics of the CONTRAST cohort and the HD patients in the national registry of The Netherlands (RENINE), our study group can be regarded as a representative sample of the Dutch dialysis population. Therefore, the following conclusions seem reliable and robust: (i) high-volume HDF ( $\geq 22$  L/session) is feasible in  $\sim 80\%$  of our dialysis patients and (ii) the convection volume that can be achieved is 26 L/session on average. Since all patients refused a longer treatment time, (iii) incremental adjustments in blood flow rate and filtration fraction alone are sufficient to obtain this effect. (iv) Despite higher venous, filter entrance and transmembrane pressures and a more negative arterial pressure, undesirable side effects or complications did not occur.

In several studies comparing postdilution online HDF with HD, an inverse association between convection volume and mortality has been demonstrated [5–12]. Although these studies are limited by their observational design, all results point in the same direction. As such, it seems justified to conclude that convection

volume is a key parameter for the adequacy of HDF, as was previously stated in a consensus meeting of the European Dialysis working group [13]. The feasibility of high-volume HDF in the vast majority of patients, irrespective of their preexisting medical conditions, is the next step in HDF research and will pave the way for an RCT to definitively answer the question of whether high-volume HDF results in better survival rates than standard HD or to investigate a dose–response relationship between the magnitude of the convection volume and reduced mortality risk.

It has repeatedly been demonstrated that treatment-related parameters, such as treatment time and blood flow rate, rather than patient-related factors, including comorbidities and biochemical parameters, determine the magnitude of the convection volume [14–16]. The present study shows that the convection volume is indeed largely independent of clinical characteristics, given the vast majority that reached high-volume HDF for a prolonged period of time (80%) when adhering to a structured stepwise protocol.

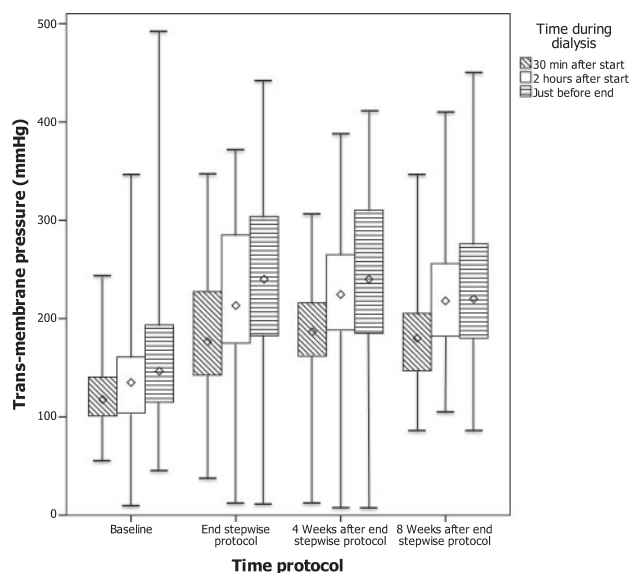


Fig. 4. Transmembrane pressure during the optimization and maintenance phases. Boxes show the 25th and 75th percentiles, diamonds showing the median, whiskers are maximum and minimum values. The baseline bars represent the values achieved for all patients at the first study session.

In this respect, it should be noted that nine participants discontinued the study and eight (9.3%) did not reach high convection volumes. Whether these individuals would have achieved higher convection volumes remains a matter of speculation, since besides blood flow and filtration fraction, they would have had to agree to an increase in treatment time as well. As calculated by Penne *et al.* [15], an increase in treatment time by 20 min would result in an average increase in the convection volume of 1800 mL. However, to imitate everyday clinical practice, patients were encouraged, but not forced, to pursue the consecutive steps of the protocol. Furthermore, the number of patients with a CVC was relatively high in participants with  $< 22$  L/session (6/12). With respect to the presence of a CVC, conflicting findings have been previously reported. Whereas the average volume did not differ between patients with a fistula and a CVC in a post hoc analysis of the CONTRAST study [14], others reported that high-volume HDF was achieved in only 33% of sessions with a CVC [17]. In the present study, 50% of patients with a CVC reached  $\geq 22$  L/session in the long term. Thus, although a CVC is not a contraindication for achieving high-volume HDF, a fistula seems preferable [18].

Our prospectively collected findings are largely in line with a recent large observational study showing that 79% of 4176 sessions could be classified as high-volume HDF ( $\geq 21$  L substitution volume/session, corresponding to 23.4 L convection volume/session) [17]. Notably, our study did not calculate the percentage of high convection volume sessions but rather the percentage of patients who achieved a high convection volume. Recently it was suggested that subjects who reach high-volume HDF over a prolonged period of time benefit particularly from this treatment [19]. Therefore, it appears more rational to investigate the feasibility of high-volume HDF on the patient level than on the session level.

Importantly, the high convection volumes were not associated with undesirable pressure changes. In this respect, it is of note that various manufacturers of dialysis equipment offer automatic optimization of the convection volume based on, for example, the transmembrane pressure [20, 21]. Such software can automatically adjust the filtration fraction (but not

treatment time or blood flow rate) during treatment. It is currently unclear, however, whether this equipment is more efficient or even as effective as our structured, manual approach.

Obviously, our study has its strengths and limitations. The most important limitation is that selection bias cannot be fully excluded, despite the structured and concise approach. Of note, important patient characteristics did not differ between the study group and the control group, the baseline characteristics of the CONTRAST cohort or data from the Dutch RENINE registry for HD patients. Moreover, despite the participation of university- and community-based dialysis centers, testing for differences in convection volume did not yield marked variations between facilities. Nevertheless, only three centers included all eligible patients in this study (either as participants or as controls) and, as such, the results must be interpreted with caution. Lastly, blood flow was not independently checked. Important strengths of the present study include its multicenter design, in which various dialyzers and dialysis machines were used, and the structured, individualized approach to optimizing convection volume. In addition, since patients were encouraged but not compelled to follow the protocol, the present study reflects current practice to a large extent. Furthermore, extending the study to 8 weeks after optimization and the exclusion of recirculation as a cause of high-volume HDF in a substantial subset of the patients increases the robustness of our findings. Lastly, the monitoring of various treatment-related pressures and the lack of undesirable side effects emphasizes the safety of the procedure pursued.

In brief, using a step-up protocol for the optimization of treatment time, blood flow rate and filtration fraction, high-volume HDF appeared to be lastingly feasible in 80% of representative patients. Moreover, the mean convection volume was  $\pm 26$  L/session, irrespective of age, body size or comorbidities. Whether more explicit encouragement to increase treatment time in selected patients will lead to even higher convection volumes is not clear from the present study. To provide definitive evidence for an inverse dose-response relation between convection volume and mortality risk, future research will be necessary.

## Supplementary data

Supplementary data are available online at <http://ckj.oxfordjournals.org>.

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## Conflicts of interest statement

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## References

1. United States Renal Data System. 2013 USRDS Annual Data Report: Epidemiology of Kidney Disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2013
2. Locatelli F, Martin-Malo A, Hannedouche T et al. Effect of membrane permeability on survival of hemodialysis patients. *J Am Soc Nephrol* 2009; 20: 645–654
3. Eknoyan G, Beck GJ, Cheung AK et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 2002; 347: 2010–2019
4. Leypoldt JK. Solute fluxes in different treatment modalities. *Nephrol Dial Transplant* 2000; 15: 3–9
5. Grooteman MP, van den Dorpel MA, Bots ML et al. Effect of online hemodiafiltration on all-cause mortality and cardiovascular outcomes. *J Am Soc Nephrol* 2012; 23: 1087–1096
6. Ok E, Asci G, Toz H et al. Mortality and cardiovascular events in online haemodiafiltration (OL-HDF) compared with high-flux dialysis: results from the Turkish OL-HDF Study. *Nephrol Dial Transplant* 2013; 28: 192–202
7. Maduell F, Moreso F, Pons M et al. High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. *J Am Soc Nephrol* 2013; 24: 487–497
8. Peters SA, Bots ML, Canaud B et al. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. *Nephrol Dial Transplant* 2016; 31: 978–984
9. Siroopol D, Canaud B, Stuard S et al. New insights into the effect of haemodiafiltration on mortality: the Romanian experience. *Nephrol Dial Transplant* 2015; 30: 294–301
10. Panichi V, Rizza GM, Paoletti S et al. Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID study. *Nephrol Dial Transplant* 2008; 23: 2337–2343
11. Canaud B, Bragg-Gresham JL, Marshall MR et al. Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. *Kidney Int* 2006; 69: 2087–2093
12. Imamovic G, Hrvacevic R, Kapun S et al. Survival of incident patients on high-volume online hemodiafiltration compared to low-volume online hemodiafiltration and high-flux hemodialysis. *Int Urol Nephrol* 2014; 46: 1191–1200
13. Tattersall JE, Ward RA. Online haemodiafiltration: definition, dose quantification and safety revisited. *Nephrol Dial Transplant* 2013; 28: 542–550
14. Chapdelaine I, Mostovaya IM, Blankestijn PJ et al. Treatment policy rather than patient characteristics determines convection volume in online post-dilution hemodiafiltration. *Blood Purif* 2014; 37: 229–237
15. Penne EL, van der Weerd NC, Bots ML et al. Patient- and treatment-related determinants of convective volume in post-dilution haemodiafiltration in clinical practice. *Nephrol Dial Transplant* 2009; 24: 3493–3499
16. Marcelli D, Kopperschmidt P, Bayh I et al. Modifiable factors associated with achievement of high-volume post-dilution hemodiafiltration: results from an international study. *Int J Artif Organs* 2015; 38: 244–250
17. Marcelli D, Scholz C, Ponce P et al. High-volume postdilution hemodiafiltration is a feasible option in routine clinical practice. *Artif Organs* 2015; 39: 142–149
18. Chapdelaine I, de Roij van Zuijdewijn CL, Mostovaya IM et al. Optimization of the convection volume in online post-dilution haemodiafiltration: practical and technical issues. *Clin Kidney J* 2015; 8: 191–198
19. Canaud B, Barbieri C, Marcelli D et al. Optimal convection volume for improving patient outcomes in an international incident dialysis cohort treated with online hemodiafiltration. *Kidney Int* 2015; 88: 1108–1116
20. Teatini U, Steckiph D, Romei LG. Evaluation of a new online hemodiafiltration mode with automated pressure control of convection. *Blood Purif* 2011; 31: 259–267
21. Maduell F, Rodriguez N, Sahdala L et al. Impact of the 5008 monitor software update on total convective volume. *Nefrologia* 2014; 34: 599–604