

**Hemodiafiltration: cardiovascular parameters  
and convection volume**

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# **Hemodiafiltration: cardiovascular parameters and convection volume.**

Hemodiafiltratie: cardiovasculaire parameters en convectie volume.

(met een samenvatting in het Nederlands)

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Irina Maximovna Mostovaya

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**Promotoren:**

Prof. dr. M.L. Bots

Prof. dr. M.C. Verhaar

**Co-promotoren:**

Dr. P.J. Blankestijn

Dr. M.P.C. Grooteman

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*Voor Alexander*

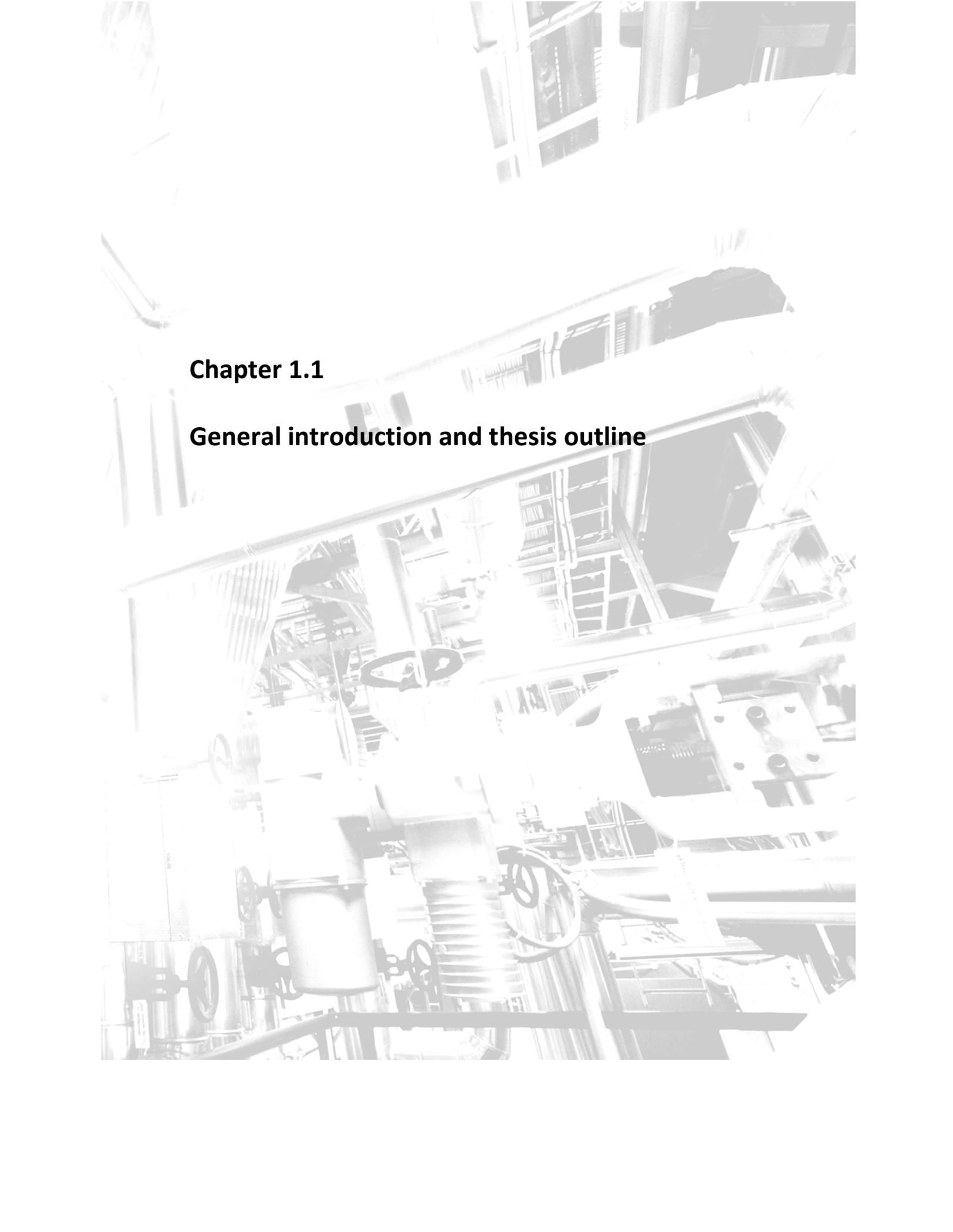
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## **Chapter 1.1**

### **General introduction and thesis outline**

End stage kidney disease (ESKD) is pathophysiologically characterized by severe irreversible kidney damage and clinically by an almost completely absent glomerular filtration rate. In the Netherlands, approximately 16 000 patients (0.1% of the population) suffer from ESKD. (1) The morbidity and mortality in this patient group is extremely high, (2) cardiovascular disease accounting for a substantial part of fatal and non-fatal events. (3) Traditional risk factors only partly explain this high risk. Other pathophysiological processes such as retention of uremic toxins, increased oxidative stress, volume overload, disorders of mineral metabolism and micro-inflammation have all been implicated in the development of accelerated cardiovascular disease. (4)

The presence of cardiovascular disease risk can be estimated directly by the occurrence of cardiovascular events, and indirectly by markers of cardiovascular damage, including systolic blood pressure (a measure of the amount of force exerted on the artery wall), left ventricular cardiac mass (an indirect measure of exposure to a large cardiac workload), left ventricular ejection fraction (a measure of cardiac function) and pulse wave velocity (a measure of arterial stiffness).

Although all these markers have been associated with an increased risk of mortality and morbidity in ESKD patients in several studies, (5-8) such risks differ between different ESKD populations (for example in different geographical areas) and change over time as treatment guidelines for ESKD patients change. Therefore, in a part of this thesis we aimed at complementing and updating information on the relation between functional and structural cardiovascular parameters and clinical events in ESKD patients.

Currently, it is largely unknown how these cardiovascular structural and functional parameters change over time in the ESKD population, and how this rate of change could be modified. In the first part of this thesis an attempt is made to closing the gap in this knowledge field.

The best treatment option for ESKD patients is a kidney transplantation. However, due to shortage of organ donors and the fact that not all ESKD patients are eligible for transplantation, a considerable proportion of the ESKD population is treated by dialysis. In the Netherlands, approximately 40% of the Dutch ESKD patients is undergoing dialysis, while 60% is living with a functional transplant (1,9). Of the patients treated with dialysis, 84% is undergoing chronic intermittent dialysis and 16% peritoneal dialysis. (9) During standard chronic intermittent hemodialysis (HD), small uremic toxins are removed by diffusion, while larger solutes are retained within the body. In hemodiafiltration (HDF) diffusion is combined with convection, enabling the removal of middle- and large molecular weight substances up to 40kDa. (10) During HDF, convective transport is obtained by filtering considerable amounts of plasma water through a dialyser with a large pore size (high-flux). At the same time, sterile substitution fluid is infused directly into the bloodstream of the patient to maintain fluid balance. As retention of middle and large uremic toxins has been related to the adverse clinical outcome in patients with ESKD, it has been suggested that removal of these substances by HDF may improve its prognosis, in particular as far as cardiovascular outcome is concerned. (11) Parallel, it is hypothesized that online HDF would have a beneficial effect on structural and functional markers of cardiovascular risk. Part of the present thesis is aimed at addressing the latter issues in particular.

Recently, the results of three large randomized controlled trials (RCTs): the CONvective TRANsport STudy (CONTRAST) (12), the Turkish HDF Study (13) and the Estudio de Supervivencia de Hemodiafiltracion On-Line (ESHOL) (14), were published. All three trials assessed the effect of HDF as compared to other hemodialysis on fatal and non-fatal cardiovascular disease and all-cause mortality. Neither CONTRAST nor the Turkish HDF study showed a significant difference in all- cause mortality or (both fatal and non-fatal) cardiovascular events between HDF and HD over a median two to three year period of follow-up. (12;13) ESHOL, the trial with the highest achieved convection volumes (defined as the sum of the net ultrafiltration volume and the amount of substitution fluid) reported

superiority of HDF over HD with respect to all-cause mortality, as well as cardiovascular mortality. (14) Sub-group analyses in all three studies consistently showed a relation between a high achieved convection volume and a lower mortality risk, which remained significant even after adjustment for potential confounders. (11-13)

Hence, although not demonstrated prospectively, it appears that delivered convection volume in HDF is of much importance. Furthermore, it would be interesting to explore if a dose-response relation exists between convection volume and mortality. If indeed confirmed, it would be relevant to know what factors determine level of convection volume and thus whether modifying convection volume would be possible in clinical practice. The final part of the present thesis aimed at solving that research question.

Therefore, the aims of this thesis are:

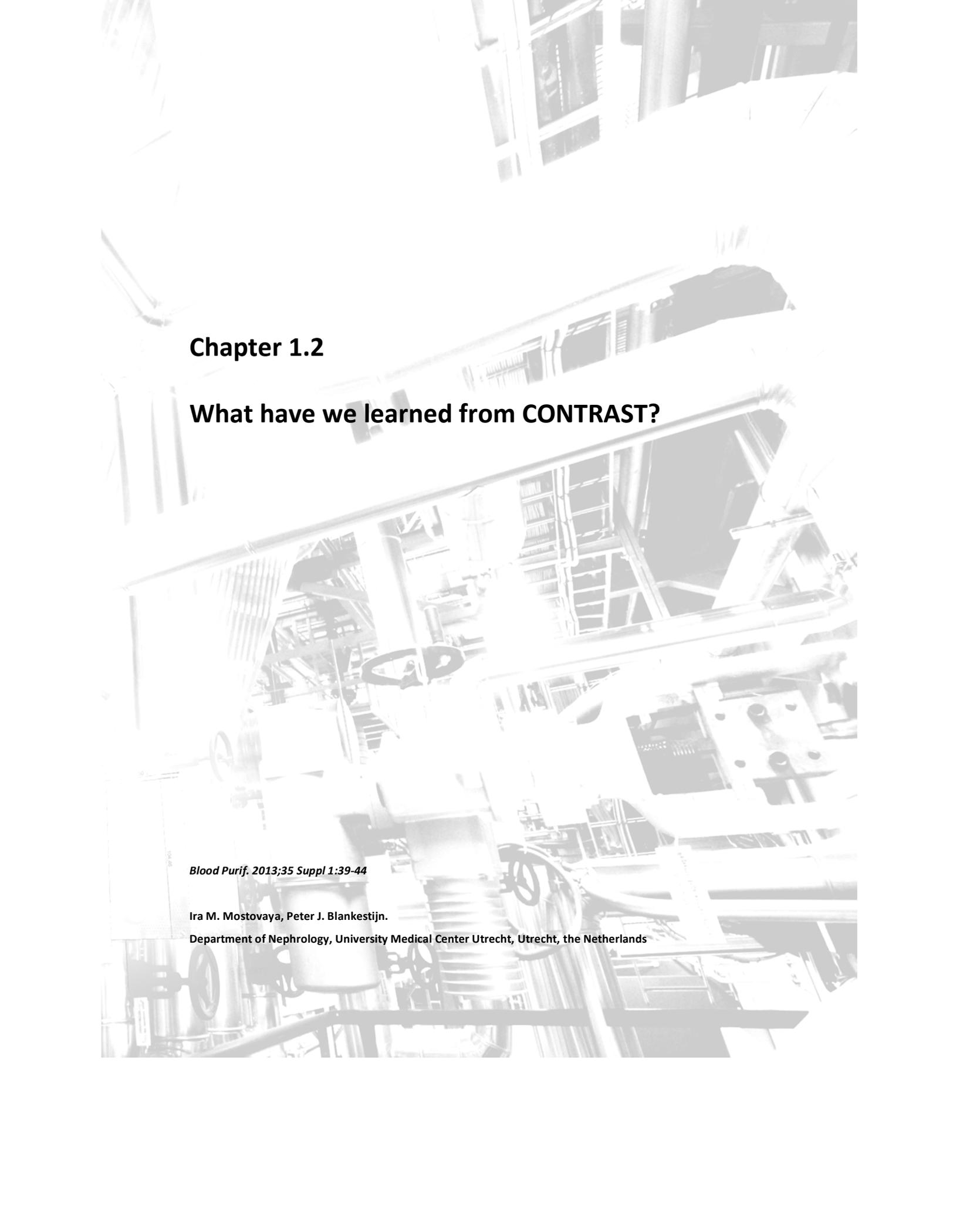
- 1) To study the relation between structural and functional cardiovascular markers and mortality / cardiovascular events in ESKD patients.
- 2) To study determinants of change (including dialysis modality) in structural and functional cardiovascular markers of risk in ESKD patients.
- 3) To assess what determines convection volume and how convection volume changes over time.

To address the above-stated research aims, data from CONTRAST was used. CONTRAST is a RCT comparing mortality and cardiovascular events between online post-dilution HDF and low-flux HD in 714 chronic intermittent dialysis patients from 29 dialysis centers in the Netherlands, Canada and Norway. The study design of CONTRAST as well as the results of earlier publications on the main outcome and secondary outcome parameters are described in the second part of the Introduction.

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## Chapter 1.2

### What have we learned from CONTRAST?

*Blood Purif. 2013;35 Suppl 1:39-44*

Ira M. Mostovaya, Peter J. Blankestijn.

Department of Nephrology, University Medical Center Utrecht, Utrecht, the Netherlands

**Abstract**

The COncvective TRansport STudy (CONTRAST) is a large randomized controlled trial, which compared online post-dilution hemodiafiltration (HDF) and low-flux hemodialysis (HD) in terms of mortality and cardiovascular events. This review summarizes and discusses currently available knowledge acquired by CONTRAST; including the main outcome, comparisons of HDF to HD as well as studies performed in subgroups of CONTRAST.

## **Introduction**

The Convective TRansport STudy (CONTRAST) is a randomized controlled trial (RCT) which was conducted between 2004 and 2011 and compared online post-dilution hemodiafiltration (HDF) and low-flux hemodialysis (HD) in terms of mortality (primary outcome) and cardiovascular events. A total of 714 chronic stable dialysis patients (597 in the Netherlands, 102 in Canada and 15 in Norway) participated in this study. From this group 358 were randomized to online HDF and 356 to HD and followed for a median time of 3 years. (1) During this period the above mentioned clinical events were recorded as well as various secondary outcome variables. (2)

The aim of this review is to discuss currently available knowledge acquired by CONTRAST; including the 1) main outcome, 2) comparisons of HDF to HD in other aspects than the main outcome as well as 3) other studies performed in subgroups of CONTRAST.

### **Mortality and cardiovascular events.**

The main outcome of CONTRAST was published in April 2012: no superiority of HDF over HD was shown with respect to overall mortality and cardiovascular morbidity and mortality. (See Table 1.) Interestingly, on-treatment analyses showed that a high mean convection volume (calculated as the sum of the intradialytic weight loss and the substitution volume of a dialysis session) was associated with a lower mortality risk. In fact, patients on HDF with a convection volume of >22.0L had a 39% decreased risk of death when compared to HD: an adjusted hazard ratio of 0.61 (95% Confidence Interval (CI) 0.38 – 0.98), with a p for trend of 0.015. (1)

Strikingly, the Turkish hemodiafiltration study showed similar results. This RCT compared high-flux HD to online post-dilution HDF in 782 patients in terms of all-cause mortality and non-fatal cardiovascular events. No difference was found between the treatment groups in terms of the above described outcomes. However, on-treatment analysis showed that patients with an ultrafiltration volume of more than 17.4L (which, with a mean intradialytic weight loss of 3.4L, is equivalent to a convection volume of more than 20.8L) had a decreased risk for all-cause mortality (adjusted hazard ratio 0.54, 95% CI 0.31 –

**Table 1:** Risk of all-cause mortality and fatal and non-fatal cardiovascular events by achieved convection volume in liters per treatment in CONTRAST. *With permission from: Grooteman MPC et al. J Am Soc Nephrol. 2012 Jun;23(6):1087-96.*

	Hemodialysis	Online Hemodiafiltration Convection Volume Tertiles			P for Trend
		<18.17 L	18.18–21.95 L	>21.95 L	
Total mortality					
crude	1.0	0.95 (0.66–1.38)	0.83 (0.57–1.22)	0.62 (0.41–0.93)	0.010
adjusted <sup>a</sup>	1.0	0.79 (0.53–1.14)	0.77 (0.51–1.14)	0.65 (0.42–0.99)	0.012
adjusted <sup>b</sup>	1.0	0.80 (0.52–1.24)	0.84 (0.54–1.29)	0.61 (0.38–0.98)	0.015
Fatal and nonfatal cardiovascular events					
crude	1.0	1.37 (0.94–1.98)	1.06 (0.72–1.56)	0.76 (0.50–1.16)	0.473
adjusted <sup>a</sup>	1.0	1.41 (0.92–2.11)	0.93 (0.62–1.40)	0.77 (0.48–1.21)	0.369
adjusted <sup>b</sup>	1.0	1.35 (0.86–2.11)	1.04 (0.66–1.62)	0.72 (0.44–1.19)	0.475

Results reported as hazard ratios and 95% Confidence interval, from Cox proportional hazards models. Reference is treatment with low-flux hemodialysis.

<sup>a</sup>Adjusted for determinants of mortality, *i.e.*, age, sex, previous vascular disease, diabetes, previous transplantation, spKt/V, baseline eGFR, baseline albumin, baseline creatinine, baseline hematocrit, and use of  $\alpha$ - and  $\beta$ -blockers, calcium antagonists and angiotensin converting inhibitors at baseline (82 missing, 206 deaths, 182 cardiovascular events).

<sup>b</sup>Adjusted for the above-mentioned determinants as well as for center differences (82 missing, 206 deaths, 182 cardiovascular events).

0.93) as well as cardiovascular mortality (adjusted hazard ratio 0.29, 95% CI 0.12 – 0.65).

(3)

Although *post hoc* analyses do not always provide reliable results, the fact that two large studies produce similar findings in such analyses is notable, and urges for further investigation.

The results of the ESHOL study: a Spanish RCT comparing survival in HD and HDF patients, are now avidly awaited. (4)

### **Quality of life**

During CONTRAST, differences in quality of life between HD and HDF patients were evaluated by assessment of a health related quality of life by questionnaire (containing a generic and a kidney-disease specific part) at baseline and yearly thereafter. The CONTRAST group showed that HDF did not affect patients' health-related quality of life (HRQOL) as compared to HD. A trend was observed for a worse Mental Composite Score and an improved 'Effects of kidney disease on daily life' in patients on HDF (for both  $p=0.06$ ). (5)

### **Intermediate outcome variables**

The inflammatory parameters high sensitivity C-reactive protein (hsCRP) and interleukin-6 were measured in 405 patients at baseline and during 3 years of follow-up. The hsCRP and Il-6 concentrations increased significantly over time in HD patients, while remaining stable in HDF patients. However, the difference in rate of change did not result in significantly different values of these inflammation markers during follow-up. Simultaneously, the changes in albumin over time were compared in 714 patients between treatment arms. No difference was found in neither rate of change nor mean concentrations between HD and HDF. (6) These results indicate that HDF is not associated with induced inflammatory activity and clinically relevant protein loss.

Beta-2 microglobulin ( $\beta_2m$ ) is a middle-weight molecule which accumulates in the blood of dialysis patients (as it is normally cleared by the kidney) and has been shown to predict all-cause and infectious related mortality in this group. (7;8) A significant lowering of  $\beta_2m$

was demonstrated in patients undergoing HDF for 6 months, especially the patients without residual renal function. (9) The  $\beta_2m$ -level remained consistently lower in the HDF group when compared to HD. (1) These results confirm that with HDF clearance of middle weight molecular substances is obtained, while this is not the case with HD.

The CONTRAST group studied the effect of HDF on phosphate levels, since hyperphosphatemia is a risk factor for overall mortality and cardiovascular morbidity and mortality in dialysis patients. (10) After 6 months of treatment phosphate levels decreased significantly by 6% in the HDF group, but remained stable in the HD group. This difference in change remained significant after adjustment for phosphate binder use. Also, the proportion of patients reaching phosphate treatment targets increased by 10% in the HDF group. (11) These results suggest that HDF may help to improve phosphate control.

### **Safety**

In online HDF large volumes of substitution fluid, which is produced from the municipal water supply, are infused directly into the patient's bloodstream. For this reason, microbiological safety is a matter of concern in HDF. The CONTRAST group has shown that infusate of adequate quality can be produced over a prolonged period of time. Moreover, no pyrogenic reactions were reported in HDF patients. (12) Also, markers of inflammation did not differ between the HDF and HD group. (1;6) Although CONTRAST has not been designed to study safety issues, it has provided no indications that HDF is unsafe.

### **Costs**

A cost-utility analysis was conducted parallel to CONTRAST in 409 of the patients. This analysis was performed from a societal perspective, which means that all costs and all effects are included in the analysis. The cost-utility analysis showed that costs of HDF are approximately 4% when compared to HD. The additional costs of HDF could mainly be attributed to higher expenses for disposables and a more frequent control for dialysis water purity. However, if the costs of disposables could be decreased, HDF would fit within the currently accepted standards of cost-effectiveness. (13)

**Other findings in the CONTRAST population.**

Apart from studies comparing different aspects of HD and HDF, data from the CONTRAST study was used to answer several other research questions concerning the population of dialysis patients.

The determinants of convection volume were evaluated in a subgroup of 235 consecutive HDF patients. In a multivariate analysis, factors related to convection volume were: serum albumin, blood flow rate, treatment time (all positively related) and hematocrit (inversely related). Furthermore, a large variation in convection volume was found between participating centres ranging from 14 to 24 Litres. These diverging results could only partly be explained by the above-mentioned patient- and treatment-related characteristics. (14) It is likely that other non-measured centre specific factors, such as awareness and motivation of doctors and nursing staff, might play an important role in this respect.

Quality of life has been studied extensively in the CONTRAST population. In a cross-sectional study with 570 patients, differences in HRQOL were examined between participating centres. Three HRQOL domains appeared to differ between the dialysis centres: the physical composite score, quality of social interaction and dialysis staff encouragement. Two centre characteristics were related to the patients' HRQOL: the type of dialysis centre and dieticians' fulltime-equivalent. (15) This study identifies modifiable centre characteristics which could contribute to a better quality of life in dialysis patients. The relationship between adherence to the six clinical performance targets as recommended by the Kidney Disease Outcomes Quality Initiative (KDOQI) and HRQOL was evaluated in 714 patients; and no significant association was found. (16) These results indicate that it would be prudent to identify clinical performance targets that are related to HRQOL, or implement HRQOL as a clinical performance target in itself.

In a cross-sectional study in 590 patients, the relationship between quality of life and nutritional status was assessed. In this population 83% of all patients were well-nourished. Multiple nutritional parameters were positively related to the physical summary of generic

HRQOL and to the following kidney disease-specific HRQOL scales: the effects of the kidney disease on daily life, the burden of the kidney disease, and overall health. (17)

Finally, the change of quality of life over time was compared between the general and the dialysis population. For this analysis HRQOL data from 515 CONTRAST patients in 2006 was compared to data from 126 patients from the Netherlands Cooperative Study on the Adequacy of Dialysis-1 (18) in 1995. Meanwhile, HRQOL in the general population in 1992 (n=1063) and 2001 (n=10600) was also assessed. This study showed that quality of life was significantly better for dialysis patients in 2006. Furthermore, the improvement was independent of global changes in the general population. (19)

The relationship between various nutritional parameters and mortality was studied in 569 patients, with the aim to develop a composite score of protein-energy nutritional status. However, the best version of a composite score of protein-energy nutritional status (based on albumin, BMI, normalized protein nitrogen appearance and creatinine) was not a better predictor than an individual parameter, namely albumin or creatinine. (20) These results put the clinical value for proposed diagnostic criteria for protein energy wasting to question.

The role of residual renal function on  $\beta_2m$ , phosphate control and anemia management was investigated in 569 patients. This study demonstrated that in patients with residual renal function pre-dialysis  $\beta_2m$  levels were significantly lower, phosphate treatment targets were reached more often (despite a significant decrease in use of phosphate binding agents) and requirements for erythropoiesis stimulating agents (ESA) were lower, while hemoglobin levels were comparable. (21) This demonstration of the beneficial effect of residual renal function stresses the importance of attempting to preserve this function in hemodialysis patients.

Compliance to anemia targets was studied in 598 patients from 26 treatment centres. This study demonstrated that the compliance with all anemia targets (Hb 11.0-12.0 g/dl, transferrin saturation ratio  $\geq 20\%$ , ferritin 100-500 ng/ml) was reached in only 12% of the patients. The adherence percentages varied greatly among centres (4-26%), even after adjustment for treatment-related factors and centre-specific characteristics. (22)

Hepcidin, a key regulator of iron homeostasis, was measured in 405 patients of CONTRAST. In a cross-sectional study, potential patient-, laboratory- and treatment-related determinants of serum hepcidin-20 and -25, were assessed. Hepcidin-25 was a marker for iron stores and erythropoiesis and was associated with inflammation. Furthermore, hepcidin-25 levels were influenced by residual kidney function. Hepcidin-25 did not reflect ESA or iron dose in the CONTRAST population. These results suggest that hepcidin is involved in the pathophysiological pathway of renal anemia and iron availability in these patients. However, the findings deprecate the use of hepcidin as a clinical parameter for ESA resistance. (23)

The relationship between hepcidin-25 and all-cause mortality and cardiovascular events was studied in 405 patients. Hepcidin-25 was found to be associated with fatal and non-fatal cardiovascular events. Inflammation appears to be a significant confounder in this relationship. (24) The exact pathophysiological mechanism of this association remains yet to be established.

The results of all the published studies performed in the CONTRAST population are summarized in Table 2.

#### **Implications for future studies**

The on-treatment analysis of the results of both CONTRAST and the Turkish hemodiafiltration study suggest that there is a potential dose-response effect between the convection volume and clinical outcome in HDF patients. This finding stresses the importance of reporting data on actually delivered (and not only target) convection volume in future studies. In a subset of the CONTRAST population treatment time, blood flow rate, albumin and hematocrit were identified as significant (and modifiable) determinants of convection volume. Additional studies on this subject in different patient populations would lead to more robust conclusions.

Meta-analyses of individual patient data from conducted RCTs are needed to provide better insight in the relationship between convection volume and mortality. To answer the question whether the convection volume can be safely manipulated in clinical practice, a

**Table 2:** Summary of published studies which were performed with data from the CONTRAST population.

<b><u>HD versus HDF</u></b>		
<b>Name</b>	<b>Patient number</b>	<b>Results</b>
Grooteman et al. 2012 (1)	714	HDF was not superior compared to HD in terms of survival and cardiovascular events.  In subgroup analysis high-volume HDF patients have a survival benefit.
den Hoedt et al 2012 (6)	714	In HD II-6 and hsCRP increased over time, but remained stable in HDF. No difference in rate of change of albumin between treatment groups.
Mazairac et al. 2012 (5)	409	HDF compared to HD did not affect quality of life over time.
Mazairac et al. 2012 (13)	714	HDF is not cost-effective when compared to HD.
Penne et al 2010 (11)	493	Decrease of phosphate levels in HDF group by 6% after 6 months; 10% more patients reach treatment target. No change in phosphate levels in HD group.
Penne et al. 2010 (9)	406	Decrease of $\beta$ 2m by 18% in HDF group in 6 months; increase of $\beta$ 2m by 8% in HD group. $\beta$ 2m decrease is not related to convection volume.

### Dialysis population

<b>Name</b>	<b>Patient number</b>	<b>Results</b>
van der Weerd 2012 (24)	405	Hepcidin-25 is associated with fatal and non-fatal cardiovascular events. Inflammation is a confounder in the relationship between hepcidin and all-cause mortality.
van der Weerd 2012 (22)	598	Compliance with anemia targets in stable HD patients is poor and shows a wide variation between treatment facilities.
van der Weerd 2012 (23)	405	Hepcidin-25 is a marker for iron stores and associated with inflammation and does not reflect ESA or iron dose in chronic stable HD patients on maintenance therapy.
Mazairac et al. 2012 (15)	570	HRQOL differs between dialysis centres. The type of dialysis centre and dieticians' fulltime equivalent are related to HRQOL.
Mazairac et al. 2012 (16)	714	The six KDOQI performance targets are not related to HRQOL in dialysis patients.
Mazairac et al. 2011 (25)	560	Albumin predicts the mortality risk as well as a combination score of multiple nutritional parameters.

Mazairac et al. 2011 (26)	590	Protein energy nutritional status is related to kidney disease specific HRQOL.
Penne et al. 2011 (21)	552	Presence of residual renal function is related to an improved phosphate and anemia control.
Mazairac et al. 2010 (19)	12 304 (CONTRAST=515)	Quality of life of dialysis patients has improved over 11 years, independent of improvement of quality of life in general population.
Penne et al. 2009 (14)	235 (HDF patients)	Ht, albumin, blood flow and treatment time are related to convection volume. Large differences in convection volume between dialysers and medical centers.
Penne et al. 2009 (12)	97 (HDF patients)	Ultrapure dialysis fluids can be produced for a prolonged period of time and with persistent adequate quality. No pyrogenic reactions reported in HDF patients.

B2m: beta-2-microglobulin; CONTRAST: CONvective TRansport STudy; ESA: erythropoiesis stimulating agents; HD: hemodialysis; HDF: hemodiafiltration; HRQOL: health-related quality of life; hsCRP: high sensitivity C-reactive protein; IL-6: interleukin 6; KDOQI: Kidney Disease Outcome Quality Initiative.

pilot study is currently in progress. Finally, new RCTs comparing high efficiency HDF to HD would answer the question whether HDF with a high convection volume would lead to a reduced mortality as compared to HD. Also, more reports on secondary endpoints of CONTRAST, such as markers of inflammation, hepcidin, erythropoiesis stimulating agents and left ventricle mass will follow.

### **Summary**

CONTRAST has allowed us to gain insight into various aspects of HDF and the dialysis population in general.

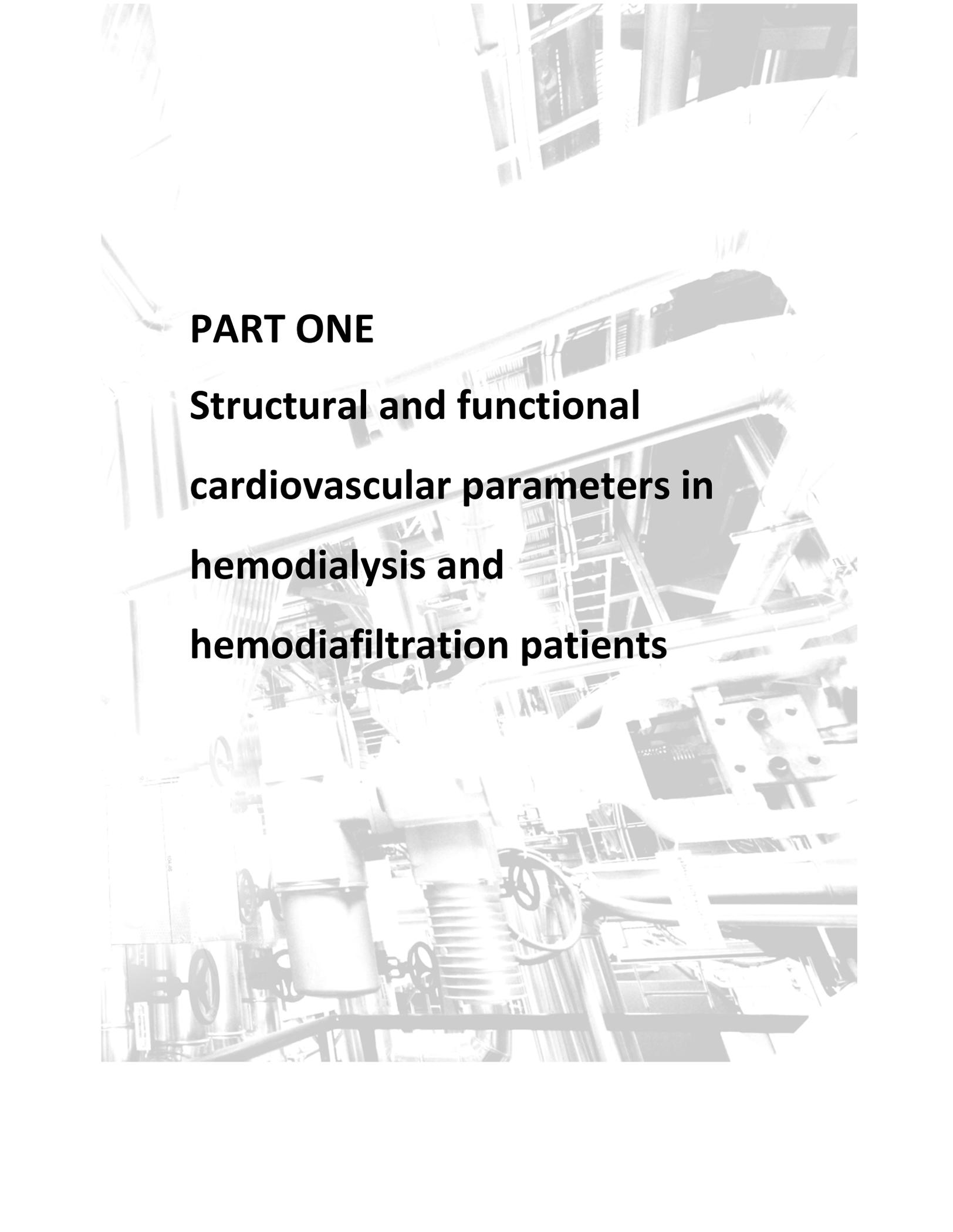
In CONTRAST online HDF has been shown not to be superior to HD regarding all-cause mortality and fatal and non-fatal cardiovascular events. However, on-treatment analysis indicated a potential dose-response relationship between convection volume and all-cause mortality. The Turkish hemodiafiltration study reported similar results. We are now eagerly awaiting the outcome of the Catalanian ESHOL study.

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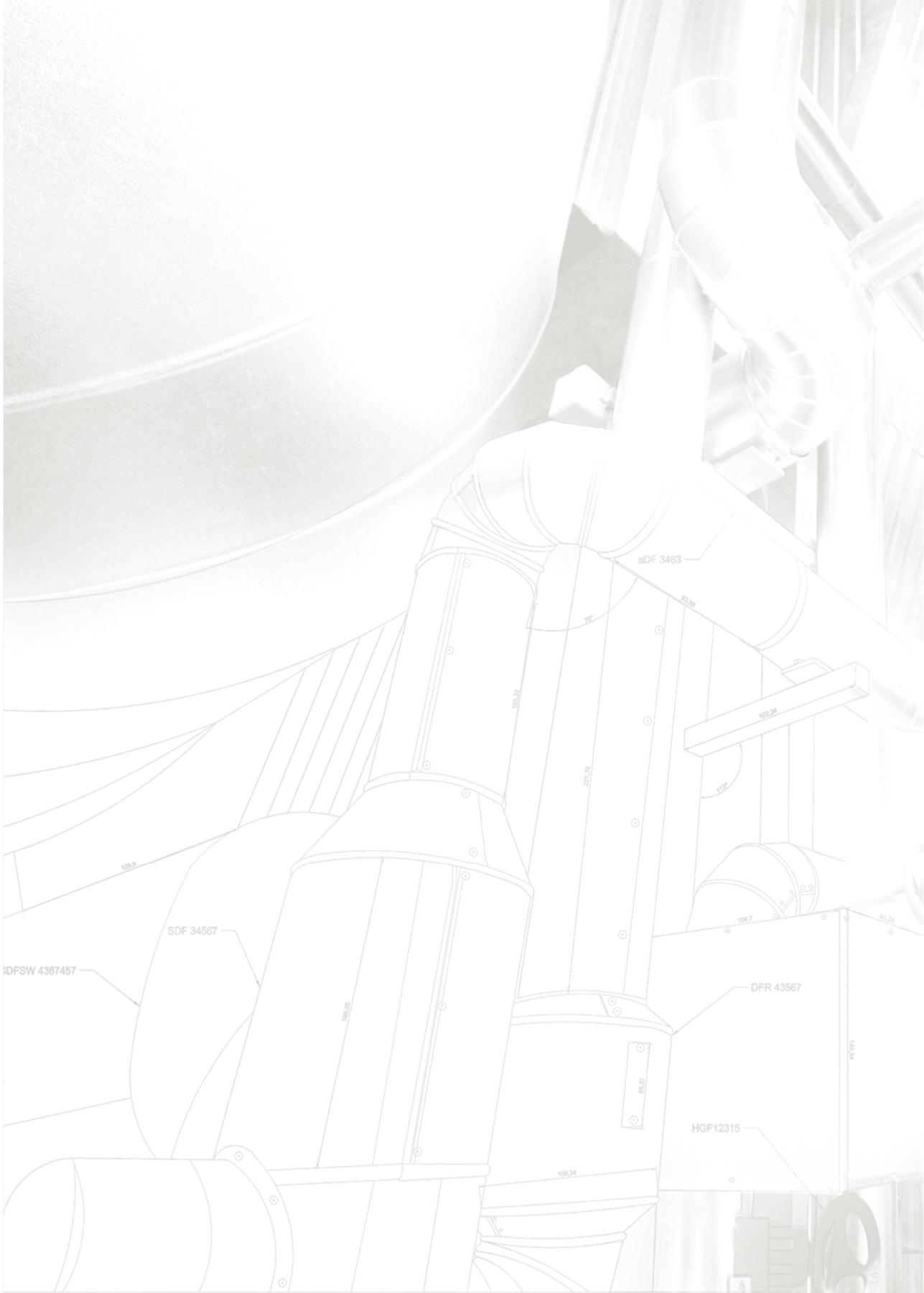
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**PART ONE**

**Structural and functional  
cardiovascular parameters in  
hemodialysis and  
hemodiafiltration patients**



## Chapter 2

### Left ventricular mass in dialysis patients, determinants and relation with outcome.

### Results from the CONvective TRANsport STudy (CONTRAST).

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Ira M. Mostovaya,<sup>1</sup> Michiel L. Bots,<sup>2</sup> Marinus A. van den Dorpel,<sup>3</sup> Roel Goldschmeding,<sup>4</sup> Claire H. den Hoedt,<sup>1,3</sup> Otto Kamp,<sup>5</sup> Renée Levesque,<sup>6</sup> Albert H.A. Mazairac,<sup>1</sup> E. Lars Penne,<sup>1,7</sup> Dorine W. Swinkels,<sup>8</sup> Neelke C. van der Weerd,<sup>1,7</sup> Piet M. ter Wee,<sup>7,9</sup> Menso J. Nubé,<sup>7,9</sup> Peter J. Blankestijn,<sup>1</sup> Muriel P.C. Grooteman.<sup>7,9</sup>

<sup>1</sup>Department of Nephrology, University Medical Center Utrecht, Utrecht

<sup>2</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht

<sup>3</sup>Department of Internal Medicine, Maastricht Hospital, Rotterdam

<sup>4</sup>Department of Pathology, University Medical Center Utrecht, Utrecht

<sup>5</sup>Department of Cardiology, VU Medical Center, Amsterdam

<sup>6</sup>Department of Nephrology, Centre Hospitalier de l'Université de Montréal, St. Luc Hospital, Montréal, Canada

<sup>7</sup>Department of Nephrology, VU Medical Center, Amsterdam

<sup>8</sup>Department of Laboratory Medicine, Laboratory of Genetic, Endocrine and Metabolic diseases, Radboud University Medical Centre Nijmegen

<sup>9</sup>Institute for Cardiovascular Research VU Medical Center (ICaR-VU), VU Medical Center, Amsterdam, the Netherlands

**Abstract****Background and objectives**

Left ventricular mass (LVM) is known to be related to overall and cardiovascular mortality in end stage kidney disease (ESKD) patients. The aims of the present study are 1) to determine whether LVM is associated with mortality and various cardiovascular events and 2) to identify determinants of LVM including biomarkers of inflammation and fibrosis.

**Design, setting, participants, & measurements**

Analysis was performed with data of 327 ESKD patients, a subset from the CONvective TRAnsport STudy (CONTRAST). Echocardiography was performed at baseline. Cox regression analysis was used to assess the relation of LVM tertiles with clinical events. Multivariable linear regression models were used to identify factors associated with LVM.

**Results**

Median age was 65 (IQR: 54-73) years, 203 (61%) were male and median LVM was 227 (IQR: 183 - 279) grams. The risk of all-cause mortality (hazard ratio (HR)=1.73, 95% CI: 1.11 – 2.99), cardiovascular death (HR=3.66, 95% CI: 1.35 – 10.05) and sudden death (HR=13.06; 95% CI: 6.60 - 107) was increased in the highest tertile (>260grams) of LVM. In the multivariable analysis positive relations with LVM were found for male gender (B=38.8±10.3), residual renal function (B=17.9±8.0), phosphate binder therapy (B=16.9±8.5), and an inverse relation for a previous kidney transplantation (B=-41.1±7.6) and albumin (B=-2.9±1.1). Interleukin-6 (Il-6), high-sensitivity C-reactive protein (hsCRP), hepcidin-25 and connective tissue growth factor (CTGF) were not related to LVM.

**Conclusion**

We confirm the relation between a high LVM and outcome and expand the evidence for increased risk of sudden death. No relationship was found between LVM and markers of inflammation and fibrosis.

## **Introduction**

Increased left ventricular mass (LVM) has been well described as a frequent component of end stage kidney disease (ESKD). (1) In fact, more than seventy percent of patients starting dialysis show left ventricular hypertrophy (LVH) on echocardiography. (2) An increase in left ventricular mass (LVM) is associated with cardiovascular morbidity and mortality. (3,4) Although the relation between LVM and overall mortality and cardiovascular events has been well established in ESKD patients, the association between LVM and certain types of cardiovascular morbidity (such as coronary heart disease: CHD) and mortality (such as sudden death) has not yet been thoroughly investigated.

Several inflammatory biomarkers associated with cardiovascular pathology and morbidity have been described for patients with chronic kidney disease (CKD). High sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6) are both well accepted markers of inflammation, related to increased risk of death and cardiovascular disease. (5) HsCRP is an acute phase reactant, which has been associated with an increased risk of major cardiovascular disease. (6) HsCRP levels are higher in HD patients than in healthy individuals (7) and have been shown to be independent predictors of LVM indexed for body surface area (LVMI) in CKD patients. (8) IL-6 is a short acting protein secreted by cells of the immune system in response to inflammatory stimuli, and is suspected to be a central regulator in the inflammatory process that leads to atherosclerosis. (9) Several studies have reported the relation between a high IL-6 and increased risk of developing CVD. (10-12) In patient deceased from acute myocardial infarction, IL-6 has been associated with mechanisms of cardiac hypertrophy. (13) Furthermore, IL-6 levels are increased in dialysis patients.(7,14)

Connective tissue growth factor (CTGF) is a signalling protein involved in the pathogenesis of renal and cardiac fibrosis. (15) In animal studies CTGF has been described to contribute to development of cardiac hypertrophy. (16,17) CKD patients have a higher plasma CTGF level than healthy individuals, since CTGF is eliminated predominantly by the kidney. (18) Hepcidin-25 is a peptide produced by the liver, which regulates intestinal absorption of iron and its distribution through the body. (19) The gene encoding for hepcidin-25 is

regulated in response to anemia, hypoxia and inflammation.(20) Furthermore, hepcidin-25 is related to increased risk of cardiovascular events in chronic hemodialysis patients. (21) Although several studies have described a relationship between hsCRP and left ventricle geometry and function (8,21,22), the relationship between LVM and the four described biomarkers has not been examined in a large population of HD patients.

We hypothesize that a high LVM will be related to a higher risk of mortality and cardiovascular events in our study, as is the case in previously studied dialysis populations. Furthermore we expect to find a positive relation between specific cardiovascular events such as risk of CHD or sudden death and LVM. Regarding hsCRP, Il-6, CTGF and hepcidin-25, since these markers are related to pathophysiological mechanisms that could theoretically promote increase of LVM, we assume to find a positive relation between the magnitude of LVM and hsCRP, Il-6, CTGF and hepcidin-25. Hence, the aims of this study are 1) to determine whether LVM is associated with mortality and various cardiovascular events in our population of ESKD patients and 2) to identify determinants of LVM including biomarkers of inflammation, systemic iron homeostasis and fibrosis in HD patients.

## **Materials and methods**

### **Patients**

The present study included a subset of patients participating in the CONvective TRANsport Study (CONTRAST): 327 hemodialysis patients from 15 dialysis centres (14 Dutch centers and 1 Canadian center). CONTRAST has been designed to investigate the effects of increased convective transport by online HDF as compared with low-flux HD on all-cause mortality and cardiovascular morbidity and mortality (ISRCTN38365125) and included a total of 714 patients. (24)

The study was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating dialysis centres. Written informed consent was obtained from all patients prior to enrolment. The names of the medical ethics committees / review boards that have approved this study are listed in the supplemental file.

**Data collection**

Baseline patient and dialysis characteristics were used for this analysis: information on demography, anthropometrics, medical history, medication and standard laboratory values. A history of cardiovascular disease was defined as a previous acute myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, angina pectoris, stroke, transient ischemic attack, intermittent claudication, amputation, percutaneous transluminal angioplasty, peripheral bypass surgery and renal percutaneous transluminal angioplasty.

Systolic and diastolic blood pressure was measured before and after three consecutive dialysis sessions at baseline using a standard electronic sphygmomanometer. The average of these measurements was computed and used for analysis.

The primary outcome of CONTRAST was all cause mortality. Cause of death was recorded and subdivided into cardiovascular mortality (fatal myocardial infarction, fatal cerebrovascular accident, fatal decompensatio cordis, a rupture of the abdominal aorta or sudden death) and non-cardiovascular mortality. Sudden death was defined as death within 1 hour of the onset of symptoms as verified by a witness.

The main secondary endpoint was a composite of fatal and non-fatal cardiovascular events. Cardiovascular events were defined as death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, therapeutic coronary procedure (percutaneous transluminal coronary angioplasty and/or stenting), therapeutic carotid procedure (endarterectomy and/or stenting), and vascular intervention not related to vascular access (revascularisation, percutaneous transluminal angioplasty and/or stenting) or amputation. Congestive heart failure was excluded as a cardiovascular event, since the distinction with fluid overload is often difficult to make in patients with end stage renal disease.

Follow-up of patients with respect to mortality and non-fatal cardiovascular events was continued even after they stopped with the randomized treatment because of a renal transplant (n= 71), a switch to peritoneal dialysis (n= 5), a move to another non-CONTRAST hospital (n=11) or a stop of participation for other reasons (n=58).

An independent Endpoint Adjudication Committee reviewed source documentation for all primary outcome events (deaths), as well as non-fatal cardiovascular events and infections.

### **Laboratory measurements**

Standard laboratory samples were analysed in the local laboratories of the participating hospitals by standard laboratory techniques.

Furthermore, in centres where storage of blood samples was logistically feasible, additional blood samples were drawn for the analysis of hsCRP, IL-6, CTGF and hepcidin prior to dialysis. Samples were placed on ice, and centrifuged within 30 min, at 1500 g for 10 minutes, and were stored at  $-80^{\circ}\text{C}$  until assayed. A total of 248 patients, out of the 327 who underwent echocardiography, were treated in such centers and therefore had additional measurements of hsCRP, IL-6, CTGF and hepcidin.

High sensitivity CRP, hepcidin-25, CTGF and IL-6 levels were measured centrally. Measurements of the bioactive hepcidin-25 were performed with time of flight mass spectrometry which has been described previously. (23) High sensitivity CRP (mg/L) was measured with a particle-enhanced immunoturbidimetric assay on a Roche-Hitachi analyzer as described elsewhere. (14) IL-6 (pg/mL) was measured with an ELISA (Sanquin, Amsterdam, The Netherlands), details have been described earlier. (13) CTGF levels in plasma were determined by sandwich ELISA, using two specific antibodies (FibroGen Inc., San Francisco, CA, USA) directed against two distinct isotopes in the amino-terminal fragment of CTGF, detecting both full length CTGF and the N-fragment, as shown earlier. (18)

### **Echocardiographic measurements**

In 15 centres, patients were requested to undergo 2-dimensional echocardiography next to the standard CONTRAST baseline data collection.

Transthoracic echocardiography studies were performed on a mid-week non-dialysis day by an echocardiographer at the participating local hospital. From the parasternal long axis position the left ventricular end-diastolic diameter (LVEDD), end-systolic diameter (LVESD)

as well as the posterior and septal wall thickness were determined. The ultrasound investigations were then assessed by an independent experienced echocardiographer at the core laboratory (VU medical Center, Amsterdam, the Netherlands), who was blinded for other patient data. LVM was calculated using the formula of Devereux and Reicke (24), modified in accordance with the recommendations of the American Society of Echocardiography.(25) LVH was defined as an  $LVM/height^{2.7} > 44g/m^{2.7}$  for women and  $> 48g/m^{2.7}$  for men. (3)

### Data analysis

Data were reported as proportions or as means with standard deviation (SD) or medians with inter-quartile ranges (IQR) when appropriate.

The average percentage of missing values per variable was 7.7%. No data were missing regarding clinical events. Multiple imputation was performed on all variables, where <40% of data were missing. One variable was not imputed due to a higher percentage of missing values, namely blood flow. Imputation was performed to prevent bias in reported estimates and to improve statistical power.(26)

To study the independent relation of each variable with LVM, linear regression analysis was used. Patient and dialysis related variables that showed a univariable relation with LVM using a cut-off p-value <0,20 were entered in a multivariate model in consequent groups: demographic data, patient history, dialysis properties, therapeutic parameters and haemodynamic measurements. In addition, height and weight were added into the model upfront.

In a separate analysis, the variables hsCRP, Il-6, hepcidin-25 and CTGF were added to the constructed multivariate model one at a time. The old and new models were compared based on direction of the estimate and the significance of the regression coefficient of the added marker.

The relations between LVM and all-cause mortality, as well as cardiovascular events, cardiovascular death, sudden death and CHD were evaluated by Cox proportional hazards models, involving the time to the first relevant endpoint in any individual patient. For this

**Table 1:** Demographic, anthropometric, biochemical, hemodynamic and dialysis characteristics of the study population.

	<b>Total Cohort n=714</b>	<b>Echo cor cohort n=327</b>
<b>Demographic data</b>		
Male gender	445 (62%)	200 (61%)
Race, Caucasian	304 (85%)	263 (80%)
Age, years	64.1 ± 13.7	63.0 ± 13.3
Smoking	133 (19%)	66 (20%)
<b>Anthropometrics</b>		
Length (cm)	168 ± 10	168 ± 11
Weight (kg)	72.4 ± 14.4	72.1 ± 14.3
BMI (kg/m <sup>2</sup> )	25.4 ± 14.4	25.5 ± 4.9
Body Surface Area (m <sup>2</sup> )	1.85 (0.28)*	1.85 (0.30)*
<b>Dialysis Properties</b>		
Dialysis vintage (years)	1.8 (1.0 – 4.0)*	2.0 (1.0 – 4.0)*
Duration of dialysis (minutes)	226 ± 23	225 ± 23
Blood flow (mL/minute)	300 (300 - 348)*	300 (300 - 350)*
spKt/Vurea	1.40 ± 0.22	1.39 ± 0.20
AV fistula	279 (78%)	260 (80%)
Patients with residual kidney function	186 (52%)	171 (52%)
<b>Comorbidities</b>		
Cardiovascular disease	313 (44%)	146 (45%)
Diabetes	170 (24%)	83 (25%)
Previous kidney transplant	78 (11%)	30 (9%)
<b>Laboratory parameters</b>		
Hemoglobin (g/dL)	11.8 ± 0.40	11.8 ± 1.3
Phosphate (mmol/L)	1.64 ± 0.49	1.67 ± 0.50
Calcium (mmol/L)	2.31 ± 0.18	2.30 ± 0.18
Albumin (g/L)	40.4 ± 3.8	41.2 (37.9 – 43.5)*
Creatinine (μmol/L), pre-dialysis	861 ± 255	883 ± 252
hsCRP (mg/L)	-	4.0 (1.6 – 11.9)*
Il-6 (pg/mL)	-	2.0 (1.2 – 3.8)*
CTGF (nmol/L)	-	3.6 (2.8 – 4.3)*
Hepcidin -25 (nM)	-	14.2 (6.3 – 22.4)*
Ferritin (ng/mL)	-	377 (211 – 597)*
TSAT (%)	-	22 (15 – 29)*

<b>Medication</b>		
Erythropoietin therapy	314 (88%)	295 (91%)
Diuretic therapy	250 (35%)	129 (39%)
Beta-blocker therapy	184 (51%)	174 (53%)
RAS inhibitor therapy	179 (50%)	162 (50%)
Lipid lowering therapy	196 (55%)	152 (47%)
Vitamin D administration	227 (63%)	222 (68%)
Phosphate binding therapy	445 (62%)	194 (59%)
Platelet aggregation therapy or coumarines	111 (34%)	122 (36%)
Iron supplements	476 (67%)	213 (65%)
<b>Hemodynamic measurements</b>		
Systolic blood pressure (mm Hg)	147 ± 21	142 ± 19
Diastolic blood pressure (mm Hg)	75 ± 12	74 ± 10
LVEDD (mm)	-	10 (9 - 11)*
LVESD (mm)	-	32 (27 - 38)*
EFLV (%)	-	65 (55 - 72)*
LVM (g)	-	227 (183 - 279)*
LVH	-	230 (71%)

\*:median and IQR (P25 – P75)

AV: arterio-venous;BMI: body mass index; CTGF: connective tissue growth factor; EFLV: ejection fraction of left ventricle; hsCRP: high sensitivity C-reactive protein; IL-6: interleukin 6; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVH: left ventricular hypertrophy; LVM: left ventricular mass; RAS: renin-angiotensin system; TSAT: transferrin saturation.

analysis LVM was both analysed as a linear variable and divided into categories (tertiles). The number of events (in particular sudden death and CHD events) was small, and thus adjusting for all relevant possible confounders would lead to an overfitted model. Propensity scores as opposed to individual variables were used to adjust the models thus omitting the problem of an overfitted model. The propensity score (66) model estimated each individuals probability of having an LVM above the median of the studied population. Propensity score was built using a logistic model including all variables associated with LVM with  $p < 0.20$ . Moreover, height, post-dialysis baseline weight and dialysis modality (intervention) were added into the propensity score model upfront. Results were considered statistically significant when  $p < 0.05$  (two-sided). All calculations were made by use of a standard statistical package (SPSS for Windows Version 18.0.1; SPSS Inc. Headquarters, Chicago, Illinois, US).

**Table 2:** Hazard ratio of clinical events by LVM in grams divided into tertiles.

	T1: <201	T2: 201<LVM<260	95% CI	T3: >260	95% CI
<b>Crude</b>					
Mortality	1	1.61*	1.01 - 2.55	2.17*	1.39 - 3.38
Cardiovascular death	1	2.24	0.90 - 5.55	3.76*	1.61 - 8.82
Sudden death	1	8.93*	1.12 - 71.4	17.8*	2.35 -135.0
Cardiovascular events	1	1.47	0.92 - 2.44	1.66*	1.06 - 2.67
CHD events	1	1.04	0.51 - 2.13	1.13	0.56 - 2.31
<b>Adjusted</b>					
Mortality	1	1.50	0.92 – 2.10	1.73*	1.11 - 2.99
Cardiovascular death	1	1.80	0.64 - 5.07	3.69*	1.35 – 10.05
Sudden death	1	6.29	0.72 - 52.70	13.06*	6.60 - 107.16
Cardiovascular events	1	1.27	0.74 - 2.18	1.49	0.85 - 2.60
CHD events	1	1.22	0.71 – 2.09	1.51	0.87 – 2.64

\*p&lt;0.05

<sup>a</sup>Adjusted with a propensity score containing determinants of LVM (male gender, residual renal function, history of kidney transplantation, albumin, use of RAS-inhibitors, use of phosphate binders, systolic blood pressure) and history of cardiovascular disease, diabetes, height, post-dialysis weight and dialysis modality (intervention).

## **Results**

327 patients participating in CONTRAST underwent echocardiography. Out of this group, in 248 patients blood was collected for a measurement of markers of inflammation and fibrosis. Median age was 65 (IQR: 54 - 73) years, 203 were male (61%) and the median dialysis vintage was 2.0 (IQR: 1.0 – 4.0) years. Median LVM was 227 (IQR: 183 – 279) grams. A total of 230 patients (71%) had LVH. The baseline characteristics of the whole CONTRAST cohort and of the echocardiography population are shown in table 1. The mean follow-up time was 2.0 (minimum 0.1, maximum 6.5) years. Within the group of patients with an LVM measurement 130 (39.8%) patients died from any cause and 116 (35.5%) had a cardiovascular event, out of which 43 (13.1%) were fatal. CHD (angina

pectoris or acute myocardial infarction) occurred in 53 (16.2%) patients, of whom 3 (0.9%) died. Sudden death occurred in 24 (7.3%) patients.

#### **Relation to LVM and outcome**

Table 2 shows proportional hazard ratios for all-cause mortality, cardiovascular death, sudden death, combined fatal and non-fatal cardiovascular events and CHD events; both crude and adjusted using propensity scores. Risk of all-cause mortality, cardiovascular death and sudden death was increased in the highest tertile (>260grams) of LVM; while no difference in risk was found for overall cardiovascular events and CHD events in the LVM tertiles. Figure 1 shows survival curves for the clinical events described above stratified by LVM tertiles.

As shown in supplementary Table 1a and 1b, when LVM was indexed for BSA or height<sup>2.7</sup>, relations with clinical events were similar.

#### **Determinants of LVM**

The univariable and multivariable analysis results of LVM are shown in Table 3. In the multivariate analysis significant positive relations with LVM were found for male gender, presence of residual renal function and phosphate binder therapy. There were inverse relations for a history of kidney transplantation and albumin. The complete-case multivariate regression analysis showed similar results as demonstrated in supplementary Table 2.

Table 4 shows that hsCRP, IL-6, hepcidin-25 and CTGF were not related to LVM.

#### **Discussion**

The present study confirmed the relation between a high LVM and outcome.(2,4,7,28) Furthermore we expanded the evidence for a strongly increased risk of sudden death in patients with a high LVM. After confirming that LVM was a strong predictor of cardiovascular and overall mortality we wanted to study what factors determine the

**Table 3:** Determinants of LVM in dialysis patients: univariable and multivariable regression analysis. The B reflects the change of total LVM (in grams) related with one unit increment of the determinant.

Determinant	Univariable model		Multivariable model	
	B	95% CI	B	95% CI
<b>Demographic data</b>				
Male gender	56.47	39.03 to 73.90	38.80	18.64 to 58.96
Race, Caucasian	12.92	-9.75 to 35.60		
Age (years)	0.75	0.08 to 1.42		
Smoking	22.20	-0.47 to 44.87		
<b>Dialysis Properties</b>				
Duration of dialysis (hours)	35.14	10.95 to 59.33		
spKt/Vurea	-102.7	-145.7 to -59.75		
AV fistula	17.59	-4.66 to 38.83		
<b>Comorbidities</b>				
Cardiovascular disease	16.54	-1.50 to 34.58		
Diabetes	1.94	-18.45 to 22.37		
Previous kidney transplant	-49.76	-80.38 to -19.01	-41.12	-55.94 to -26.31
Dialysis vintage (years)	-5.45	-8.61 to -2.30		
Residual kidney function	29.28	-11.52 to 47.04	17.88	2.16 to 33.61
<b>Laboratory parameters</b>				
Hemoglobin (g/dL)	-1.00	-12.53 to 10.53		
Phosphate (mmol/L)	0.89	-17.17 to 18.94		
Calcium (mmol/L)	13.37	-32.36 to 63.99		
Calcium*Phosphate	1.28	-6.48 to 9.03		
Albumin (g/L)	-1.99	-4.17 to 0.20	-2.94	-5.08 to -0.81
Creatinin ( $\mu$ mol/L)	-0.02	-0.05 to 0.02		
<b>Therapeutic parameters</b>				
Erythropietin	-9.68	-38.78 to 19.38		
Diuretic	0.97	-18.99 to 20.94		
Beta-blocker	16.26	-1.70 to 34.21		
Alpha-blocker	21.44	-13.64 to 56.51		
RAS inhibitor	21.67	3.82 to 39.51	14.08	-2.46 to 30.62
Lipid lowering therapy	0.95	-17.06 to 18.95		
Phosphate binder	17.82	-0.420 to 36.05	16.87	0.14 to 33.56
Platelet aggregation inhibitor	10.35	-8.44 to 29.13		
Coumarine derivatives	22.50	-14.09 to 59.08		
Iron supplements	22.56	3.81 to 41.32		
<b>Hemodynamic measurements</b>				
Systolic blood pressure (mm Hg)	0.54	0.08 to 1.00	0.37	-0.77 to 0.82

R<sup>2</sup> of the multivariable model = 0.22.

**Table 4:** Hepcidin, hsCRP, Il-6 and CTGF as determinants of LVM. The B reflects the change of total LVM (in grams) related with one unit increment of the determinant.

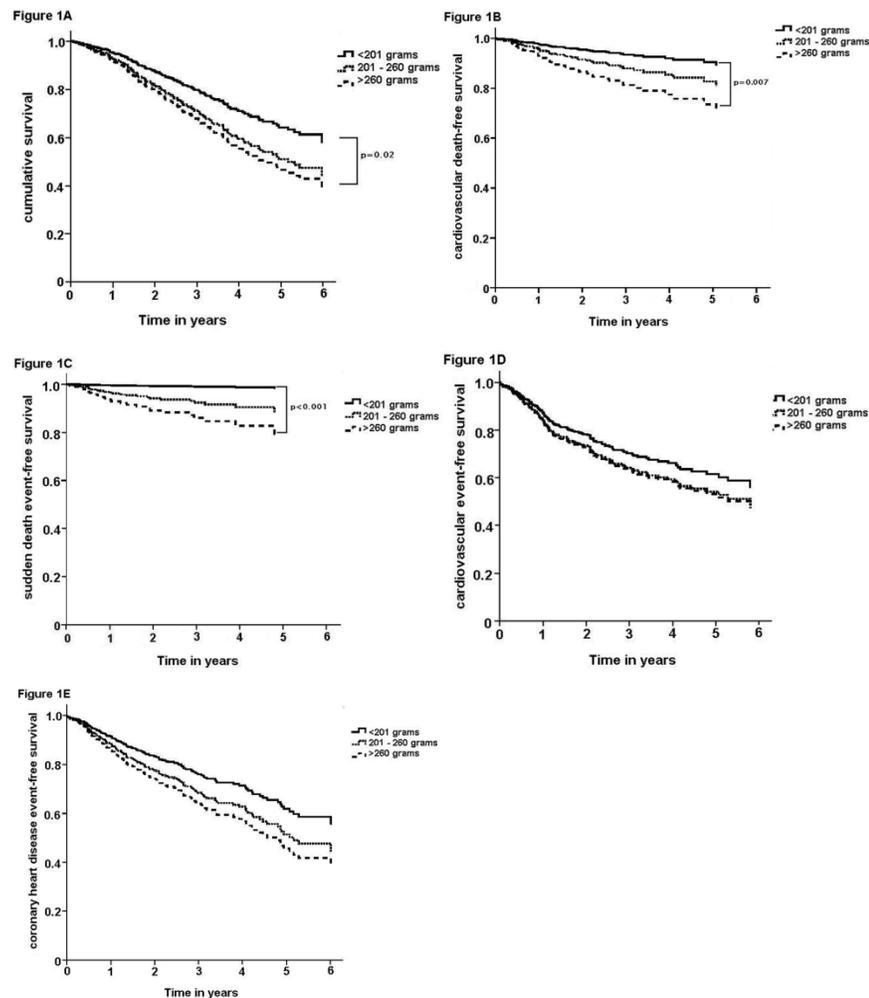
Determinant	Univariable model		Adding to 'basic' multivariable model		
	B	95% CI	B	95% CI	$\Delta R^2$
Hepcidin-25 (nM)	-0.04	-0.46 to 0.38	0.04	-0.38 to 0.45	-0.003
hsCRP (mg/L)	0.22	-0.46 to 0.90	0.07	-0.43 to 0.57	-0.003
Il-6 (pg/mL)	0.03	-0.17 to 0.22	0.06	-0.13 to 0.23	-0.002
CTGF (nmol/L)	0.05	-3.92 to 4.01	0.67	-3.45 to 4.78	-0.001

magnitude of LVM, and in particular if these determinants were potentially modifiable. In our analysis, factors related to LVM were: male gender, history of kidney transplantation, residual kidney function (RKF), albumin and use of phosphate binders. Thus we did not find determinants of LVM that could easily be altered in daily clinical practice. Lastly, we explored whether novel markers of inflammation, fibrosis and iron homeostasis (hsCRP, Il-6, CTGF and hepcidin-25), which in theory could lead to a higher LVM, were related to LVM in a large population of hemodialysis patients. Apparently, although hsCRP, Il-6, CTGF, hepcidin-25 have previously been found to be associated with cardiovascular damage, no relation exists between these biomarkers and the magnitude of LVM in ESKD patients.

#### **LVM and clinical events**

A summary of previous papers in which the relation between left ventricular geometry and clinical events was studied in dialysis patients is shown in Table 5. Foley et al studied the relation between LVM and mortality risks in 433 ESKD patients and found a significant linear association between LVM and overall mortality as well as cardiovascular mortality in particular. (2) Zoccali et al studied the prognostic impact of LVM indexed for body surface area or height<sup>2.7</sup> in 254 dialysis patients and found that both types of LVMi were related to both overall mortality and cardiovascular mortality. (3)

**Figure 1:** Survival curve for time to (A) death from any cause (B) cardiovascular death (C) sudden death (D) cardiovascular events (both fatal and non-fatal) (E) coronary heart disease events (both fatal and non-fatal) stratified by LVM tertiles adjusted using propensity scores.



We are among the first to describe the relationship between LVM and sudden death specifically in ESKD patients. In fact, ESKD patients in the highest tertile of LVM had an almost 14-fold higher risk of sudden death when compared to the lowest LVM tertile, while their risk of dying from a cardiac cause in general was 'only' increased by a factor

3.5. The underlying mechanism may be through a decrease in myocardial capillary density, diastolic and systolic dysfunction, disturbances in interventricular conduction, chamber dilatation and eventually more compensatory hypertrophy. These processes lead to an increased risk of triggering a fatal arrhythmia. (1,29) Autopsy studies in ESKD patients point to the presence of diffuse inter-myocardiocyte fibrosis specific for this group, which may indicate an electrical instability predisposing to sudden death. (30) The percentage of sudden deaths (56%) from all cardiac deaths in our population was similar to those of earlier studies. (29)

For a combination of fatal- and non-fatal cardiovascular events no relation with LVM size was found. To our knowledge, no such relation has been described in earlier literature; although Zoccali et al found a significant relation between LVM indexed for height<sup>2.7</sup> and fatal- and non-fatal cardiovascular events combined. (3) Since there were only 3 lethal CHD events in our study, this association could not be explored in our population.

#### **Determinants of LVM**

Factors related to LVM were: male gender, history of kidney transplantation, residual kidney function (RKF), albumin and use of phosphate binders.

It was a surprising finding that a history of CVD and blood pressure (BP) were not found to be associated with LVM. Regarding the lack of relation between LVM and CVD this could be attributed to the fact that our definition of CVD encompassed several periphery vasculature diseases/interventions, which do not necessarily lead to an enlargement of LVM. Also, many ESKD patients have a high LVM without a history of CVD. (41) While BP is very variable over time in dialysis patients (mostly due to rigorous changes in extracellular volume during and in-between dialysis treatments), our BP results are an average of three pre- and three post-dialysis BP measurements. Hence our BP measurements could be a poor representative of the total BP burden of a patient (which is truly related to LVM).

The relation between LVM and a history of kidney transplantation (31,32) and albumin (33) is in accordance with earlier literature.

The positive relation between LVM and RKF may be explained by a 'survivor bias': patients that still have RKF have been on dialysis for a shorter period of time. As time passes, the

patients with a high LVM are more likely to die, the patient with a lower LVM remain and lose their RKF. In our population, the dialysis vintage differs significantly between patient with RKF ( $1.92 \pm 1.58$  years) and without RKF ( $4.00 \pm 3.4$  years).

Previous studies on predictors of LVM and LVMi in HD patients identified phosphate and the calcium-phosphate product as patient characteristics associated with LVH.(34-36) In our analysis however, these laboratory values were not significantly related to LVM, while there was a positive association between LVM and use of phosphate binders. The serum calcium and phosphate are well controlled in our dialysis population, and phosphate binders were prescribed to 74% of the patients (mainly sevelamer, a non-calcium containing phosphate binder: 54%). Hyperphosphatemia can lead to vascular calcification and myocardial fibrosis, resulting in increased cardiovascular risk. (37-41) Thus, it is plausible that in our population the prescription of phosphate binders is a reflection of higher phosphate intake at present and/or hyperphosphatemia in the past, resulting in higher LVM.

#### **Relation between LVM and hsCRP, Il-6, CTGF, hepcidin**

We are among the first to investigate the association between LVM and the biomarkers hsCRP, Il-6, CTGF and hepcidin in a population of ESKD patients, which is also large enough to perform appropriate corrections for clinically relevant variables without creating an overfitted model. Although there is a theoretical incentive, as described in the Introduction, to hypothesize that these biomarkers may contribute to LVM, we do not find such a relation in our population. Apparently, although hsCRP, Il-6, CTGF, hepcidin-25 have previously been found to be associated with cardiovascular damage, no relation exists between these biomarkers and the magnitude of LVM in ESKD patients.

In earlier papers concerning LVM and prognosis, LVM was indexed for body surface area, or divided by height<sup>2.7</sup>. It was shown that these indexations, especially LVM/height<sup>2.7</sup> are linear association between LVM and overall mortality as well as cardiovascular mortality in particular. (2) Zoccali et al studied the prognostic impact of LVM indexed for body surface area or height<sup>2.7</sup> in 254 dialysis patients and found that both types of LVMi were related to both overall mortality and cardiovascular mortality. (3)

**Table 5:** Summary of previous studies in which the relation between LV geometry and clinical events was examined in dialysis patients.

Author	patient nr	LV measurement	event	Risk measure	Conclusion
Silverberg et al 1989 (32)	133	LVMi (g/m <sup>2</sup> )	mortality CV mortality	RR: 2.9 (p=0.013) RR: 2.7 (0.08)	LVH is an important determinant of survival in incident dialysis patients
Foley et al 1995 (2)	433	LVMi (g/m <sup>2</sup> )	mortality late (>2yr) mortality	RR: 1.003 (p=0.11) RR: 1.009 (p<0.001)	LVH is highly prevalent in th dialysis population and is a risk factor for mortality
London et al 2001 (4)	153	more than 10% decrease in LVMi (g/height <sup>2.7</sup> )	mortality CV mortality	RR: 0.78 (p=0.001) RR: 0.72 (p=0.002)	partial regression of LVM has a favorable effect on mortlity and CV-mortality
Zoccali et al 2001 (31)	254	LVMi (g/m <sup>2</sup> ) LVMi (g/height <sup>2.7</sup> )	mortality CV mortality CV event	HR: 1.01 (p<0.001) / 1.03 (p<0.001) HR: 1.01 (p<0.001) / 1.03 (p<0.001) HR: 1.00 (ns) / 1.02 (p=0.004)	LVM indexed for height <sup>2.7</sup> provides a more powerful predictor for death and CV events compared to LVM indexed for BSA
Zoccali et al 2004 (3)	161	in top 75% progression in LVMi (g/height <sup>2.7</sup> )	mortality CV event	HR: 3.07 (p=0.008) HR: 3.02 (p=0.02)	Changes in LVMi have an independent prognostic value for death and CV events

CV events are defined as a combination of both fatal and non-fatal cardiovascular events.

BSA: body surface area; CV: cardiovascular; HR: hazard ratio; LV: left ventricular; LVH: left ventricular hypertrophy; LVM: left ventricular mass; LVMi: left ventricular mass index; nr: number; RR: relative risk

and weight in the propensity scores for optimal statistical adjustment. As shown in our supplementary Tables 1a and 1b, when LVM was adjusted for height and weight, the relation with clinical events was similar to that of LVM indexed for BSA or height<sup>2,7</sup>.

### **Strengths and limitations**

This study had several limitations. First, 7.7% of data was missing and biomarkers were measured in only 75.5% of the patients. However, since multiple imputation was performed for missing variables included in the multivariable analysis, this prevents the drawing of wrong conclusions due to the fact that data may be missing in specific patients for a reason, and not by chance and by increasing the power of our analyses.<sup>(65)</sup> Furthermore, our sensitivity analyses of complete cases showed no marked differences with the regression performed on the imputed data. Second, the number of CHD events and sudden deaths was small, thus limiting the precision of our estimates. Third, since cross-sectional data was used to determine variables related to LVM, causality of relations cannot be established. Fourth, measurements of LVM by echocardiography is less precise and reliable than measurement by cardiac magnetic resonance imaging (CMRI). (1) However, while CMRI is recognized as the “gold standard” for ventricular geometry measurements, it is less often applied in clinical practice since it is more expensive, not widely available and has contra-indications such as claustrophobia and use of cardiac implantable devices. (1) Thus it was not feasible to perform CMRI measurements in our relatively large cohort of dialysis patients. This may have led to misclassification, which generally leads to an underestimation of the magnitude of the relations under study.

The strengths of this study are the large sample size, the concise and prospective data collection, the independent review of source documentation for all primary and secondary outcomes and the double independent analysis of the echocardiography recordings blinded for patient characteristics.

### **Conclusion**

In this study we confirmed the relation between LVM and all-cause mortality. Furthermore we demonstrated a markedly increased risk of sudden death in patients with a high LVM.

No relationship was found for markers of inflammation (except for a negative association with albumin) and fibrosis.

### Supplementary tables

**Supplementary table 1a:** Hazard ratio of clinical events by LVMi in grams per m<sup>2</sup> divided into tertiles.

	T1: <108	T2: 108<LVMi<142	95% CI	T3: >142	95% CI
<b>Crude</b>					
Mortality	1	1.38	0.89 - 2.18	2.16*	1.40 - 3.34
Cardiovascular death	1	1.46	0.61 - 3.46	2.98*	1.37 - 6.48
Sudden death	1	3.28*	1.09 - 12.13	4.83*	2.36 - 17.13
Cardiovascular events	1	1.06	0.67 - 1.70	1.51	0.98 - 2.35
CHD events	1	1.07	0.53 - 2.19	1.01	0.50 - 2.03
<b>Adjusted</b>					
Mortality	1	1.10	0.91 - 2.36	1.46*	1.16 - 2.59
Cardiovascular death	1	1.24	0.48 - 3.13	2.62*	1.10 - 6.24
Sudden death	1	2.42	0.83 - 9.27	3.30*	1.09 - 12.33
Cardiovascular events	1	1.00	0.60 - 1.07	1.35	0.82 - 2.22
CHD events	1	0.96	0.44 - 2.11	0.79	0.35 - 1.78

**Supplementary table 1b:** Hazard ratio of clinical events by LVMi in grams per height<sup>2.7</sup> divided into tertiles.

	T1: <48	T2: 48<LVMi<64	95% CI	T3: >64	95% CI
<b>Crude</b>					
Mortality	1	1.28	0.81 - 2.01	1.90*	1.23 - 2.93
Cardiovascular death	1	2.12	0.91 - 4.95	2.71*	1.18 - 6.19
Sudden death	1	3.54*	1.07 - 12.86	4.17*	1.17 - 14.96
Cardiovascular events	1	1.11	0.70 - 0.75	1.30	0.83 - 2.03
CHD events	1	1.26	0.62 - 2.35	0.90	0.45 - 1.80
<b>Adjusted</b>					
Mortality	1	1.04	0.64 - 1.69	1.33*	1.08 - 2.31
Cardiovascular death	1	2.08	0.84 - 5.16	2.93*	1.09 - 7.24
Sudden death	1	2.64	0.65 - 9.32	2.94*	1.79 - 10.96
Cardiovascular events	1	1.13	0.69 - 1.86	1.06	0.64 - 1.75
CHD events	1	0.91	0.39 - 2.14	0.76	0.35 - 1.64

\*p<0.05

<sup>a</sup>Adjusted with a propensity score containing determinants of LVMi (male gender, residual renal function, history of kidney transplantation, albumin, use of RAS-inhibitors, use of phosphate binders, systolic blood pressure) and history of cardiovascular disease, diabetes, post-dialysis weight and dialysis modality (intervention).

**Supplementary table 2:** Whole-case analysis (n=289) of determinants of LVM in dialysis patients: univariable and multivariable regression analysis. The B reflects the change of total LVM (in grams) related with one unit increment of the determinant.

Determinant	Univariable model		Multivariable model	
	B	95% CI	B	95% CI
<b>Demographic data</b>				
Male gender (n=327)	56.47	39.03 to 73.90	54.17	37.30 to 71.03
Race, caucasian (n=327)	12.92	-9.75 to 35.60		
Age, years (n=327)	0.75	0.08 to 1.42		
Smoking (n=311)	24.51	-1.85 to 47.18		
<b>Dialysis Properties</b>				
Duration of dialysis, hours (n=321)	36.84	13.02 to 60.66		
spKt/Vurea (n=324)	-102.8	--146.1 to -59.48		
AV fistula (n=327)	17.59	-4.66 to 38.83		
<b>Comorbidities</b>				
Cardiovascular disease (n=327)	16.54	-1.50 to 34.58		
Diabetes (n=314)	2.65	-18.36 to 23.66		
Previous kidney transplant (n=327)	-49.76	-80.38 to -19.01	-42.96	-72.35 to -13.55
Dialysis vintage, years (n=326)	-5.45	-8.61 to -2.30		
Residual kidney function (n=326)	29.28	-11.52 to 47.04	19.26	2.29 to 36.23
<b>Laboratory parameters</b>				
Hemoglobin, g/dL (n=326)	-1.00	-12.58 to 10.58		
Phosphate, mmol/L (n=326)	0.88	-17.16 to 18.93		
Calcium, mmol/L (n=327)	13.37	-32.36 to 63.99		
Calcium*Phosphate (n=326)	1.28	-6.49 to 9.03		
Albumin, g/L (n=325)	-1.99	-4.22 to 0.24	-2.80	-4.86 to -7.41
Creatinin, $\mu$ mol/L (n=325)	-0.02	-0.05 to 0.02		
<b>Therapeutic parameters</b>				
Erythropietin (n=325)	-9.68	-38.84 to 19.49		
Diuretic (n=325)	0.97	-18.98 to 20.94		
Beta-blocker (n=325)	16.26	-1.70 to 34.23		
Alpha-blocker (n=325)	21.15	-13.77 to 56.64		
RAS inhibitor (n=325)	21.67	3.75 to 39.58	12.09	-5.40 to 29.58
Lipid lowering therapy (n=325)	1.66	-16.37 to 19.90		
Phosphate binder (n=325)	17.82	-0.50 to 36.12	19.83	3.09 to 36.66
Platelet aggregation inhibitor (n=325)	10.35	-8.41 to 29.18		
Coumarine derivatives (n=325)	22.50	-14.22 to 59.22		
Iron supplements (n=325)	22.56	3.74 to 41.39		
<b>Hemodynamic measurements</b>				
Systolic blood pressure, mmHg (n=327)	0.54	0.08 to 1.00	0.32	-0.13 to 0.77

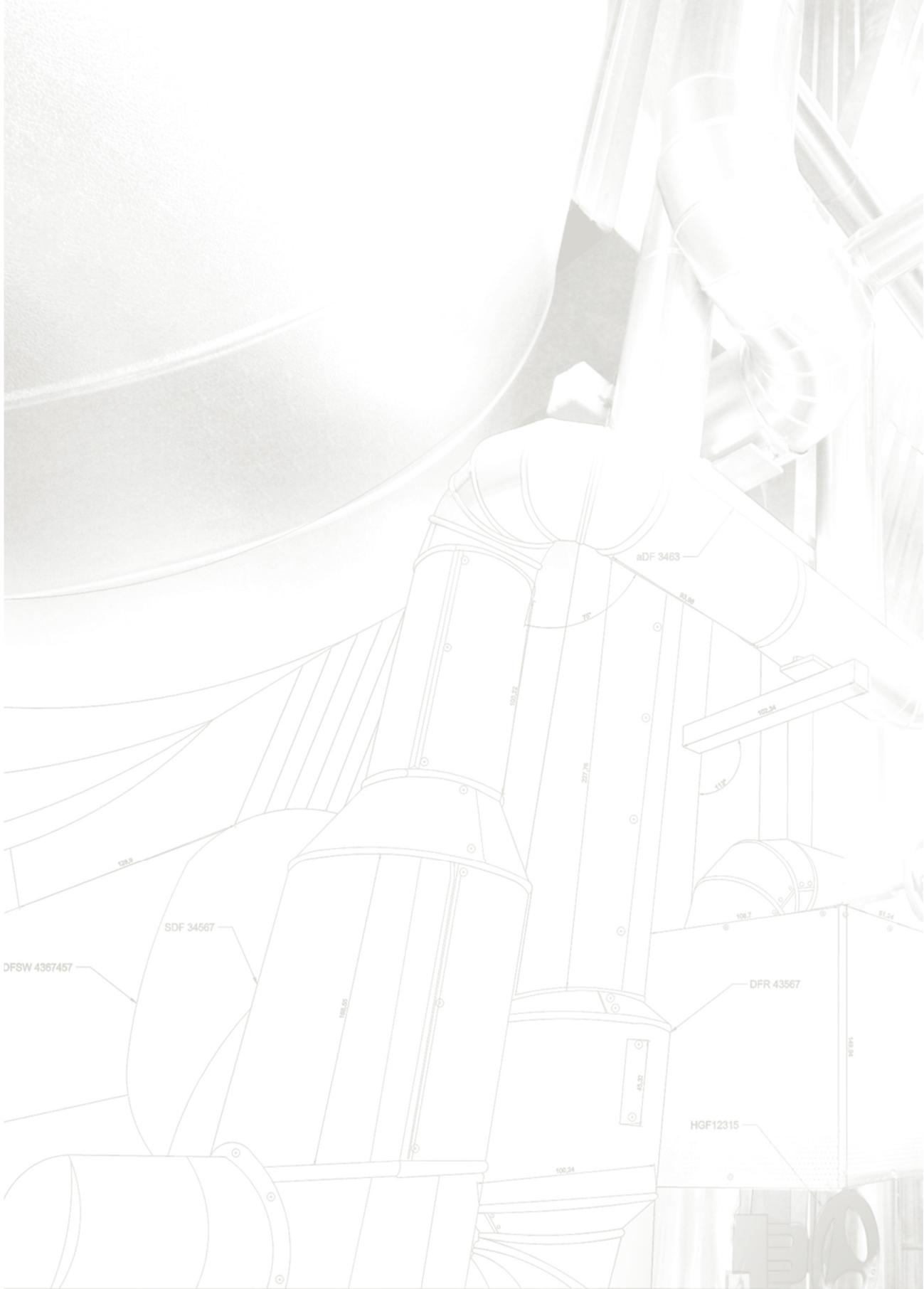
R<sup>2</sup> of the multivariable model = 0.19.

For univariate analyses, all the cases for which the variable was complete were included in the analysis.

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## Chapter 3

# Effects of hemodiafiltration on change in cardiovascular parameters over time, results from a randomized trial.

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Ira M. Mostovaya,<sup>1</sup> Michiel L. Bots,<sup>2</sup> Marinus A. van den Dorpel,<sup>3</sup> Muriel P.C. Grooteman,<sup>4,5</sup> Otto Kamp,<sup>6</sup> Renée Levesque,<sup>7</sup> Piet M. ter Wee,<sup>4,5</sup> Menso J. Nubé,<sup>4,5</sup> Peter J. Blankestijn.<sup>1</sup>

<sup>1</sup>Department of Nephrology, University Medical Center Utrecht, Utrecht

<sup>2</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht

<sup>3</sup>Department of Internal Medicine, Maastad Hospital, Rotterdam

<sup>4</sup>Department of Nephrology, VU Medical Center, Amsterdam

<sup>5</sup>Institute for Cardiovascular Research VU Medical Center (ICaR-VU), VU Medical Center, Amsterdam, the Netherlands

<sup>6</sup>Department of Cardiology, VU Medical Center, Amsterdam

<sup>7</sup>Department of Nephrology, Centre Hospitalier de l'Université de Montréal, St. Luc Hospital, Montréal, Canada

**Abstract****Background and objectives**

Increased left ventricular mass (LVM), low ventricular ejection fraction (EF) and high pulse wave velocity (PWV) relate to overall and cardiovascular mortality in end stage kidney disease (ESKD) patients. The aim of this study was to determine the effect of online hemodiafiltration (HDF) versus low flux hemodialysis (HD) on LVM, EF and PWV.

**Design, setting, participants, & measurements**

Echocardiography was used to assess LVM and EF in 342 patients of the CONvective TRANsport STudy (CONTRAST) followed up to 4 years, while PWV was measured in 189 patients up to 3 years. Effect of HDF versus HD on LVM, EF and PWV was evaluated using linear mixed models.

**Results**

Patients had a mean age of 63 years and 61% were male. At baseline, median LVM was 227 g (interquartile range (IQR): 183 – 279g), and median EF was 65% (IQR: 55-72%). Median PWV was 9.8 m/s (IQR: 7.5 – 12.0m/s). There was no significant difference between the HDF and HD treatment arms in rate of change in LVM (HDF  $\Delta$ -0.9g/year (95%CI: -8.9 - 7.7); HD  $\Delta$ 12.5g/year (95%CI: -3.0 - 27.5), p for difference: 0.13), EF (HDF  $\Delta$ -0.3%/year (95%CI: -2.3 - 1.8); HD  $\Delta$ -3.4%/year (95%CI: -5.9 - -0.9), p: 0.17) or PWV (HDF  $\Delta$ -0.0(m/s)/year (95%CI: -0.4 - 0.4); HD  $\Delta$ 0.0(m/s)/year (95%CI: -0.3 - 0.2), p: 0.89). No differences in rate of change between treatment groups were observed for subgroups of age, gender, residual kidney function, dialysis vintage, history of cardiovascular disease, diabetes or convection volume.

**Conclusions**

Treatment with online HDF did not affect changes in LVM, EF or PWV over time, as compared to HD. However, non-significant trends were observed for 1) an increase of LVM in HD, while LVM in HDF remained stable and 2) a decrease of EF in HD, while EF in HDF remained stable.

## **Introduction**

Cardiovascular disease is a considerable cause of morbidity and mortality in patients with end stage kidney disease (ESKD). (1) The origin of cardiovascular disease is multifactorial; factors such as retention of uremic toxins, micro-inflammation, atherosclerosis, a fluctuating extracellular fluid volume and hypertension have been implicated. (2-4)

Important alternative markers of cardiovascular risk are left ventricular mass (LVM), ejection fraction (EF) and pulse wave velocity (PWV), the latter as a measure of arterial stiffness. LVM, EF and PWV have all been repeatedly demonstrated to be relevant predictors of cardiovascular morbidity and mortality in ESKD patients. (5-9) Regression of LVM has also been shown to be associated with a more favourable outcome in this population. (10) Studies on the natural course of LVM in ESKD patients have reported either stabilization or decrease of these parameters over time, (9;11) while the natural course of EF is to decrease slowly over time in this population. (7;12)

Hemodiafiltration (HDF) is a dialysis modality which uses a combination of convective transport and diffusion to clear more and larger solutes than conventional hemodialysis (HD). (13) HDF reduces inflammatory parameters related to atherosclerosis and improves intradialytic haemodynamic stability (14), possibly advantageous factors in decreasing the risk of cardiovascular disease. Extended or frequent hemodialysis has been established to have a beneficial effect on cardiac morphology and function. (15) Thus the question arises whether HDF may also have such an effect.

The aim of this study is to determine the effect of online HDF versus low flux HD on the rate of change in LVM, EF and PWV over time in a large population of ESKD patients.

## **Materials and methods**

### **Patients**

The present study included a subset of patients participating in the CONvective TRANsport Study (CONTRAST). Patients were recruited between June of 2004 and December of 2009. CONTRAST has been designed to investigate the effects of increased convective transport by online post-dilution HDF as compared with low-flux HD on all-cause mortality and

cardiovascular morbidity and mortality (International Clinical Trials Registrations Platform: ISRCTN38365125). (13;16) This subset of the population consisted of patients who were treated in a medical center, where performance of additional echocardiography measurements and pulse wave velocity measurements was logistically possible. Patients in these centers who had given informed consent to participate in CONTRAST were requested to undergo echocardiography / PWV measurements.

CONTRAST was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating dialysis centres. Written informed consent was obtained from all patients prior to enrolment.

All patients were randomized centrally by a computer-based randomization service (Julius Center University Medical Center Utrecht, the Netherlands) into a 1:1 ratio for treatment with online HDF or continuation of low-flux HD, stratified by participating center (permuted blocks). Due to the nature of the intervention it was not possible to blind the patients, local study nurses or investigators for the treatment assignment.

#### **Dialysis procedures**

Dialysis procedures have elaborately been described elsewhere. (13;16) Routine patient care was performed according to the guidelines of the Quality of Care Committee of the Dutch Federation of Nephrology.

#### **Data collection**

At baseline standardized forms were used to collect demographical, clinical and laboratory data, type of vascular access, duration of dialysis (dialysis vintage), and medical history. The data collection in CONTRAST has been elaborately described earlier. (13;16)

In HDF patients infusion volumes (litres per treatment) were reported as the mean value of three consecutive treatment sessions preceding the quarterly visit. Convection volumes (litres per treatment) were calculated as the sum of the intradialytic weight loss and the substitution volume per session. The mean delivered convection volume during the trial was estimated as: mean delivered convection volume = (HDF treatments/total number of

treatments) x mean convection volume of the three treatments preceding the quarterly visit.

Standard laboratory samples were analysed in the local laboratories of the participating hospitals by standard laboratory techniques.

### **Echocardiography and PWV measurements**

Participants in 18 centres (n=342) were requested to undergo echocardiography at baseline, after 6 months, 12 months and annually thereafter.

Transthoracic two-dimensional echocardiography studies were performed on a mid-week non-dialysis day by an echocardiographer at the participating local hospital. The ultrasound investigations were assessed centrally by an independent experienced echocardiographer at the core laboratory (Vrije Universiteit Medisch Centrum, Amsterdam, the Netherlands), who was blinded for all other patient data including treatment assignment. LVM was calculated using the formula of Devereux and Reicke (17), modified in accordance with the recommendations of the American Society of Echocardiography. (18) EF was computed automatically by the echocardiography software.

Participants in 8 centres (n=189) were requested to undergo aortic pulse wave velocity (PWV) measurements next to the standard CONTRAST data collection at baseline and annually thereafter, on a mid-week non-dialysis day. The SphygomoCor system (PWV system and BP analysis system; PWV Inc., Sydney, Australia) was used to assess PWV and analyse the arterial pulse contours. The method has a high reproducibility and is described elaborately elsewhere. (19-21)

### **Data analysis**

Data were reported as means with standard deviations, medians with ranges, or proportions when appropriate. Comparisons between treatment modality groups were analysed with unpaired t-test for normally distributed variables, Mann-Whitney test for not normally distributed variables and chi-square test for binomial variables.

**Table 1a:** Baseline characteristics of study population by treatment modality for patients who underwent echocardiography.

	HDF n=164	HD n=167	p-value
<b>Demographic data</b>			
Gender (% male)	59	64	0.38
Race, (% caucasian)	81	80	0.61
Age (year)	63.6 ± 13.8	62.5 ± 12.8	0.46
Smoking (%)	21	19	0.53
<b>Anthropometrics</b>			
Height (m)	1.67 ± 0.11	1.69 ± 0.11	0.17
Weight (kg)	70.8 ± 14.8	73.4 ± 13.7	0.10
BMI (kg/m <sup>2</sup> )	25.3 ± 5.3	25.6 ± 4.6	0.50
Body Surface Area (m <sup>2</sup> )	1.82 ± 0.22	1.87 ± 0.21	0.07
<b>Dialysis Properties</b>			
Duration of dialysis (minute)	225 ± 24	226 ± 22	0.71
Blood flow (mL/minute)	309 ± 34	309 ± 38	0.99
spKt/V <sub>urea</sub>	1.40 ± 0.22	1.37 ± 0.18	0.22
AV fistula (%)	76	83	0.12
<b>Patient History</b>			
Cardiovascular disease (%)	45	44	0.92
Diabetes (%)	29	24	0.38
Kidney Transplant (%)	6	12	0.09
Patients with residual kidney function (%)	58	47	0.06
Dialysis vintage (year)	1.8 (1.1 – 3.3)*	2.3 (1.1 – 4.1)*	0.13
<b>Laboratory parameters</b>			
Hemoglobin (g/dL)	11.8 ± 1.4	11.7 ± 1.2	0.21
Phosphorus (mg/dL)	5.17 ± 1.58	5.17 ± 1.52	0.93
Beta-2 microglobulin (g/L)	31.9 ± 14.1	34.0 ± 13.1	0.06
Albumin (g/dL)	4.1 ± 0.4	4.1 ± 0.4	0.96
Creatinin (mg/dL), pre-dialysis	9.96 ± 2.67	10.34 ± 2.76	0.22
<b>Hemodynamic measurements</b>			
Systolic blood pressure (mmHg)	142 ± 20	142 ± 19	0.87
Diastolic blood pressure (mmHg)	74 ± 10	74 ± 10	0.67
LVEDD (mm)	50 (45 – 55)*	50 (45 – 55)*	0.66
LVESD (mm)	32 (28 – 39)*	32 (27 – 37)*	0.32
LVM (g)	227 (180 – 286)*	231 (185 – 280)*	0.23
LVMi (g/m <sup>2</sup> )	124 (97 – 155)*	126 (104 – 150)*	0.54
LVMi (g/height <sup>2.7</sup> )	31 (24 – 38)*	30 (24 – 38)*	0.81

\*median and IQR (P25-P75) are shown AV: arterio-venous; BMI: body mass index; EFLV: ejection fraction of left ventricle; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricle end systolic diameter; LVM: left ventricular mass; LVMi: left ventricular mass index.

**Table 1b:** Baseline characteristics of study population by treatment modality for patients who underwent pulse wave velocity (PWV) measurements.

	HDF n=90	HD n=78	p-value
<b>Demographic data</b>			
Gender (% male)	62	63	0.85
Race (% caucasian)	78	82	0.42
Age (year)	61.9 ± 14.2	62.4 ± 13.7	0.78
Smoking (%)	22	22	0.96
<b>Anthropometrics</b>			
Height (m)	1.70 ± 0.10	1.70 ± 0.09	0.97
Weight (kg)	70.4 ± 15.5	71.8 ± 12.8	0.49
BMI (kg/m <sup>2</sup> )	24.3 ± 4.5	24.8 ± 3.8	0.38
Body Surface Area (m <sup>2</sup> )	1.83 ± 0.23	1.85 ± 0.20	0.51
<b>Dialysis Properties</b>			
Duration of dialysis (minute)	229 ± 24	227 ± 21	0.52
Blood flow (mL/minute)	307 ± 35	310 ± 32	0.75
spKt/V <sub>urea</sub>	1.39 ± 0.21	1.36 ± 0.18	0.31
AV fistula (%)	78	84	0.35
<b>Patient History</b>			
Cardiovascular disease (%)	45	49	0.60
Diabetes (%)	27	21	0.41
Kidney Transplant (%)	9	16	0.11
Residual kidney function (%)	59	51	0.28
Dialysis vintage (year)	1.5 (0.8 – 2.5)*	2.0 (0.8 – 3.7)*	0.31
<b>Laboratory parameters</b>			
Hemoglobin (g/dL)	11.9 ± 1.4	11.6 ± 1.3	0.26
Phosphorus (mg/dL)	5.17 ± 1.86	5.20 ± 1.49	0.92
Beta-2 microglobulin (g/L)	29.6 ± 11.3	31.1 ± 11.4	0.75
Albumin (g/dL)	4.0 ± 0.4	3.9 ± 0.4	0.70
Creatinin (mg/dL), pre-dialysis	9.63 ± 2.88	10.16 ± 2.64	0.19
<b>Hemodynamic measurements</b>			
Systolic blood pressure (mmHg)	141 ± 22	142 ± 22	0.77
Diastolic blood pressure (mmHg)	74 ± 11	75 ± 10	0.98
PWV (m/s)	10.2 ± 3.1	9.9 ± 3.6	0.61

\*median and IQR (P25-P75) are shown

AV: arterio-venous; BMI: body mass index; PWV: pulse wave velocity.

Linear mixed effect models with a random intercept and slope were used to model changes over time of PWV, EF and LVM. Both the means of LVM, EF and PWV between treatment arms, as well as the rates of change were compared. To explore if rates of

change differed depending on follow-up time, we calculated rates of change from baseline to 12 months, and baseline to end of follow-up of measurements. To elucidate, data from 1 year follow-up included the slopes of patients followed from baseline to 1 year. Data from 3 years of follow-up included the slopes of patients followed from baseline to 3 years.

Additional linear mixed models were performed with adding interaction terms for age, gender, residual kidney function, dialysis vintage, presence of diabetes and presence of cardiovascular disease. Age and dialysis vintage were both tested as continuous variables and stratified below or above the median for the patient group under study. For HDF patients additional linear mixed effect models were performed with adding interaction terms for mean convection volume. Mean convection volume was tested as a continuous variable, stratified above and below the median and in tertiles. All models were performed with adjustment for baseline LVM, EF or PWV.

Results were considered statistically significant when  $p < 0.05$  (two-sided). All calculations were made by use of a standard statistical package (SPSS for Windows Version 20.0.1; SPSS Inc. Headquarters, Chicago, Illinois, US).

## **Results**

The baseline characteristics of the patients in whom LVM/EF and PWV were measured are depicted in Table 1a and 1b respectively. No differences in patient characteristics were observed between treatment groups, neither in the echocardiography, nor in the PWV cohort. 342 CONTRAST participants underwent repeated echocardiography ( HDF: n=171, HD: n=171), and 189 underwent repeated PWV measurements ( HDF: n=103, HD: n=86). 159 patients underwent both the echocardiography and the PWV assessment.

The median baseline LVM was 227 g (P25 – P75: 183 – 279g), median EF was 65% (P25-P75: 55-72%), while median PWV was 9.82 m/s (P25 – P75: 6.5 – 12.0m/s).

Patients who had echocardiography had a similar characteristics as the other CONTRAST patients who did not receive echocardiography (supplementary Table 1a). Patients who received PWV measurements were younger, had a lower body mass index (BMI) and a

higher diastolic blood pressure than the other CONTRAST patients (supplementary Table 1b).

The participant flowchart of the echocardiography cohort and the PWV cohort are shown in the supplementary Figures 1 and 2 respectively. Dropout was high, mainly due to death and kidney transplantation. However, when baseline patient characteristics were compared, patient characteristics did not differ in those who were followed for <1 year, as compared to those followed for 1-3 years or >3 years (supplementary Tables 2a and b).

#### **Effect of HDF on LVM**

LVM did not differ between HDF and HD during the trial, nor were there differences between treatment modalities in rate of change over time (Table 2). When additional adjustments for pre-dialysis systolic blood pressure, hemoglobin, beta 2-microglobulin and phosphate as time varying covariates were made, results were similar (data not shown). Figure 1a shows the linear mean changes of LVM over time in HDF versus HD. Results were similar when LVM was indexed for body surface area (BSA) or for height<sup>2.7</sup> (supplementary Table 3).

No evidence was found for different effects of HDF compared to HD on LVM in different subgroups (supplementary Table 4a).

#### **Effect of HDF on EF**

EF remained stable in HDF patients ( $\Delta$ : -0.3% per year; 95% CI: -2.3 to 1.8,  $p=0.78$ ), but decreased in HD patients ( $\Delta$ : -3.4% per year; 95% CI: -5.9 to -0.9,  $p=0.009$ ) (Table 2). However, the rate of change did not differ significantly between dialysis modalities ( $p=0.17$ ), and did not result in significantly different mean EF. When additional adjustments described in the “Effect of HDF on LVM” paragraph were made, the results were similar ( $p$  for difference in rate of change between HDF and HD: 0.15). Figure 1b shows the linear mean changes of EF over time in HDF versus HD.

**Table 2:** Changes over time of left ventricular mass (LVM), ejection fraction (EF) and PWV in post-dilution online hemodiafiltration and low-flux hemodialysis.

Mean change in LVM or PWV ( $\Delta$ ) per year (95% CI)					
Follow-up	HDF		HD		HDF versus HD
	$\Delta$	P	$\Delta$	P	P for slope
<b>1 year</b>					
LVM (g)	2.48 (-17.89 to 22.85)	0.77	12.98 (-9.68 to 25.65)	0.16	0.34
EF (%)	-3.06 (-6.94 to 0.82)	0.12	-4.48 (-7.83 to -1.12)	0.009	0.64
PWV (m/s)	-0.41 (-1.21 to 0.40)	0.32	-0.25 (-0.78 to 0.28)	0.36	0.76
<b>3 years</b>					
LVM (g)	-2.04 (-10.12 to 6.03)	0.61	12.47 (-4.22 to 21.15)	0.11	0.12
EF (%)	-0.39 (-2.51 to 1.73)	0.72	-2.96 (-5.49 to -0.42)	0.02	0.31
PWV (m/s)	-0.01 (-0.41 to 0.40)	0.98	-0.04 (-0.31 to 0.23)	0.76	0.89
<b>4 years</b>					
LVM (g)	-0.86 (-8.85 to 7.71)	0.87	12.48 (-3.00 to 27.46)	0.09	0.13
EF (%)	-0.29 (-2.34 to 1.76)	0.78	-3.39 (-5.90 to -0.88)	0.009	0.17

$\Delta$ : change per year; CI: confidence interval; EF: ejection fraction; HD: low-flux hemodialysis; HDF: online post-dilution hemodiafiltration; EF: ejection fraction; LVM: left ventricle mass; PWV: pulse wave velocity  
Analyses were adjusted for baseline LVM / PWV. P value comparing the slope to be different from zero

No evidence was found for different effects of HDF compared to HD on EF in different subgroups, (supplementary Table 4b).

#### Effect of HDF on PWV

PWV did not differ between HDF and HD during the trial, nor were there differences between treatment modalities in rate of change over time (Table 2). When additional adjustments described in the “Effect of HDF on LVM” paragraph were made, the results were similar (data not shown). Figure 1c shows the linear mean changes of PWV over time in HDF versus HD.

No evidence was found for different effects of HDF compared to HD on PWV in different subgroups (supplementary Table 4c).

**Table 3:** Mean difference in left ventricular mass (LVM) and pulse wave velocity (PWV) values during follow-up between the hemodialysis (HD) group and the hemodiafiltration (HDF) group in halves of delivered convection volume.

Mean change in LVM and PWV ( $\Delta$ ) per year (95% CI) by convection volume.				
	$\Delta$	P	versus HD P for slope	P for interaction time*convection group
<b>LVM (grams)</b>				
<b>1 year</b>				
≤ 18.8 L/ treatment	6.10 (-19.1 to 31.20)	0.63	0.61	0.98
> 18.8 L/ treatment	-13.22 (-30.90 to 4.41)	0.14		
<b>3 years</b>				
≤ 19.0 L/ treatment	-8.87 (-19.23 to 7.46)	0.83	0.45	0.82
> 19.0 L/ treatment	13.77 (-8.95 to 26.48)	0.23		
<b>EF (%)</b>				
<b>1 year</b>				
≤ 18.8 L/ treatment	-1.44 (-5.99 to 1.11)	0.53	0.99	0.98
> 18.8 L/ treatment	-3.94 (-8.78 to 0.88)	0.11		
<b>3 years</b>				
≤ 19.0 L/ treatment	0.14 (-1.89 to 2.16)	0.89	0.98	0.23
> 19.0 L/ treatment	-1.46 (-4.51 to 1.59)	0.68		
<b>PWV (m/s)</b>				
<b>1 year</b>				
≤ 18.8 L/ treatment	0.20 (-0.47 to 0.78)	0.30	0.87	0.79
> 18.8 L/ treatment	-0.24 (-0.88 to 0.27)	0.61		
<b>3 years</b>				
≤ 18.9 L/ treatment	0.37 (-0.25 to 0.98)	0.23	0.98	0.62
> 18.9 L/ treatment	-0.01 (-0.59 to 0.57)	0.99		

**Convection volume**

Rate of change of LVM, EF and PWV during follow-up was not different across the halves of mean convection volume in the HDF patients, when compared to HD (Table 3). When mean convection volume was divided into tertiles, or tested as a continuous variable, results were the same (data not shown).

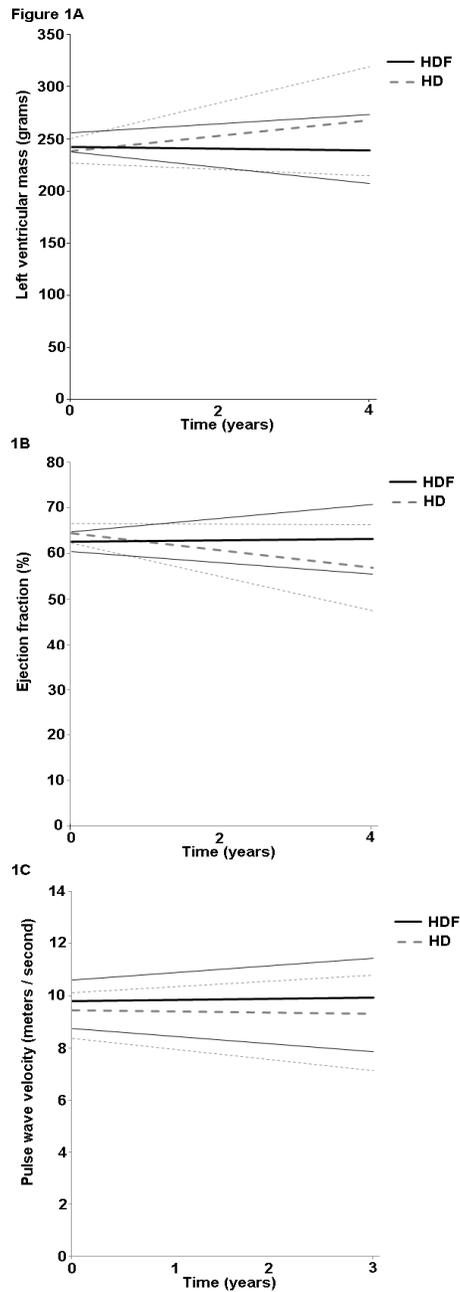
**Discussion**

To the best of our knowledge this is the first randomized trial in a large ESKD population comparing the effects of online post-dilution HDF versus HD on LVM, EF and PWV. In this study, performed in a subpopulation of CONTRAST, we showed that HDF did not affect LVM, EF and PWV levels compared to HD over a time period of three to four years. However, trends were observed for 1) an increase of LVM in HD, while LVM in HDF remained stable and 2) a decrease of EF in HD, while EF in HDF remained stable, although the differences between treatment groups were not significant.

**Effect of HDF on LVM, EF and PWV**

Data regarding effect of HDF on alternative markers of cardiovascular risk is limited. Ohtake et al published a randomized trial in 22 patients (9 on HD, 13 on online pre-dilution HDF), showing a significant decrease of LVM index (LVMI) by 12% in HDF patients, while the LVMI remained stable in the HD group after 1 year. Also, PWV increased significantly by 11% in the HD patients, while remaining stable in the HDF group. (22) Our results did not confirm these findings, although with respect to LVM a relation in the same direction, albeit not statistically significant, was found. The differences between the results of Ohtake et al and our findings may be explained by the difference in the method of administration of HDF (pre- versus post-dilution) and the difference in study population. As compared to CONTRAST, patients in the Ohtake study had a lower prevalence of cardiovascular disease and used less antihypertensive medication. (22) We could

**Figure 1:** Linear mean changes over time (with 95% confidence limits) of A) left ventricular mass (LVM), B) ejection fraction (EF) and C) pulse wave velocity (PWV) stratified by dialysis modality for 4 years and 3 years of follow-up respectively.



speculate that these patients had less cardiovascular damage at baseline, and be prone to a more favorable course of surrogate marker change. Francisco et al published a randomized trial in 24 patients (10 on HD, 14 on online post-dilution HDF), showing a significant increase of EF in HDF after 3 months of follow-up (from  $52\pm 8\%$  to  $58\pm 6\%$ ) versus no significant change in HD. (23) Since we did not perform echocardiography at 3 months after randomization, the findings of Francisco et al cannot be confirmed with our data. Also, residual confounding may play a role in both of the above described trials since the study sample was rather small.

Publication bias (ie studies with statistically significant results are more likely to be published) may be an explanation for the difference between our results and the positive results of two small trials comparing LVM, EF and PWV in HDF and HD patients. (24)

Two observational studies, comparing HDF and HD, performed in 118 (HDF: n=58) respectively 333 (HDF: n=65) patients, both found a decrease of LVMi in the HDF group, while the LVMi in HD patients remained stable over a follow-up period of 2, respectively 4 years. (25;26) However, non-randomised studies are prone to confounding by indication: it cannot be ruled out that patients with a more favourable prognosis were allocated to HDF. Furthermore, in both of the above-mentioned studies, changes in LVMi were shown without adjustments for potential confounders.

Our results, based on a large ESKD population, with extensive follow-up and with exploration of treatment effect in subgroups indicate that during treatment with HD, the cardiac markers tend to worsen over 4 years (decrease in EF -3.4%,  $p=0.009$ , increase in LVM 12.5 g,  $p=0.09$ ), whereas no change occurred during treatment with HDF. The difference between HD and HDF however, is not significant ( $p=0.13$  and  $p=0.17$ ). Earlier studies (in sub-groups) of CONTRAST have shown that both phosphate and beta-2-microglobulin levels decrease in HDF patients, while remaining stable in HD. (16;27;28) We cannot deduct from our data that better phosphate control and middle molecule clearance lead to a more beneficial development of LVM, EF and PWV over a period of 3-4 years in our population.

### **Convection volume**

In *post hoc* analyses of three large randomized controlled trials, namely CONTRAST (16), Turkish HDF Study (29) and the ESHOL (30) comparing HDF to HD in terms of mortality and cardiovascular events, a relation between high convection volumes and lower mortality risk was found. We did not find that high convection volumes were related to rate of change of LVM, EF and PWV. Thus we cannot determine that the relation between high convection volume and low mortality is mediated by changes in cardiovascular anatomy or function.

### **Echocardiography measurements**

In our analyses LVM was not indexed for body surface area, or divided by height<sup>2.7</sup> as has been done in analogous studies. (22;25;26) A downside of ratios is that an observed relation may be due to (changes in) the nominator, the denominator or both. Therefore in the present analyses we chose to use sheer LVM. Since mixed models take account for variability within patients, adjustment for body dimensions was not deemed necessary. For accuracy, when we performed the analyses with LVM indexed for height<sup>2.7</sup> or BSA, results were similar (supplementary Table 4).

Measurement errors could be considered a possible explanation for finding no associations. This is a multicentre trial which may increase measurement variability, despite a uniform trained protocol. Yet an experienced echocardiographer blinded for treatment assignment quantified the LVM measurements in a central core lab thus reducing measurement variability.

### **Strength and limitations**

This study had several limitations. First, not all patients participating in CONTRAST underwent echocardiographic examinations, and not all of those patients had PWV assessments. Therefore it is likely that we do not have the power to demonstrate significant differences of LVM, EF and PWV in HDF versus HD in particular for PWV, as the sample size was smaller and the confidence intervals of the rate of change were wide in this group. Lack of power is even more probable in the analyses which demonstrate

differences across subgroups of conventional risk factors. Second, some patients dropped out or missed examinations during the follow-up period. Although mixed effect models can estimate rate of change well with some missing data, the precision of the estimates decreases.

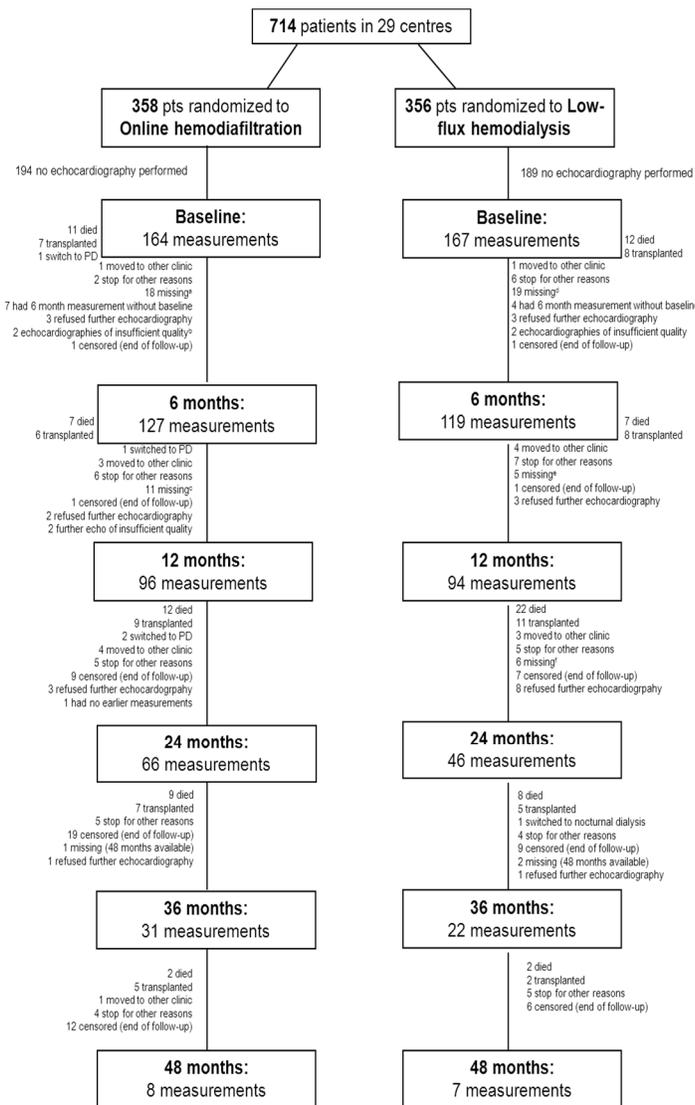
The strengths of this study are the randomized design, the concise data collection over a long period of follow-up, and the double independent analysis of the echocardiography recordings. Furthermore, the study was performed in a large dialysis population, involving patients from 6 university and 12 community hospitals and is among the largest reported thus far on this topic.

### **Conclusion**

In conclusion, we did not find that treatment with HDF has a significant effect on changes in LVM, EF and PWV as compared to HD. Furthermore, no statistically significant differences in changes of LVM, EF and PWV were found across subgroups of conventional risk factors.

Supplementary Figures and Tables

Supplementary Figure 1: Flowchart of echocardiography cohort.



<sup>a</sup>8 available at 12 months, 9 available at 24 months, 2 available at 36 months

<sup>b</sup>3 echocardiographies of insufficient quality from baseline; 2 echocardiographies of insufficient quality from baseline measurement on

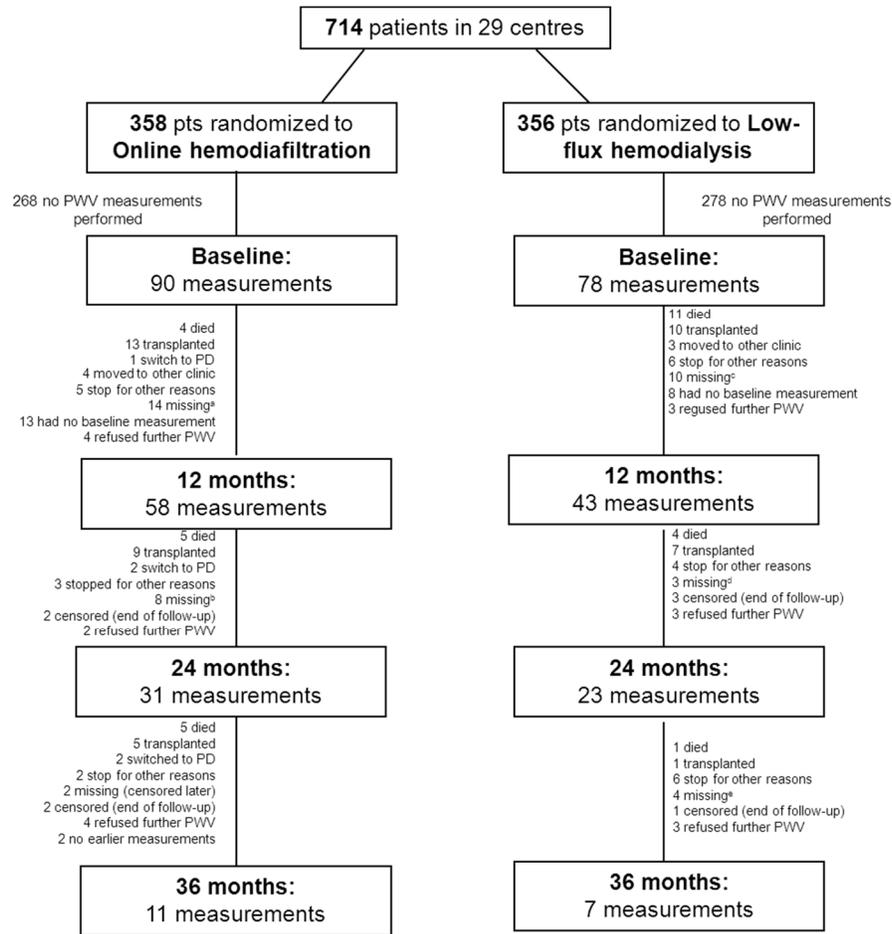
<sup>c</sup>6 available at 24 months, 5 available at 36 months

<sup>d</sup>10 available at 12 months, 9 available at 24 months

<sup>e</sup>5 available at 24 months

<sup>f</sup>6 available at month 36

**Supplementary Figure 2:** Flowchart of the pulse wave velocity cohort.



<sup>a</sup>6 available at 24 months, 1 transplanted later, 2 died later, 5 censored (end of follow-up) later

<sup>b</sup>3 available at 36 months, 3 died later, 1 transplanted later, 1 censored (end of follow-up) later

<sup>c</sup>3 available at 24 months, 2 died later, 1 stopped for other reasons later, 4 censored (end of follow-up) later

<sup>d</sup>1 available at 36 months, 1 transplanted later, 1 censored later

<sup>e</sup>1 died later, 3 censored later

**Supplementary Table 1a:** Baseline characteristics of patients receiving echocardiography versus the other participants of the CONvective TRANsport Study.

	echo cor cohort n=331	other CONTRAST participants n=383	p-value
<b>Demographic data</b>			
Gender (% male)	61	63	0.60
Race (% caucasian)	81	87	0.06
Age (year)	63.1 ± 13.3	64.9 ± 13.9	0.08
<b>Anthropometrics</b>			
BMI (kg/m <sup>2</sup> )	25.4 ± 4.9	25.3 ± 4.7	0.78
Body Surface Area (m <sup>2</sup> )	1.84 ± 0.21	1.86 ± 0.21	0.41
<b>Dialysis Properties</b>			
Duration of dialysis (minute)	226 ± 23	227 ± 23	0.48
Blood flow (mL/minute)	309 ± 36	307 ± 41	0.48
Kt/V <sub>urea</sub>	1.39 ± 0.20	1.40 ± 0.23	0.28
<b>Comorbidities</b>			
Cardiovascular disease (%)	45	43	0.74
Diabetes (%)	27	23	0.29
Kidney Transplant (%)	9	12	0.16
Dialysis vintage (year)	2.92 ± 2.81	2.93 ± 2.84	0.96
Patients with residual renal function (%)	52	53	0.80
<b>Hemodynamic measurements</b>			
Systolic blood pressure, pre-dialysis (mm Hg)	148 ± 21	147 ± 22	0.45
Diastolic blood pressure, pre-dialysis (mm Hg)	77 ± 12	75 ± 13	0.07
Pulse pressure, pre-dialysis (mmHg)	72 ± 19	72 ± 17	0.75
Systolic blood pressure, post-dialysis (mmHg)	136 ± 22	134 ± 21	0.23
Diastolic blood pressure, post-dialysis (mm Hg)	72 ± 11	70 ± 12	0.16
Pulse pressure, post-dialysis (mmHg)	64 ± 19	64 ± 16	0.89

AV: arterio-venous; BMI: body mass index.

**Supplementary Table 1b:** Baseline characteristics of patients receiving PWV measurements versus the other participants of the CONvective TRANsport Study.

	aPWV cohort n=168	other CONTRAST participants n=546	p-value
<b>Demographic data</b>			
Gender (% male)	67	25	0.28
Race (% caucasian)	82	84	0.53
Age (year)	60.0 ± 13.9	64.9 ± 13.5	<0.001
<b>Anthropometrics</b>			
BMI (kg/m <sup>2</sup> )	24.4 ± 2.6	25.6 ± 5.0	0.015
Body Surface Area (m <sup>2</sup> )	1.84 ± 0.20	1.85 ± 0.22	0.69
<b>Dialysis Properties</b>			
Duration of dialysis (minute)	229 ± 22	226 ± 23	0.18
Blood flow (mL/minute)	311 ± 31	307 ± 42	0.60
Kt/V <sub>urea</sub>	1.38 ± 0.18	1.40 ± 0.22	0.13
<b>Comorbidities</b>			
Cardiovascular disease (%)	41	45	0.43
Diabetes (%)	27	25	0.51
Kidney Transplant (%)	14	10	0.26
Dialysis vintage (year)	2.76 ± 2.77	2.96 ± 2.84	0.46
Patients with residual renal function (%)	50	53	0.58
<b>Hemodynamic measurements</b>			
Systolic blood pressure, pre-dialysis (mm Hg)	148 ± 24	148 ± 21	0.72
Diastolic blood pressure, pre-dialysis (mm Hg)	78 ± 12	75 ± 12	0.013
Pulse pressure, pre-dialysis (mmHg)	70 ± 21	72 ± 17	0.21
Systolic blood pressure, post-dialysis (mmHg)	135 ± 23	135 ± 21	0.80
Diastolic blood pressure, post-dialysis (mm Hg)	74 ± 12	70 ± 10	0.002
Pulse pressure, post-dialysis (mmHg)	61 ± 19	65 ± 17	0.08

AV: arterio-venous; BMI: body mass index.

**Supplementary Table 2a:** Baseline patient characteristics by duration of follow-up time in patients who underwent echocardiography.

	<1 year FU n=64	1-3 years FU n=171	>3 years FU n=92	p-value
<b>Demographic data</b>				
Gender (% male)	50	65	63	0.12
Race (% caucasian)	84	79	80	0.40
Age (year)	62.2 ± 13.4	64.0 ± 13.4	62.0 ± 13.1	0.45
<b>Anthropometrics</b>				
Body Mass Index (kg/m <sup>2</sup> )	25.0 ± 4.8	25.7 ± 4.9	25.3 ± 5.0	0.55
Body Surface Area (m <sup>2</sup> )	1.81 ± 0.24	1.83 ± 0.22	1.84 ± 0.19	0.30
<b>Dialysis Properties</b>				
Duration of dialysis (minute)	229 ± 22	224 ± 23	226 ± 22	0.47
Blood flow (mL/minute)	309 ± 55	314 ± 27	301 ± 35	0.33
Kt/V <sub>urea</sub>	1.39 ± 0.21	1.40 ± 0.21	1.35 ± 0.18	0.18
<b>Comorbidities</b>				
Cardiovascular disease (%)	48	41	48	0.47
Diabetes (%)	18	29	29	0.28
Kidney Transplant (%)	14	7	10	0.24
Dialysis vintage (year)	3.19 ± 2.72	2.86 ± 2.79	2.88 ± 2.93	0.77
Patients with residual renal function (%)	45	54	54	0.47
<b>Hemodynamic measurements</b>				
Systolic blood pressure, pre-dialysis (mm Hg)	146 ± 23	148 ± 21	151 ± 20	0.32
Diastolic blood pressure, pre-dialysis (mm Hg)	78 ± 12	76 ± 11	77 ± 12	0.47
Pulse pressure, pre-dialysis (mmHg)	68 ± 19	72 ± 19	74 ± 18	0.16
Systolic blood pressure, post-dialysis (mmHg)	133 ± 24	137 ± 23	134 ± 19	0.41
Diastolic blood pressure, post-dialysis (mm Hg)	71 ± 14	72 ± 11	71 ± 11	0.67
Pulse pressure, post-dialysis (mmHg)	63 ± 17	65 ± 20	63 ± 17	0.58

FU: follow-up

**Supplementary Table 2b:** Baseline patient characteristics by duration of follow-up time in patients who underwent PWV measurements.

	<1 year FU n=25	1-3 years FU n=53	>3 years FU n=45	p-value
<b>Demographic data</b>				
Gender (% male)	68	62	71	0.64
Race (% caucasian)	84	77	87	0.55
Age (year)	59.8 ± 12.9	61.3 ± 13.7	58.7 ± 14.7	0.67
<b>Anthropometrics</b>				
Body Mass Index (kg/m <sup>2</sup> )	25.5 ± 4.3	24.5 ± 4.0	24.3 ± 3.4	0.67
Body Surface Area (m <sup>2</sup> )	1.85 ± 0.22	1.83 ± 0.21	1.86 ± 0.18	0.88
<b>Dialysis Properties</b>				
Duration of dialysis (minute)	233 ± 22	227 ± 23	229 ± 22	0.53
Blood flow (mL/minute)	328 ± 45	315 ± 27	297 ± 29	0.06
Kt/V <sub>urea</sub>	1.34 ± 0.18	1.37 ± 0.26	1.34 ± 0.16	0.72
<b>Comorbidities</b>				
Cardiovascular disease (%)	48	34	44	0.40
Diabetes (%)	8	25	27	0.18
Kidney Transplant (%)	84	91	82	0.46
Dialysis vintage (year)	2.87 ± 1.99	2.53 ± 2.46	2.96 ± 3.43	0.72
Patients with residual renal function (%)	44	55	49	0.66
<b>Hemodynamic measurements</b>				
Systolic blood pressure, pre-dialysis (mm Hg)	147 ± 23	147 ± 25	151 ± 23	0.64
Diastolic blood pressure, pre-dialysis (mm Hg)	81 ± 11	78 ± 10	77 ± 13	0.51
Pulse pressure, pre-dialysis (mmHg)	66 ± 19	69 ± 23	74 ± 20	0.28
Systolic blood pressure, post-dialysis (mmHg)	136 ± 27	136 ± 23	134 ± 22	0.90
Diastolic blood pressure, post-dialysis (mm Hg)	74 ± 15	74 ± 10	72 ± 13	0.69
Pulse pressure, post-dialysis (mmHg)	62 ± 20	61 ± 20	61 ± 19	0.99

FU: follow-up

**Supplementary Table 3:** Changes over time of left ventricular mass (LVM) indexed for body surface area (LVMI) and LVM indexed for height<sup>2.7</sup> in post-dilution online hemodiafiltration and low-flux hemodialysis.

Mean change in concentration ( $\Delta$ ) per year (95% CI)					
Follow-up	HDF		HD		HDF versus HD P for slope
	$\Delta$	P	$\Delta$	P	
<b>1 year</b>					
LVMI (g/m <sup>2</sup> )	1.97 (-7.32 to 11.26)	0.68	6.42 (-2.23 to 15.07)	0.15	0.19
LVM/height <sup>2.7</sup>	0.29 (-2.01 to 2.59)	0.80	1.19 (-0.94 to 3.32)	0.27	0.06
<b>3 years</b>					
LVMI (g/m <sup>2</sup> )	-0.91 (-6.04 to 4.23)	0.73	6.51 (-0.23 to 13.27)	0.06	0.19
LVM/height <sup>2.7</sup>	-0.26 (-1.30 to 0.79)	0.63	1.10 (-0.44 to 2.64)	0.16	0.08
<b>4 years</b>					
LVMI (g/m <sup>2</sup> )	-0.38 (-5.39 to 4.61)	0.88	6.55 (-0.05 to 13.15)	0.05	0.13
LVM/height <sup>2.7</sup>	-0.05 (-1.10 to 1.00)	0.92	1.13 (-0.35 to 2.62)	0.13	0.09



**Supplementary Table 4a:** Left ventricular mass changes in hemodiafiltration versus hemodialysis in various subgroups of patients.

Subgroups	Mean change in LVM in grams ( $\Delta$ ) per year (95% CI)					
	HDF $\Delta$	P	HD $\Delta$	P	HDF versus HD P for slope	P for interaction time*HDF*subgroup
Age $\leq$ 64.9 years	-2.77 (-14.32 to 8.97)	0.63	-1.74 (-14.98 to 11.49)	0.79	0.10	0.26
Age > 64.9 years	0.93 (-9.08 to 10.93)	0.85	18.04 (0.52 to 35.56)	0.044		
Male	-1.57 (-9.95 to 6.80)	0.71	4.17 (-9.75 to 18.10)	0.55	0.54	0.83
Female	1.52 (-8.76 to 11.81)	0.77	10.05 (-7.49 to 27.60)	0.25		
RKF	-2.54 (-11.75 to 6.67)	0.59	12.61 (-7.71 to 32.93)	0.20	0.17	0.34
No RKF	3.16 (-10.26 to 16.59)	0.63	1.98 (-10.39 to 14.16)	0.76		
CVD	3.22 (-5.74 to 12.17)	0.48	0.57 (-13.80 to 14.92)	0.94	0.55	0.90
No CVD	0.58 (-8.49 to 9.64)	0.89	12.50 (-3.39 to 28.38)	0.12		
Diabetes	-1.56 (-16.16 to 13.04)	0.83	-4.52 (-26.68 to 17.65)	0.67	0.79	0.34
No diabetes	-1.00 (-9.91 to 7.92)	0.82	10.40 (-2.49 to 23.28)	0.11		
Dialysis vintage $\leq$ 2 years	6.62 (-8.67 to 21.89)	0.38	4.86 (-7.92 to 17.64)	0.45	0.88	0.33
Dialysis vintage > 2 years	-4.57 (-12.87 to 3.73)	0.28	7.58 (-12.61 to 27.76)	0.41		

CVD: cardiovascular disease; RKF: residual kidney function.

**Supplementary Table 4b:** Ejection fraction changes in hemodiafiltration versus hemodialysis in various subgroups of patients.

Subgroups	Mean change in EF in % ( $\Delta$ ) per year (95% CI)					
	HDF $\Delta$	P	HD $\Delta$	P	HDF versus HD P for slope	P for interaction time*HDF*subgroup
Age $\leq$ 64.9 years	-0.32 (-3.26 to 2.62)	0.83	-4.21 (-7.08 to -1.35)	0.005	0.90	0.27
Age > 64.9 years	-0.35 (-3.32 to 2.61)	0.81	-2.30 (-7.06 to 2.46)	0.34		
Male	-1.12 (-4.19 to 1.95)	0.47	-3.22 (-6.38 to -0.05)	0.047	0.22	0.81
Female	-0.60 (-4.24 to 3.03)	0.74	-3.39 (-7.48 to 0.69)	0.10		
RKF	-0.14 (-2.94 to 2.68)	0.92	-1.69 (-5.77 to 2.37)	0.41	0.57	0.75
No RKF	1.47 (-0.92 to 3.86)	0.23	-4.92 (-7.94 to -1.89)	0.002		
CVD	-0.37 (-3.76 to 3.02)	0.82	-2.76 (-6.44 to 0.92)	0.14	0.60	0.59
No CVD	-0.35 (-3.01 to 2.31)	0.79	-3.97 (-7.47 to -0.47)	0.027		
Diabetes	-2.31 (-5.87 to 1.25)	0.19	-2.09 (-8.04 to 3.88)	0.48	0.96	0.39
No diabetes	0.32 (-2.19 to 2.83)	0.80	-3.86 (-6.78 to -0.95)	0.010		
Dialysis vintage $\leq$ 2.0 years	-1.23 (-4.00 to 1.53)	0.38	-2.66 (-6.83 to 1.51)	0.21	0.22	0.67
Dialysis vintage > 2.0 years	0.79 (-2.34 to 3.92)	0.61	-3.83 (-6.97 to -0.69)	0.018		

CVD: cardiovascular disease; RKF: residual kidney function.

**Supplementary Table 4c:** Pulse wave velocity changes in hemodiafiltration versus hemodialysis in various subgroups of patients.

Subgroups	Mean change in PWV in m/s ( $\Delta$ ) per year (95% CI)					
	HDF		HD		HDF versus HD	
	$\Delta$	P	$\Delta$	P	P for slope	P for interaction time*HDF*subgroup
Age $\leq$ 61.7 years	-0.15 (-1.03 to 0.74)	0.73	-0.01 (-0.80 to 0.79)	0.99	0.99	0.95
Age > 61.7 years	-0.23 (-1.75 to 1.30)	0.76	-0.24 (-1.48 to 1.00)	0.69		
Male	-0.13 (-1.26 tot 1.01)	0.82	0.02 (-0.92 to 0.96)	0.96	0.81	0.94
Female	-0.36 (-1.68 to 0.96)	0.56	-0.28 (-1.28 to 0.73)	0.57		
RKF	-0.49 (-1.65 to 0.67)	0.39	0.12 (-0.83 to 1.08)	0.79	0.43	0.28
No RKF	0.35 (-0.84 to 1.54)	0.53	-0.25 (-1.18 to 0.68)	0.58		
CVD	0.14 (-1.40 to 1.69)	0.85	0.23 (-1.08 to 1.55)	0.70	0.91	0.88
No CVD	-0.58 (-1.34 to 0.30)	0.20	-0.24 (-1.04 to 0.57)	0.55		
Diabetes	-0.88 (-3.49 to 1.73)	0.48	-0.03 (-2.30 to 2.85)	0.98	0.51	0.48
No diabetes	0.08 (-0.65 to 0.78)	0.86	-0.14 (-0.83 to 0.56)	0.69		
Dialysis vintage $\leq$ 2.0 years	-0.10 (-0.86 to 0.65)	0.78	0.05 (-0.99 to 1.09)	0.92	0.99	0.84
Dialysis vintage > 2.0 years	-0.30 (-2.04 to 1.46)	0.73	-0.21 (-1.15 to 0.73)	0.65		

CVD: cardiovascular disease; RKF: residual kidney function

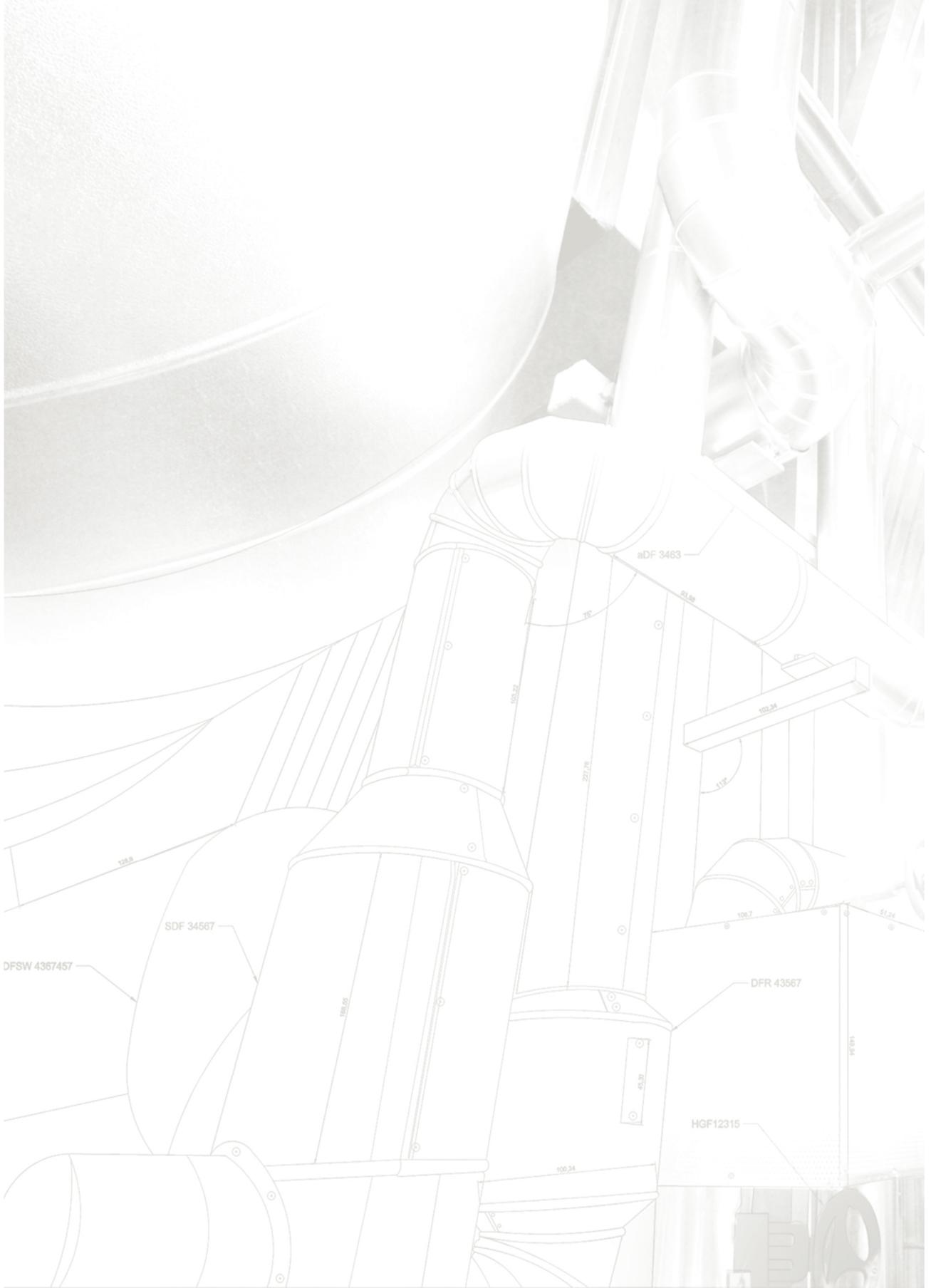


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## Chapter 4

# Left ventricular mass, ejection fraction and pulse wave velocity over time in end stage kidney disease patients.

*Submitted for publication*

Ira M. Mostovaya,<sup>1</sup> Michiel L. Bots,<sup>2</sup> Marinus A. van den Dorpel,<sup>3</sup> Muriel P.C. Grooteman,<sup>4,5</sup> Otto Kamp,<sup>5,6</sup> Renée Levesque,<sup>7</sup> Piet M. ter Wee,<sup>4,5</sup> Menso J. Nubé,<sup>4,5</sup> Peter J. Blankestijn.<sup>1</sup>

<sup>1</sup>Department of Nephrology, University Medical Center Utrecht, Utrecht

<sup>2</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht

<sup>3</sup>Department of Internal Medicine, Maastad Hospital, Rotterdam

<sup>4</sup>Department of Nephrology, VU Medical Center, Amsterdam

<sup>5</sup>Institute for Cardiovascular Research VU Medical Center (ICaR-VU), VU Medical Center, Amsterdam, the Netherlands

<sup>6</sup>Department of Cardiology, VU Medical Center, Amsterdam

<sup>7</sup>Department of Nephrology, Centre Hospitalier de l'Université de Montréal, St. Luc Hospital, Montréal, Canada

**Abstract****Objective**

Increased left ventricular mass (LVM), decreased ejection fraction (EF) and increased pulse wave velocity (PWV) are related to overall and cardiovascular mortality in end stage kidney disease (ESKD) patients. The aim of this study is to identify determinants of rate of change of LVM, EF and PWV over time in this population.

**Methods**

Analysis was performed with data of two subgroups from the CONvective TRANsport Study (CONTRAST): 342 patients who underwent echocardiography and 189 who had PWV measurements. Linear mixed models were used to study determinants of rate of change of LVM, EF and PWV.

**Results**

Patients had a mean age of 63 years and 61% were male. At baseline, median LVM was 238 g (IQR: 183 – 279g) and median EF was 65% (IQR: 55-72%). Median PWV was 9.82 m/s (IQR: 7.5 – 12.0m/s). Over time, LVM (2.13 g/year, 95% CI: -4.16 to 8.41, p=0.27) and PWV (-0.15 m/s per year, 95% CI:-0.68 to 0.38, p=0,32) remained stable, while a borderline significant decrease was found for EF (1.59%/year, 95%CI -3.33 to 0.15, p=0.07). None of the baseline factors: age, gender, residual renal function, dialysis vintage, history of cardiovascular disease, diabetes, blood pressure, ultrafiltration volume, phosphate levels or phosphate binder use were related to rate of change of LVM, EF or PWV.

**Conclusion**

LVM and PWV remain stable within a three year interval, while EF seems to decrease over time. Traditional risk factors do not explain differences in rate of change of these parameters.

## **Introduction**

Cardiovascular disease is an important cause of morbidity and mortality in patients with ESKD. [7] The origin of cardiovascular disease is multifactorial: retention of uremic toxins, micro-inflammation, atherosclerosis, a fluctuating extracellular fluid volume and hypertension have all been implicated in the development of accelerated cardiovascular pathology. [10, 30]

Important alternative markers of cardiovascular risk are left ventricular mass (LVM), ejection fraction (EF) and pulse wave velocity (PWV), the latter as a measure of arterial stiffness. An increased LVM is a sign of heart disease when the cardiac afterload is increased. The EF, or the volumetric fraction of the blood pumped out of the ventricle per stroke, decreases when myocardial damage occurs. PWV, the rate at which pressure waves move down an artery, increases when arteries become stiffer, for example due to damage by hypertension and atherosclerosis.

LVM, EF and PWV have all been repeatedly demonstrated to be relevant predictors of cardiovascular morbidity and mortality in ESKD patients. [4, 12, 24, 27, 29] Regression of LVM has been shown to be associated with a more favourable outcome in this population. [6] Studies on the natural course of LVM in ESKD patients have reported either stabilization or an increase of these parameters over a period of 18-24 months, [17, 29] while the natural course of EF is to slowly decrease. [20, 29] Regarding the natural course of PWV in ESKD patients, either a stabilization or increase has been reported over a period of 1.2 – 3 years. [16, 25]

Although some information is available on the natural course of LVM, EF and PWV, the factors that influence these changes have not been studied elaborately. It is not clear whether patient characteristics influence rate of change of LVM, EF and PWV or not. The aim of this paper is to study the natural history of LVM, EF and PWV in ESKD patients from the CONTRAST cohort during long term follow-up (up to three years) and investigate the influence of conventional risk factors at baseline on these parameters and their changes over time.

## **Materials and methods**

### **Patients**

Analysis was performed with data of two subgroups from the CONvective TRANsport Study (CONTRAST): 342 patients who underwent echocardiography and 189 who had PWV measurements from 15 dialysis centres (14 Dutch centers and 1 Canadian center). CONTRAST has been designed to investigate the effects of increased convective transport by online HDF as compared with low-flux HD on all-cause mortality and cardiovascular morbidity and mortality (ISRCTN38365125). [9, 19] This subset of the population consisted of patients who were treated in a medical center where performance of additional echocardiography measurements and pulse wave velocity measurements was logistically possible. Furthermore, patients signed informed consent for these additional measurements.

Patients were eligible if treated with haemodialysis two or three times a week, for at least 2 months, with a minimum dialysis urea  $\text{spKt/V} \geq 1.2$ . Furthermore, patients had to be able to understand the study procedures. Exclusion criteria were age  $< 18$  years, treatment by HDF or high flux HD in the 6 months preceding randomization, severe incomppliance defined as non-adherence to the dialysis prescription, a life expectancy  $< 3$  months due to non-kidney disease and participation in another clinical intervention trial evaluating cardiovascular outcomes. Randomization was stratified by participating center. From June 2004 until January 2010 a total of 714 patients were enrolled in CONTRAST.

CONTRAST was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating dialysis centres. Written informed consent was obtained from all patients prior to enrolment.

### **Dialysis procedures**

Before randomization, all patients had to be stable with a minimum dialysis single-pool  $\text{Kt/V}$  for urea ( $\text{spKt/V}_{\text{urea}}$ ) of 1.2. Treatment times were fixed during follow-up in both treatment arms unless  $\text{spKt/V}_{\text{urea}}$  was less than 1.2. Online HDF was performed in the post-dilution mode; target volume was 6L/hour. Synthetic high-flux dialyzers were used for both HDF and HD (polysulphone[Fresenius Medical Care, Bad Homburg, Germany]; or

polyamide [Gambro AB, Stockholm, Sweden]). All patients were treated with ultrapure dialysis fluid, defined as containing less than 0.1 colony forming units per mL and less than 0.03 endotoxin units per mL. Routine patient care was performed according to the guidelines of the Quality of Care Committee of the Dutch Federation of Nephrology.

### **Data collection**

At baseline standardized forms were used to collect demographical, clinical and laboratory data. Type of vascular access, duration of dialysis (dialysis vintage), and medical history (presence of diabetes mellitus (DM), history of kidney transplantation and previous cardiovascular disease (CVD)) were also assessed. A history of cardiovascular disease was defined as a confirmative answer on any of the questions regarding a previous acute myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, angina pectoris, stroke, transient ischemic attack, intermittent claudication, amputation, percutaneous transluminal angioplasty, peripheral bypass surgery and renal percutaneous transluminal angioplasty. Dialysis vintage was determined as the sum of time patients were treated with HD or PD before inclusion in CONTRAST. The mean of three consecutive post-dialysis weights was used to calculate weight at baseline. Patients' height was determined once at inclusion in the study. Body mass index (BMI) was computed as the quotient of weight by height squared. Body surface area (BSA) was computed using the formula by Gehan and George. [8]

Patients with a urinary production of less than 100mL per day were considered anuric. In patients with residual diuresis of more than 100mL per day, interdialytic 24 hour urinary samples were collected.

At each three-monthly visit, data on clinical events, clinical characteristics, dialysis treatment, medication, and standard laboratory values were recorded. Standard laboratory samples were analysed in the local laboratories of the participating hospitals by standard laboratory techniques. Systolic and diastolic blood pressure was also assessed at these visits: blood pressure was measured three times before and after dialysis using a standard electronic sphygmomanometer. The average of these measurements was computed and used for analysis.

**Table 1:** Baseline characteristics of study population.

	<b>Total Cohort n=714</b>	<b>LVM cohort n=327</b>	<b>PWV cohort n=123</b>
<b>Demographic data</b>			
Male gender	445 (62%)	200 (61%)	82 (67%)
Race, caucasian	304 (85%)	263 (80%)	101 (82%)
Age, years	64.1 ± 13.7	63.0 ± 13.3	60.0 ± 13.9
<b>Anthropometrics</b>			
Length (cm)	168 ± 10	168 ± 11	170 ± 10
Weight (kg)	72.4 ± 14.4	72.1 ± 14.3	71.3 ± 12.9
BMI (kg/m <sup>2</sup> )	25.4 ± 14.4	25.5 ± 4.9	24.7 ± 3.8
Body Surface Area (m <sup>2</sup> )	1.85 (1.23 - 2.58)*	1.85 (1.23 - 2.51)*	1.85 (1.36 - 2.58)*
<b>Dialysis Properties</b>			
Dialysis vintage (years)	1.8 (1.0 - 3.7)*	2.00 (2.00 - 16.3)*	2.00 (2.00 - 4.33)*
Duration of dialysis (minutes)	226 ± 23	225 ± 23	229 ± 25
Blood flow	300 (300 - 348)*	300 (200 - 400)*	289 (300 - 227)*
spKt/Vurea	1.40 ± 0.22	1.39 ± 0.20	1.30 (1.24 - 0.97)*
AV fistula	279 (78%)	260 (80%)	105 (85%)
Ultrafiltration volume (L/treatment)	1.88 ± 0.05	1.85 ± 0.06	1.88 ± 0.05
<b>Patient History</b>			
Cardiovascular disease	313 (44%)	146 (45%)	50 (41%)
Diabetes	170 (24%)	83 (25%)	19 (32%)
Kidney Transplant	78 (11%)	30 (9%)	17 (14%)
Patients with residual kidney function	186 (52%)	171 (52%)	62 (50%)
Smoking	133 (19%)	66 (20%)	27 (22%)
<b>Laboratory parameters</b>			
Hemoglobin (g/dL)	7.32 ± 0.81	7.30 ± 0.78	7.40 ± 0.75
Phosphate (mmol/L)	1.64 ± 0.49	1.67 ± 0.50	1.72 ± 0.60
Beta-2 microglobulin (mg/L)	31.5 ± 14	32.5 ± 13.7	32.9 ± 10.8
Albumin (g/L)	40.4 ± 3.8	41.2 (25.5 - 52.5)*	36.4 ± 4.7
Creatinin (μmol/L), pre-dialysis	861 ± 255	883 ± 252	843 ± 277
<b>Therapeutic parameters</b>			
Erythropoietin therapy	314 (88%)	295 (91%)	114 (93%)
Diuretic therapy	250 (35%)	129 (39%)	36 (29%)
Beta-blocker therapy	184 (51%)	174 (53%)	63 (51%)
RAS inhibitor therapy	179 (50%)	162 (50%)	71 (58%)
Lipid lowering therapy	196 (55%)	152 (47%)	56 (46%)
Phosphate binding therapy	551 (77%)	242 (74%)	100 (81%)
Platelet aggregators	111 (34%)	122 (36%)	17 (14%)
<b>Hemodynamic measurements</b>			
Systolic blood pressure (mmHg)	147 ± 21	142 ± 19	148 ± 24
Diastolic blood pressure (mmHg)	75 ± 12	74 ± 10	78 ± 12

LVEDD (mm)	-	10 (9 – 11)*	-
LVESD (mm)	-	32 (27 – 38)*	-
EFLV (%)	-	65 (55 – 72)*	-
LVM (g)	-	227 (183 – 279)	-
LVMi (g/m <sup>2</sup> )	-	124 (100 – 153)*	-
LVMi (g/height <sup>2.7</sup> )	-	31.2 (23.8 – 38.1)*	-
PWV (m/s)	-	-	9.82 ± 3.28

\*median and IQR (P25-P75) are shown

### Echocardiography measurements

Participants in 15 centres were requested to undergo echocardiography on top of the standard CONTRAST data collection, at baseline, after 6 months, after 12 months and annually thereafter. The measurements were carried out using standard American Society of Echocardiography protocols. [22] Transthoracic M-mode echocardiography studies were performed on a mid-week non-dialysis day and <24 hours after a dialysis session by an echocardiographer at the participating local hospital. From the parasternal long axis position the left ventricular end-diastolic diameter (LVEDD), end-systolic diameter (LVESD) as well as the posterior and septal wall thickness were determined. The ultrasound investigations were recorded digitally and then assessed by an independent experienced echocardiographer at the core laboratory (Vrije Universiteit Medisch Centrum, Amsterdam, the Netherlands), who was blinded for all other patient data. LVM was calculated using the formula of Devereux and Reickek [5], modified in accordance with the recommendations of the American Society of Echocardiography. [22] EF was computed automatically by the echocardiography software.

### PWV measurements

Participants in 8 centres were requested to undergo aortic pulse wave velocity (PWV) measurements on top of the standard CONTRAST data collection at baseline and annually thereafter. The SphygomoCor system (PWV system and BP analysis system; PWV Inc., Sydney, Australia) was used to assess PWV and analyze the arterial pulse contours. Pulse contours were obtained by applanation tonometry at the carotid artery and femoral artery. With this technique, the artery is pressed gently [11] with a pencil-type probe that

incorporates a high-fidelity strain-gauge transducer at the tip with a small pressure-sensitive ceramic sensor area (Millar Instruments, Houston, TX). To determine PWV, pressure waves at two sites were recorded sequentially: carotid-femoral for aortic PWV. Wave transit time was calculated by the system software using the R-wave of simultaneously recorded ECG as reference frame. [26] The distance travelled by the pulse wave was measured over the body surface as the distance between the recording sites at the femoral or radial artery to the suprasternal notch minus the distance from the recording site at the carotid artery to the suprasternal notch as has been described by others. [26] PWV was calculated as  $PWV \text{ (in m/s)} = D/t$ . The PWV was measured over 10 consecutive heartbeats to cover a complete respiratory cycle. We used the average of three measurements. The reproducibility of this method in our hands is high. [13, 26]

### **Outcome**

The primary study aim in the present analysis was the rate of change per year of LVM, EF and PWV, based on 4 and 3 years of follow-up respectively.

The secondary study outcome was the effect of baseline patient characteristics on the rate of change over time of LVM and PWV.

### **Data analysis**

Data were reported as means with standard deviations, medians with ranges, or proportions when appropriate.

Linear mixed effect models were performed with a random intercept and random slope or a random intercept alone (depending on the lowest Aikaike's information criterion value) to model changes over time of LVM, EF and PWV. Subsequently, the changes over time were modelled with a linear mixed effect model in strata of the conventional risk factors. Each model was adjusted for dialysis modality as well as the other baseline risk factors by adding them as fixed effects to the model. Differences between these strata were tested with the interaction term of the conventional risk factor with time. For continuous variables such as age and dialysis vintage, the interaction terms age\*time and vintage\*time were tested, with age and vintage as continuous variables. Continuous

variables were also stratified below or above the median for the patient group under study, to show differences between young and old patients, patients with a short and long dialysis vintage and so on. For accuracy we also repeated these analyses for rate of change of LVM indexed for BSA and for height<sup>2,7</sup>.

Results were considered statistically significant when  $p < 0.05$  (two-sided). All calculations were made by use of a standard statistical package (SPSS for Windows Version 20.0.1; SPSS Inc. Headquarters, Chicago, Illinois, US).

## **Results**

The baseline demographic, anthropometric, biochemical, therapeutic and dialysis-related characteristics of the patients in whom LVM and PWV were measured are depicted in Table 1. 342 patients participating in CONTRAST underwent repeated echocardiography, and 189 underwent repeated PWV measurements. A total of 113 patients underwent both the echocardiography and the PWV assessment. In total, 933 echocardiography examinations and 326 PWV measurements were performed over a period of 4 and 3 years respectively.

At baseline, the median LVM was 238 g (IQR: 183 – 279g) and median EF was 65% (IQR: 55-72%). The median PWV was 9.82 m/s (IQR: 6.5 – 12.0m/s).

Patients who had echocardiography had similar characteristics as the other CONTRAST patients who did not receive echocardiography (Supplementary Table 1a). Patients who received PWV measurements were younger, had a lower body mass index (BMI) and a higher diastolic blood pressure than the other CONTRAST patients (Supplementary Table 1b).

The participant flowchart of the entire population, the LVM cohort and the PWV cohort are shown in the supplementary Figures 1 and 2 respectively.

**Table 2:** Annual rate of change of LVM (grams) in various clinical strata.

Stratum	Estimate slope	95% CI	p-value slope	p-value interaction term
Age < 64.9 years	4.44	-8.41 to 17.29	0.44	Age x Time 0.65
Age > 64.9 years	5.53	-4.67 to 15.74	0.26	
Men	4.04	-6.65 to 14.73	0.42	Gender x Time 0.76
Women	6.03	-6.79 to 18.85	0.29	
Residual Kidney Function	4.84	-9.19 to 18.86	0.39	RKF x Time 0.91
No Residual Kidney Function	4.61	-6.72 to 15.94	0.40	
Cardiovascular disease	0.26	-13.28 to 13.80	0.96	CVD x Time 0.32
No Cardiovascular disease	8.54	-1.73 to 18.80	0.10	
Diabetes Mellitus	5.84	-2.90 to 14.59	0.83	DM x Time 0.27
No Diabetes Mellitus	7.21	-2.78 to 17.19	0.14	
Dialysis Vintage < 2.0 years	1.12	-20.12 to 22.36	0.64	Vintage x Time 0.25
Dialysis Vintage > 2.0 years	9.38	-1.77 to 20.53	0.09	
Pre-dialysis SBP <147 mmHg	10.00	-3.72 to 43.80	0.10	SBP x Time 0.90
Pre-dialysis SBP >147 mmHg	1.23	-7.46 to 12.51	0.86	
UF < 1.87 L/treatment	2.75	-6.34 to 12.84	0.85	UF x Time 0.48
UF >1.87 L/treatment	29.45	2.26 to 56.64	0.034	
Phosphate binder use	6.90	-15.81 to 29.61	0.32	Phosphate b x Time 0.70
No phosphate binder use	7.71	-3.11 to 38.5	0.078	
Serum phosphate <1.58 mmol/L	10.33	-11.52 to 32.18	0.35	Phosphate x Time 0.92
Serum phosphate >1.58 mmol/L	11.33	-27.23 to 49.91	0.56	

Estimates slope indicate mean longitudinal change per year in LVM associated with the presence or absence of the conventional risk factor.

All analyses on strata were adjusted for age, sex, presence of diabetes, presence of cardiovascular disease, presence of residual kidney function, dialysis vintage and allocated treatment (excluding the conventional risk factor of the stratum under study).

UF: ultrafiltration fluid volume; SBP: systolic blood pressure

**Table 3:** Annual rate of change of EF (%) in various clinical strata.

Stratum	Estimate slope	95% CI	p-value slope	p-value interaction term
Age < 64.9 years	-2.30	-5.57 to 0.96	0.11	Age x Time 0.49
Age > 64.9 years	-0.92	-3.77 to 1.94	0.46	
Men	-1.70	-4.45 to 1.05	0.17	Gender x Time 0.50
Women	-1.54	-4.20 to 1.11	0.21	
Residual Kidney Function	-0.65	-3.54 to 2.24	0.58	RKF x Time 0.14
No Residual Kidney Function	-2.40	-5.25. to 0.46	0.08	
Cardiovascular disease	-1.73	-4.58 to 1.11	0.18	CVD x Time 0.74
No Cardiovascular disease	-1.63	-4.63 to 1.37	0.20	
Diabetes Mellitus	-2.13	-8.67 to 4.42	0.30	DM x Time 0.76
No Diabetes Mellitus	-1.34	-3.46 to 0.77	0.18	
Dialysis Vintage < 2.0 years	-1.67	-4.00 to 0.67	0.14	Vintage x Time 0.95
Dialysis Vintage > 2.0 years	-1.17	-1.80 to 2.57	0.59	
Pre-dialysis SBP <147 mmHg	-2.84	-7.50 to 2.27	0.54	SBP x Time 0.40
Pre-dialysis SBP >147 mmHg	-0.55	-2.33 to 1.23	0.72	
UF < 1.87 L/treatment	-0.12	-1.91 to 1.68	0.90	UF x Time 0.83
UF >1.87 L/treatment	-1.94	-6.40 to 8.06	0.78	
Phosphate binder use	-0.76	-7.51 to 1.53	0.17	Phosphate binder x Time 0.55
No phosphate binder use	-1.11	-3.15 to 0.94	0.29	
Serum phosphate <1.58 mmol/L	-1.33	-3.45 to 0.80	0.21	Phosphate x Time 0.98
Serum phosphate >1.58 mmol/L	-1.28	-3.18 to 0.61	0.19	

Estimates slope indicate mean longitudinal change per year in EF associated with the presence or absence of the conventional risk factor.

All analyses on strata were adjusted for age, sex, presence of diabetes, presence of cardiovascular disease, presence of residual kidney function, dialysis vintage and allocated treatment (excluding the conventional risk factor of the stratum under study).

UF: ultrafiltration fluid volume; SBP: systolic blood pressure.

**Table 4:** Annual rate of change of PWV (m/s) in various clinical strata.

Stratum	Estimate slope	95% CI	p-value slope	p-value interaction term
Age < 61.8 years	-0.37	-1.03 to 0.29	0.45	Age x Time
Age > 61.8 years	0.10	-0.30 to 0.72	0.33	0.84
Men	-0.31	-1.11 to 0.50	0.54	Gender x Time
Women	-0.07	-1.18 to 1.05	0.80	0.86
Residual Kidney Function	0.30	-1.03 to 1.36	0.66	RKF x Time
No Residual Kidney Function	-0.30	-1.39 to 0.80	0.78	0.78
Cardiovascular disease	-0.36	-1.46 to 0.70	0.55	CVD x Time
No Cardiovascular disease	-0.14	-1.36 to 1.08	0.91	0.75
Diabetes Mellitus	-0.03	-0.08 to 0.78	0.94	DM x Time
No Diabetes Mellitus	-0.58	-1.46 to 0.29	0.48	0.76
Dialysis Vintage < 2.0 years	-0.26	-1.75 to 1.23	0.89	Vintage x Time
Dialysis Vintage > 2.0 years	-0.01	-0.55 to 0.47	0.94	0.45
Pre-dialysis SBP <147 mmHg	-0.03	-0.98 to 0.44	0.55	SBP x Time
Pre-dialysis SBP >147 mmHg	-0.18	-1.32 to 0.78	0.34	0.75
UF < 1.87 L/treatment	-0.14	-0.67 to 0.54	0.87	UF x Time
UF >1.87 L/treatment	-0.02	-1.17 to 1.14	0.99	0.54
Phosphate binder use	-0.32	-2.39 to 1.66	0.60	Phosphate binder x Time
No phosphate binder use	-0.04	-1.16 to 1.98	0.84	0.88
Serum phosphate <1.61 mmol/L	-0.10	-1.10 to 0.54	0.48	Phosphate x Time
Serum phosphate >1.61 mmol/L	-0.26	-1.16 to 0.98	0.81	0.89

Estimates slope indicate mean longitudinal change per year in PWV associated with the presence or absence of the conventional risk factor.

All analyses on strata were adjusted for age, sex, presence of diabetes, presence of cardiovascular disease, presence of residual kidney function, dialysis vintage and allocated treatment (excluding the conventional risk factor of the stratum under study).

UF: ultrafiltration fluid volume; SBP: systolic blood pressure.

**LVM over time**

In the echocardiography study population, during 4 years of follow-up, LVM did not change significantly over time (adjusted for treatment modality rate of change: 2.13 g/year, 95% CI: -4.16 to 8.41,  $p=0.27$ ). No statistically significant relations were found between conventional baseline risk factors age, gender, residual renal function, dialysis vintage, history of cardiovascular disease, diabetes, pre-dialysis systolic blood pressure, ultrafiltration volume, phosphate levels or phosphate binder use with rate of change over time of LVM (Table 2).

When analyses were repeated with LVM indexed for BSA or height<sup>2.7</sup>, the results were similar (data not shown).

**EF over time**

During 4 years of follow-up, EF decreased, albeit not significantly, over time (adjusted for treatment modality rate of change: 1.59%/year, 95%CI -3.33 to 0.15,  $p=0.07$ ).

No statistically significant relations were found between conventional baseline risk factors age, gender, residual renal function, dialysis vintage, history of cardiovascular disease, diabetes, pre-dialysis systolic blood pressure, ultrafiltration volume, phosphate levels or phosphate binder use with rate of change over time of EF (Table 3).

**PWV over time**

In the PWV study population, during 3 years of follow-up PWV did not change significantly over time (adjusted for treatment modality rate of change: -0.15 m/s per year, 95% CI: -0.68 to 0.38,  $p=0.32$ ). No statistically significant relations were found between conventional baseline risk factors age, gender, residual renal function, dialysis vintage, history of cardiovascular disease, diabetes, pre-dialysis systolic blood pressure, ultrafiltration volume, phosphate levels or phosphate binder use with rate of change over time of PWV (Table 4).

### **Discussion**

In this study, performed in a population of ESKD patients treated with chronic intermittent hemodialysis or hemodiafiltration, we showed that LVM and PWV did not change significantly over time during a period of 3-4 years, while EF decreased, albeit not significantly. Nor were rates of change of LVM, EF and PWV different in subgroups of conventional cardiovascular risk factors.

#### **LVM, EF and PWV changes over time**

Earlier observational studies have described that patients receiving conventional HD experience either an increase of LVM over time, or no change [1, 17, 29], which is in accordance with our findings. In an observational study in 155 patients with a follow-up of 2 years, MacMahon described a relation between a decrease of LVM and younger age [17], a finding that we could not confirm. However, the analysis was performed in pre-dialysis and ESKD patients combined, and patients were approximately 10 years younger than the CONTRAST population. [17]

Zoccali et al showed in an observational study in 161 hemodialysis patients, followed for 1.5 years that LVMi (indexed for height<sup>2.7</sup>) increases over time by 4g/m<sup>2.7</sup> (p<0.001) while EF decreases by 0.9%, although this decrease was not significant (p=0.29). These results are more or less comparable to our findings.

Bansal et al showed in an observational study in 190 patients with advanced CKD progressing to ESKD, followed for 2 years, that LVM remained stable, while a decrease in EF (mean 53% to 50%, p=0.002) was observed. Rate of change of LVM or EF was not different in subgroups of age, race and diabetes. [1] These results are in accordance with our findings: a decrease of 3% of EF in two years versus our 1.6% decrease in EF per year, although the decrease in EF was borderline significant in our population. Of note, our population consisted of prevalent dialysis patients, while Bansal et al performed echocardiographies before and after progression to ESKD. [1]

In an observational study (n=148) Matsumae et al followed HD patients for 3 years and described that PWV could either decrease (n=54), increase slowly ( $\Delta$ PWV: 0-0.33m/s per

year) (n=47) or increase rapidly ( $\Delta$ PWV:  $>0.33\text{m/s}$  per year) (n=47) over time, while overall no significant change was found. [21] This is in accordance with our finding that PWV does not change significantly over time. However Matsumae et al also showed that age was associated with annual change in PWV. [21] We could not confirm these findings, nor in subgroups of age, nor when age was entered as a continuous variable into the analysis. A recent observational study by Utescu et al in 109 hemodialysis patients followed for a period of 1.2 years reported a significant ( $0.9\text{m/s}$  per year,  $p<0.001$ ) increase in PWV over time. No differences in rate of change of PWV was found in subgroups of age, atherosclerotic cardiovascular disease, diabetes and dialysis vintage, which is similar to our findings. [25]

LVM, EF and PWV are all important risk factors of mortality and cardiovascular disease in ESKD patients. [2, 4, 28] Regression of LVM and PWV and stabilization of EF could potentially be beneficial to improve prognosis. In our study, despite elaborate treatment and extensive efforts these risk factors remain stable over time; EF even seems to decrease. Apparently it is difficult to effectuate amelioration of LVM, EF and PWV in this final phase of chronic kidney disease, even in subgroups of patients. Emphasis would better be placed on prevention of achieving high values of LVM and PWV and low values of EF in this population.

Another possibility could be to intensify the treatment of ESKD patients further. For example, a randomized trial in 120 dialysis patients (60 receiving intervention) that nocturnal hemodialysis (8 hours, 2 times weekly) is associated with a decrease in PWV and LVMi. [3] A recent meta-analysis has also shown that frequent (2-8 hours  $>3$  times weekly) or extended hemodialysis ( $>4$  hours, 3 times weekly) is associated with a more beneficial progression of LVM and EF when compared to standard hemodialysis ( $<4$  hours, 3 times weekly). [23]

### **Echocardiography measurements**

In our analyses LVM was not indexed for body surface area, or divided by  $\text{height}^{2.7}$  as has been done in analogous studies. [14, 18, 21] A disadvantage of ratios is that the observed

relation may be due to the nominator, the denominator or both. Therefore in the present analyses we chose to use LVM only. Since mixed models take variability within patients into account, adjustment for body dimensions was automatically performed during the analysis. For accuracy, we studied the rate of change and determinants thereof for LVM indexed for body surface area and height<sup>2.7</sup> also, and found similar results as for LVM.

Measurement errors could be considered a possible explanation for finding no statistically significant associations. This is a multicentre trial which may increase measurement variability, despite a uniform trained protocol. Yet a central core lab quantified the LVM measurements thus aimed to reduce measurement variability. Furthermore, all LVM measurements were re-evaluated by a blinded experienced echocardiographer. Moreover, in line with other literature [15, 29], we found a significant graded relation between high LVM and an increased risk of overall and cardiovascular mortality in our population. [ref Mostovaya et al. "LVM and clinical events."]

#### **Strength and limitations**

This study had several limitations. First, not all patients participating in CONTRAST underwent echocardiographic examinations, and not all of those patients had PWV assessments. Therefore we might not have the power to demonstrate significant differences of LVM and PWV across subgroups of conventional risk factors, in particular for PWV as the sample size was rather small. Second, some patients dropped out or missed examinations during the follow-up period. Although mixed effect models can calculate rate of change well, with some missing data, the precision of the estimates decreases, increasing the likelihood of non-statistically significant results.

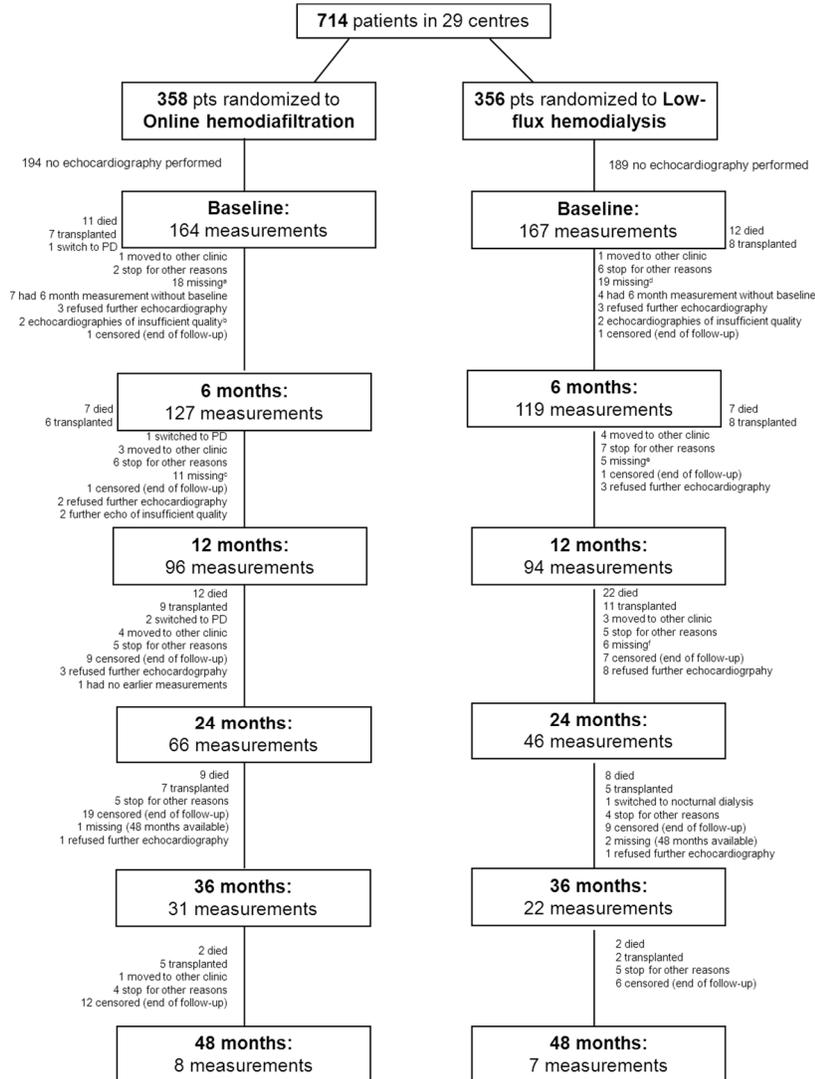
The strengths of this study are the concise data collection over a long follow-up, and the double independent analysis of the echocardiography recordings.

#### **Conclusion**

In conclusion, LVM and PWV remain stable over time during 3-4 years in prevalent hemodialysis patients, while EF seems to decrease. Rates of change of LVM, EF and PWV do not differ across subgroups of conventional risk factors.

## Supplementary Figures and Tables.

Supplementary Figure 1: Flowchart of LVM cohort.



<sup>a</sup>8 available at 12 months, 9 available at 24 months, 2 available at 36 months

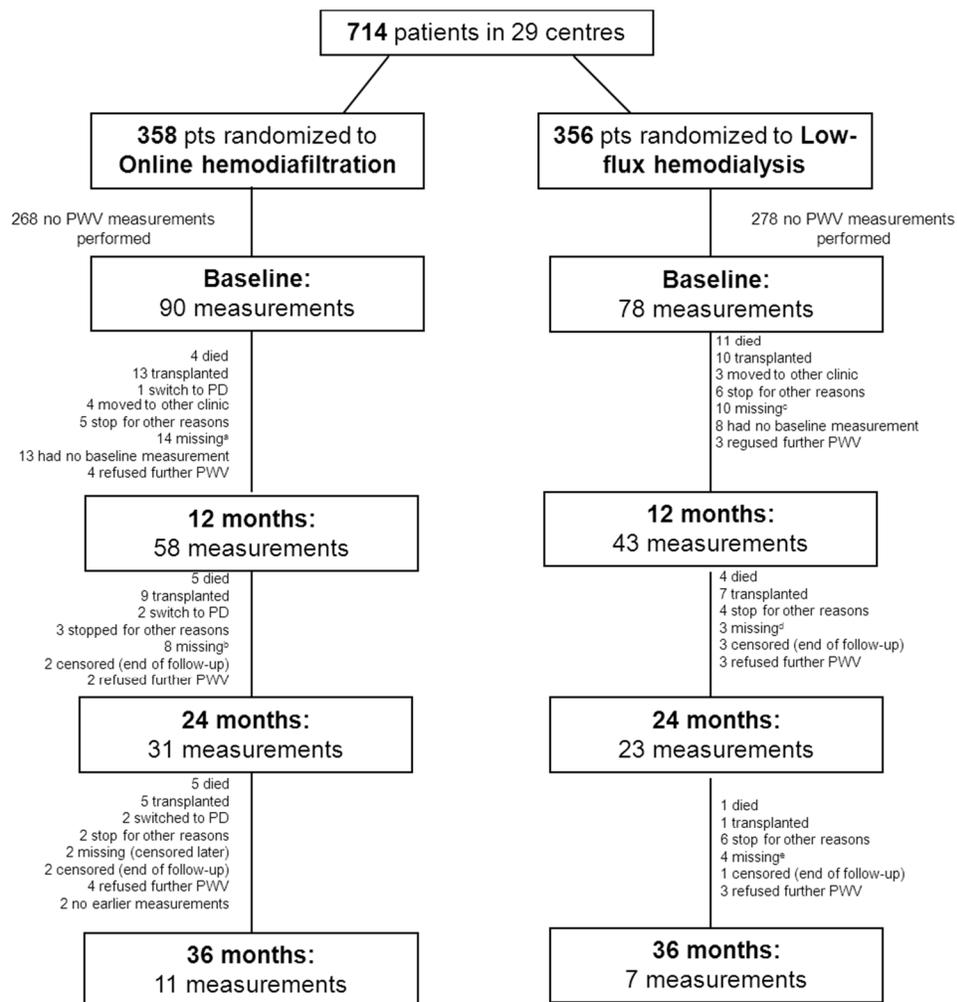
<sup>b</sup>3 echocardiographies of insufficient quality from baseline; 2 echocardiographies of insufficient quality from baseline measurement on

<sup>c</sup>6 available at 24 months, 5 available at 36 months

<sup>d</sup>10 available at 12 months, 9 available at 24 months

<sup>e</sup>5 available at 24 months

<sup>f</sup>6 available at month 36

**Supplementary Figure 2:** Flowchart of the PWV cohort.

<sup>a</sup>6 available at 24 months, 1 transplanted later, 2 died later, 5 censored (end of follow-up) later

<sup>b</sup>3 available at 36 months, 3 died later, 1 transplanted later, 1 censored (end of follow-up) later

<sup>c</sup>3 available at 24 months, 2 died later, 1 stopped for other reasons later, 4 censored (end of follow-up) later

<sup>d</sup>1 available at 36 months, 1 transplanted later, 1 censored later

<sup>e</sup>1 died later, 3 censored later

**Supplementary Table 1a:** Baseline characteristics of patients receiving echocardiography versus the other participants of the CONvective TRANsport Study.

	echo cor cohort n=331	other CONTRAST participants n=383	p-value
<b>Demographic data</b>			
Gender (% male)	61	63	0.60
Race (% caucasian)	81	87	0.06
Age (year)	63.1 ± 13.3	64.9 ± 13.9	0.08
<b>Anthropometrics</b>			
BMI (kg/m <sup>2</sup> )	25.4 ± 4.9	25.3 ± 4.7	0.78
Body Surface Area (m <sup>2</sup> )	1.84 ± 0.21	1.86 ± 0.21	0.41
<b>Dialysis Properties</b>			
Duration of dialysis (minute)	226 ± 23	227 ± 23	0.48
Blood flow (mL/minute)	309 ± 36	307 ± 41	0.48
Kt/V <sub>urea</sub>	1.39 ± 0.20	1.40 ± 0.23	0.28
<b>Comorbidities</b>			
Cardiovascular disease (%)	45	43	0.74
Diabetes (%)	27	23	0.29
Kidney Transplant (%)	9	12	0.16
Dialysis vintage (year)	2.92 ± 2.81	2.93 ± 2.84	0.96
Patients with residual renal function (%)	52	53	0.80
<b>Hemodynamic measurements</b>			
Systolic blood pressure, pre-dialysis (mm Hg)	148 ± 21	147 ± 22	0.45
Diastolic blood pressure, pre-dialysis (mm Hg)	77 ± 12	75 ± 13	0.07
Pulse pressure, pre-dialysis (mmHg)	72 ± 19	72 ± 17	0.75
Systolic blood pressure, post-dialysis (mmHg)	136 ± 22	134 ± 21	0.23
Diastolic blood pressure, post-dialysis (mm Hg)	72 ± 11	70 ± 12	0.16
Pulse pressure, post-dialysis (mmHg)	64 ± 19	64 ± 16	0.89

AV: arterio-venous; BMI: body mass index.

**Supplementary Table 1b:** Baseline characteristics of patients receiving PWV measurements versus the other participants of the CONvective TRANsport Study.

	aPWV cohort n=168	other CONTRAST participants n=546	p-value
<b>Demographic data</b>			
Gender (% male)	67	25	0.28
Race (% caucasian)	82	84	0.53
Age (year)	60.0 ± 13.9	64.9 ± 13.5	<b>&lt;0.001</b>
<b>Anthropometrics</b>			
BMI (kg/m <sup>2</sup> )	24.4 ± 2.6	25.6 ± 5.0	<b>0.015</b>
Body Surface Area (m <sup>2</sup> )	1.84 ± 0.20	1.85 ± 0.22	0.69
<b>Dialysis Properties</b>			
Duration of dialysis (minute)	229 ± 22	226 ± 23	0.18
Blood flow (mL/minute)	311 ± 31	307 ± 42	0.60
Kt/V <sub>urea</sub>	1.38 ± 0.18	1.40 ± 0.22	0.13
<b>Comorbidities</b>			
Cardiovascular disease (%)	41	45	0.43
Diabetes (%)	27	25	0.51
Kidney Transplant (%)	14	10	0.26
Dialysis vintage (year)	2.76 ± 2.77	2.96 ± 2.84	0.46
Patients with residual renal function (%)	50	53	0.58
<b>Hemodynamic measurements</b>			
Systolic blood pressure, pre-dialysis (mm Hg)	148 ± 24	148 ± 21	0.72
Diastolic blood pressure, pre-dialysis (mm Hg)	78 ± 12	75 ± 12	<b>0.013</b>
Pulse pressure, pre-dialysis (mmHg)	70 ± 21	72 ± 17	0.21
Systolic blood pressure, post-dialysis (mmHg)	135 ± 23	135 ± 21	0.80
Diastolic blood pressure, post-dialysis (mm Hg)	74 ± 12	70 ± 10	<b>0.002</b>
Pulse pressure, post-dialysis (mmHg)	61 ± 19	65 ± 17	0.08

AV: arterio-venous; BMI: body mass index.

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## Chapter 5

### Blood pressure in dialysis patients, relation with mortality and cardiovascular events.

### Results from the CONvective TRANsport Study (CONTRAST).

*Submitted for publication*

Ira M. Mostovaya,<sup>1</sup> Michiel L. Bots,<sup>2</sup> Marinus A. van den Dorpel,<sup>3</sup> Muriel P.C. Grooteman,<sup>4,5</sup> Piet M. ter Wee,<sup>4,5</sup> Menso J. Nubé,<sup>4,5</sup> Peter J. Blankestijn.<sup>1</sup>

<sup>1</sup>Department of Nephrology, University Medical Center Utrecht, Utrecht

<sup>2</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht

<sup>3</sup>Department of Internal Medicine, Maastad Hospital, Rotterdam

<sup>4</sup>Department of Nephrology, VU Medical Center, Amsterdam

<sup>5</sup>Institute for Cardiovascular Research VU Medical Center (ICaR-VU), VU Medical Center, Amsterdam, the Netherlands

**Abstract****Background**

Reports on the relation between blood pressure and clinical events in patients with end stage kidney disease (ESKD) are contradictory. The aim of this study is to determine what relation exists between different measures of blood pressure and all-cause mortality, cardiovascular (CV) mortality and (both fatal and non-fatal) CV events in this population.

**Methods**

Data from all 714 patients from the CONvective TRANsport STudy (CONTRAST), a randomized trial comparing online hemodiafiltration and low-flux hemodialysis, were used for this analysis. The primary outcome of CONTRAST was all-cause mortality. The main secondary endpoint was the composite of fatal and non-fatal major CV events. At baseline, blood pressure was measured three times pre-, and three times post-dialysis. The means of these pre- and post-dialysis measurements were computed, as well as the mean of all six blood pressure measurements. Adjusted Cox proportional hazard models were used to study the relation between different measures of blood pressure and clinical events.

**Results**

At baseline mean age was  $64 \pm 14$  years, and 445 (62%) of patients were male. After a median follow-up of 2.9 (range 0.4-6.6) years 269 patients died and 228 (83 fatal) had a cardiovascular event. Increased DBP was gradually related to all-cause mortality (hazard ratio (HR): 1.49, 95%CI: 1.06 to 2.10, and HR: 1.40, 95%CI: 1.04 – 1.90 for upper and middle tertile), versus patients in the lowest tertile. SBP was not related to increased all-cause mortality of cardiovascular risk. Averaged blood pressure measurements provided the strongest relations as compared to pre or post dialysis measurements only.

**Conclusion**

DBP is more strongly related to mortality risk than SBP and PP in ESKD patients. The mean of both the pre- and the post-dialysis blood pressure measurements is a better predictor for mortality, and cardiovascular events when compared to only pre- or only post-measurements.

**Introduction**

Elevated blood pressure (BP) represents a large burden of morbidity and mortality in patients with end stage kidney disease (ESKD). (1) The prevalence of hypertension (140/90 mmHg or above) in ESKD patients is high: 58-86%, out of which two thirds is uncontrolled despite antihypertensive medication. (1;2)

The pathophysiology of elevated BP is multifactorial. Activation of the renin-angiotensin-aldosterone system through primary vascular disease scarring, increased sympathetic activity and altered endothelial cell function leading to impaired vasodilatation play an important role. (3-5) Other factors include reduced arterial compliance and calcification, increased intracellular calcium due to parathyroid hormone excess, erythropoietin administration or pre-existing hypertension. (1;6) One of the most important causes of elevated blood pressure in dialysis patients is volume excess. (7) ESKD patients have a low sodium excretory capacity combined with an increased sodium sensitivity, which leads to a sodium overload and an increase in extracellular volume (ECV). The expanded ECV causes an increased venous return and cardiac output. While cardiac output normalizes over time, BP is maintained due to an inappropriately increased total peripheral resistance, so that adequate perfusion of peripheral tissues can be preserved. (8)

Although it is widely accepted that ambulatory blood pressure measurements (ABPM) provide a superior estimation of mortality risk and risk of cardiovascular events when compared to momentary BP measurements (9), performing ABPMs in a large population is often not feasible. Therefore, the relation between momentary BP measurements and clinical outcome has been extensively studied. (10-17) However, it is not clear what type of blood pressure measurement (pre-dialysis, post-dialysis, the average) provides the strongest information with respect to CV or mortality risk. Most studies describe a relation between mortality and pre-dialysis BP measurements (10-12), although sometimes a relation between mortality and post-dialysis BP is emphasized. (13) Again another study shows results for both pre- and post-dialysis BPs and concludes that both pre- and post-dialysis SBP are related to cardiovascular mortality and that the relation is of the same magnitude. (14)

Data on the nature of the relation between BP and mortality are not consistent. Several large observational studies have shown a “U-shaped” relation between systolic BP (SBP) and mortality (11-13;15), while other describe a “reverse J-shaped” (11) or an inverse linear relation. (16;17) For pulse pressure (PP), a positive relation with mortality has been found, when PP is corrected for SBP. (13) However, very little is known about the relation between DBP and mortality: only one study describes a “U-shaped” relation between DBP and risk of death. (12)

The aim of this study is to determine what relation exists between different measures of blood pressure and all-cause mortality, cardiovascular (CV) mortality and (combined fatal and non-fatal) CV events in our population of dialysis patients. In the process we will also examine whether such a relationship is strongest for pre-dialysis blood pressure measures, post-dialysis blood pressure measures or the average of the pre- and post-dialysis measurements.

## **Materials and Methods**

### **Patients**

This study included patients participating in the CONvective TRansport STudy (CONTRAST): 714 hemodialysis patients from 29 dialysis centres (26 Dutch centers and 2 Canadian centers and 1 Norwegian center). CONTRAST has been designed to investigate the effects of increased convective transport by online HDF as compared with low-flux HD on all-cause mortality and cardiovascular morbidity and mortality (ISRCTN38365125). (18;19)

Patients with ESRD undergoing chronic intermittent hemodialysis for at least 2 months and aged  $\geq 18$  years were recruited from June 2004 through December 2009 and followed until December 31, 2010. Primary renal diagnoses were as follows: renal vascular disease (29%), diabetes mellitus (19%), primary glomerulopathy/GN (12%), interstitial nephropathy (9%), cystic kidney disease (7%), multisystem disease (4%), other (12%), or unknown (8%). Patients were eligible if treated with haemodialysis two or three times a week, for at least 2 months, with a minimum dialysis urea  $Kt/V \geq 1.2$  and who were able to understand the study procedures. Exclusion criteria were age  $< 18$  years, treatment by HDF

or high flux HD in the 6 months preceding randomization, severe non-compliance defined as non-adherence to the dialysis prescription, a life expectancy <3 months due to non-kidney disease and participation in another clinical intervention trial evaluating cardiovascular outcomes.

The study was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating dialysis centres. Written informed consent was obtained from all patients prior to enrolment.

### **Data collection**

Baseline patient and dialysis characteristics were used for this analysis: information on demography, anthropometrics, medical history, medication and standard laboratory values.

A history of cardiovascular disease was defined as a confirmative answer on any of the questions regarding a previous acute myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, angina pectoris, stroke, transient ischemic attack, intermittent claudication, amputation, percutaneous transluminal angioplasty, peripheral bypass surgery and renal percutaneous transluminal angioplasty.

Residual kidney function was defined as a diuresis of more than 100mL per 24 hours.

Standard laboratory samples were analysed in the local laboratories of the participating hospitals by standard laboratory techniques.

Serum albumin was measured in local hospitals with the bromcresol green method or bromcresol purple method and samples that were measured with the bromcresol purple method were converted to bromcresol green concentrations with the formula: bromcresol green = bromcresol purple + 5.5. (20)

The primary outcome of CONTRAST was all cause mortality. Deaths were reported within 24 hours to the data management centre by fax or email. The main secondary endpoint was a composite of fatal and non-fatal cardiovascular events. Cardiovascular events were defined as death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, therapeutic coronary procedure (percutaneous transluminal coronary angioplasty

**Table 1:** Baseline characteristics of the CONTRAST participants

Variable	CONTRAST participants (n=714)
<b>Demographic data</b>	
Male gender	445 (62%)
Race, caucasian	600 (84%)
Age (year)	64.1 ± 13.7
Smoking	133 (19%)
Region	
Netherlands	597 (84%)
Norway	15 (2%)
Canada	102 (14%)
<b>Anthropometrics</b>	
Length (cm)	1.69 ± 0.10
Weight, postdialysis (kg)	72.4 ± 14.4
Body Mass Index (kg/m <sup>2</sup> )	25.4 ± 4.8
Body Surface Area (m <sup>2</sup> )	1.85 ± 0.21
<b>Dialysis Properties</b>	
Hemodiafiltration	358 (50%)
Duration of dialysis (minutes)	226 ± 23
Blood flow (mL/minute)	308 ± 39
spKt/Vurea	1.40 ± 0.22
Vascular access	
Arterio-venous fistula	567 (80%)
Graft	100 (14%)
Central venous catheter	47 (6%)
<b>Comorbidities</b>	
Cardiovascular disease	313 (44%)
Diabetes	170 (24%)
Previous kidney transplant	78 (11%)
Dialysis vintage (years)	2.0 (1.0 - 4.0)*
Patients with residual kidney function	376 (53%)
<b>Laboratory parameters</b>	
Hemoglobin (g/dL)	7.3 ± 7.8
Hematocrit (%)	37 ± 4
Phosphate (mmol/L)	1.64 ± 0.49
Albumin (g/L)	40.4 ± 3.8

Creatinine, pre-dialysis ( $\mu\text{mol/L}$ )	861 $\pm$ 225
Beta-2-microglobulin (mg/L)	31.5 $\pm$ 14.0
eGFR ( $\text{mL}/\text{min}/1.73\text{m}^2$ )	3.2 (1.3 - 5.5)*
<b>Medication</b>	
Erythropoietin therapy	633 (89%)
Diuretic therapy	185 (26%)
Alpha blocker therapy	69 (10%)
Beta-blocker therapy	378 (53%)
RAAS inhibitor therapy	350 (49%)
Lipid lowering therapy	367 (51%)
Platelet aggregation inhibitor therapy	238 (33%)
<b>Hemodynamic measurements</b>	
Pre-dialysis systolic blood pressure (mmHg)	148 $\pm$ 22
Pre-dialysis diastolic blood pressure (mmHg)	76 $\pm$ 12
Pre-dialysis pulse pressure (mmHg)	72 $\pm$ 18
Pre-dialysis mean arterial pressure (mmHg)	100 $\pm$ 13
Post-dialysis systolic blood pressure (mmHg)	135 $\pm$ 21
Post-dialysis diastolic blood pressure (mmHg)	71 $\pm$ 12
Post-dialysis pulse pressure (mmHg)	64 $\pm$ 17
Post-dialysis mean arterial pressure (mmHg)	92 $\pm$ 13
Mean systolic blood pressure (mmHg)	141 $\pm$ 19
Mean diastolic blood pressure (mmHg)	73 $\pm$ 11
Mean pulse pressure (mmHg)	68 $\pm$ 16
Mean mean arterial pressure (mmHg)	96 $\pm$ 12

\* medians and interquartile ranges (P25 - P75) are shown

eGFR: estimated glomerular filtration rate; RAAS: renin angiotensin aldosterone system  
divide by 0.323; albumin in g/L to g/dL, divide by 10; creatinine in  $\mu\text{mol/L}$  to mg/dL divide by 88.4.

and/or stenting), therapeutic carotid procedure (endarterectomy and/or stenting), and vascular intervention (revascularisation, percutaneous transluminal angioplasty and/or stenting) or amputation. Congestive heart failure was excluded as a cardiovascular event, since the distinction with fluid overload is often difficult to make in patients with end stage renal disease.

Follow-up of patients with respect to mortality and non-fatal cardiovascular events was continued even after they stopped with the randomized treatment because of a renal

transplant (n= 151), a switch to peritoneal dialysis (n= 11), a move to another non-CONTRAST hospital (n=24) or a stop of participation for other reasons (n=53).

An independent Endpoint Adjudication Committee reviewed source documentation for all primary outcome events (deaths), as well as non-fatal cardiovascular events and infections.

Routine patient care was performed according to the guidelines of the Quality of Care Committee of the Dutch Federation of Nephrology.

### **Blood pressure measurements**

Systolic and diastolic blood pressure (SBP and DBP) was measured using a standard electronic sphygmomanometer. SBP and DBP were recorded before and after three consecutive dialysis sessions. The mean of the pre-dialysis measurements was considered the pre-dialysis SBP and DBP. The mean of the three post-dialysis measurements was considered the post-dialysis SBP and DBP. The mean of the pre-dialysis SBP and DBP and the post-dialysis SBP and DBP was defined as the mean SBP and mean DBP. Pulse pressure (PP) was computed as the difference between systolic and diastolic blood pressure, for pre-dialysis, post-dialysis and the mean. Mean arterial pressure (MAP) was computed as  $(SBP \cdot 1/3 + DBP \cdot 2/3)$  for pre-dialysis, post-dialysis and the mean thereof.

### **Data analysis**

Data were reported as proportions or as means with standard deviation (SD) or standard errors (SE) when appropriate. Normal distribution of variables and residuals was tested using the Kolmogorov-Smirnov test with Lilliefors significance correction.

The relations between the different BP measurements (pre-dialysis SBP, pre-dialysis DBP, pre-dialysis PP, pre-dialysis MAP, post-dialysis SBP, post-dialysis DBP, post-dialysis PP, post-dialysis MAP, mean SBP, mean DBP, mean PP, mean MAP) and all-cause mortality, as well as cardiovascular events and cardiovascular death were evaluated by Cox proportional hazards models, involving the time to the first relevant endpoint in any individual patient. For this analysis BP measurements were both tested as linear variables and divided into categories (tertiles). First crude analysis was presented. Second, variables

were identified that had an independent influence on the outcomes all-cause mortality, cardiovascular events and cardiovascular death by a backward elimination strategy with a cut-off value of  $p > 0.20$ . The following variables were included at the start in the Cox backward regression models: age, gender, body mass index, history of cardiovascular disease, diabetes, history of kidney transplantation, dialysis vintage, presence of residual diuresis,  $\text{spKt}/V_{\text{urea}}$ , estimated glomerular filtration rate (eGFR), hemoglobin, serum albumin, serum phosphate, serum creatinine, serum cholesterol, use of renin angiotensin aldosterone (RAAS) inhibitors, use of beta-blockers, use of alpha-blockers and use of diuretics. The survival models studying the relation between BP measures and clinical events were then adjusted for the determinants of all-cause mortality, cardiovascular events (fatal and non-fatal) and cardiovascular mortality respectively, as well as dialysis modality (intervention). When a risk trend changed direction (from positive to inverse or vice versa) after adjustment, adjustment for each of the determinants of a clinical event was performed separately, to study which variable in particular caused the change of direction.

After determination of the final adjusted models we studied differences in the predictive power for all-cause mortality between pre-dialysis BP, post-dialysis BP and mean BP. To compare different models we used the  $-2\log$  likelihood ( $-2 \log L$ ) statistics. This procedure compares different models fitted to the same set of survival data. The smaller the  $-2 \log L$  value, the better the agreement between the model and the observed data. The difference between the  $-2 \log L$  of the models, which are being compared, gives a statistical estimate as to which of them provides a better fit to the data. A 3.841 difference in  $-2 \log L$  coincides with a significance level of 0.05 in a chi-squared distribution with 1 degree of freedom and indicates a better prediction of risk estimate provided by the method leading to the lowest  $-2 \log L$  value. (21)

Results were considered statistically significant when  $p < 0.05$  (two-sided). All calculations were made by use of a standard statistical package (SPSS for Windows Version 18.0.1; SPSS Inc. Headquarters, Chicago, Illinois, US).

## **Results**

The baseline patient characteristics of the 714 participants of CONTRAST are shown in Table 1. Mean age was  $64.1 \pm 14.7$  years, 445 were male (62%) and the median dialysis vintage was 2.0 (P25-P75: 1.0 – 4.0) years. After inclusion patients were followed for an average of 3.04 years (range, 0.4–6.6 years; median 2.9 years). During follow-up 269 (38%) patients died from any cause and 228 (32%) had a cardiovascular event, out of which 83 (12%) were fatal.

### **Determinants of mortality, cardiovascular events and cardiovascular death**

The determinants of mortality, cardiovascular events and cardiovascular death, as well as their hazard ratios are shown in supplementary Table 1.

#### **Systolic blood pressure**

No significant relation was found between tertiles of SBP (either pre-dialysis, post-dialysis or the mean of the two) at baseline and risk of mortality, cardiovascular events (fatal and non-fatal combined) and cardiovascular death (Table 2a). As shown in the supplementary table 2a, results were similar when SBP was examined as a continuous variable.

#### **Diastolic blood pressure**

Crude analysis showed a significant inverse relation between DBP and all-cause mortality: the higher the DBP, the lower the death risk (Table 2b). After adjustments for determinants of all-cause mortality the relation between DBP and all-cause mortality was significantly positive: HR 1.40 (95% CI 1.04 – 1.90) for mean DBP 68-77mmHg and HR 1.49 (95% CI 1.06 – 2.10) for mean DBP >77mmHg when compared to patients with mean DBP <68mmHg (figure 1). When we adjusted the relation between DBP and all-cause mortality separately for each of the determinants of all-cause mortality, we found that age (having a strong positive relation with death risk, but also with DBP) was the variable responsible for the switch of direction of the relation between DBP and all-cause mortality in the adjusted model. The model with mean DBP (as compared to pre-dialysis and post-dialysis DBP) was deemed the best fit.

Crude analysis showed a significant inverse relation between DBP and cardiovascular events (fatal and non-fatal combined): HR: 0.93 (95% CI 0.69 – 1.26) for mean DBP 68 – 77mmHg and HR 0.53 (0.38 – 0.73) for DBP>77mmHg when compared to patients with mean DBP <68mmHg. After adjustment for determinants of cardiovascular events, this relation was positive and no longer significant. Adjustment for age in particular was responsible for changing the direction of the relation between cardiovascular events and DBP. Again, the model with mean DBP (as compared to pre-dialysis and post-dialysis DBP) was deemed the best fit.

The crude relation between cardiovascular death and DBP was not significant: HR: 1.39 (95% CI 0.83 – 3.21) for mean DBP 68 – 77mmHg and HR 0.64 (0.33 – 1.14) for DBP>77mmHg when compared to patients with mean DBP <68mmHg. After adjustment for determinants of cardiovascular death, patients in the middle tertile of DBP had a significantly higher risk of cardiovascular risk: HR: 1.95 (95% CI 1.14 – 3.34) for mean DBP 68 – 77mmHg and HR 1.59 (0.83 – 3.05) for DBP>77mmHg when compared to patients with mean DBP <68mmHg (figure 2). The model with mean DBP (as compared to pre-dialysis and post-dialysis DBP) was deemed the best fit.

As shown in the supplementary table 2b, results were similar when DBP was examined as a continuous variable.

### **Pulse pressure**

Patients in the highest tertile of PP had a significantly increased risk of all-cause mortality, cardiovascular events and cardiovascular mortality in the crude analysis (table 2c). After adjustment for confounders, the relation between PP and all-cause mortality and the relation between PP and cardiovascular mortality was no longer significant. Patients in the highest tertile of mean PP still had a significantly higher risk of cardiovascular events (fatal and non-fatal combined): HR 1.14 (95% CI 0.79 – 1.65) if mean PP 60 – 74mmHg and HR 1.85 (95% CI 1.08 – 2.29) if mean PP >74mmHg, when compared to mean PP<60mmHg (figure 3). The model with mean PP (as compared to pre-dialysis and post-dialysis PP) was deemed the best fit.

**Table 2a:** Systolic blood pressure in tertiles and risk of all-cause mortality, cardiovascular events (both fatal and non-fatal) and cardiovascular death.

	Low HR	Middle HR (95% CI)	p	High HR (95% CI)	p
<b><u>All cause mortality</u></b>					
<b>Crude</b>					
Pre-dialysis SBP (mmHg)	1	0.86 (0.63 - 1.16)	0.31	1.00 (0.75 - 1.33)	0.99
Post-dialysis SBP (mmHg)	1	0.99 (0.75 - 1.33)	0.98	0.98 (0.73 - 1.31)	0.87
Mean SBP (mmHg)	1	0.89 (0.66 - 1.20)	0.46	1.02 (0.77 - 1.36)	0.88
<b>Adjusted</b>					
Pre-dialysis SBP (mmHg)	1	0.93 (0.68 - 1.27)	0.65	1.13 (0.82 - 1.55)	0.47
Post-dialysis SBP (mmHg)	1	0.92 (0.67 - 1.25)	0.57	0.97 (0.70 - 1.35)	0.87
Mean SBP (mmHg)	1	0.90 (0.66 - 1.23)	0.51	1.16 (0.86 - 1.58)	0.34
<b><u>Cardiovascular events</u></b>					
<b>Crude</b>					
Pre-dialysis SBP (mmHg)	1	0.82 (0.59 - 1.16)	0.26	1.27 (0.93 - 1.73)	0.13
Post-dialysis SBP (mmHg)	1	0.91 (0.66 - 1.25)	0.54	1.08 (0.79 - 1.47)	0.64
Mean SBP (mmHg)	1	0.94 (0.68 - 1.31)	0.73	1.19 (0.87 - 1.62)	0.28
<b>Adjusted</b>					
Pre-dialysis SBP (mmHg)	1	0.79 (0.55 - 1.12)	0.19	1.19 (0.85 - 1.65)	0.31
Post-dialysis SBP (mmHg)	1	0.94 (0.67 - 1.33)	0.74	1.08 (0.76 - 1.53)	0.67
Mean SBP (mmHg)	1	0.92 (0.65 - 1.29)	0.62	1.20 (0.85 - 1.70)	0.29
<b><u>Cardiovascular mortality</u></b>					
<b>Crude</b>					
Pre-dialysis SBP (mmHg)	1	1.12 (0.69 - 2.09)	0.53	1.48 (0.86 - 2.53)	0.16
Post-dialysis SBP (mmHg)	1	1.06 (0.62 - 1.80)	0.83	1.12 (0.66 - 1.90)	0.68
Mean SBP (mmHg)	1	0.90 (0.52 - 1.55)	0.69	1.23 (0.74 - 2.05)	0.43
<b>Adjusted</b>					
Pre-dialysis SBP (mmHg)	1	1.24 (0.70 - 2.18)	0.46	1.56 (0.89 - 2.76)	0.12
Post-dialysis SBP (mmHg)	1	0.99 (0.57 - 1.74)	0.99	1.17 (0.66 - 2.08)	0.59
Mean SBP (mmHg)	1	0.93 (0.53 - 1.63)	0.80	1.33 (0.75 - 2.35)	0.33

Tertiles for pre-dialysis SBP: <137mmHg; 137 – 156mmHg; >156mmHg.

Tertiles for post-dialysis SBP: <124mmHg; 124 – 143mmHg; >143mmHg.

Tertiles for mean SBP: <132mmHg, 132 – 149mmHg; >149mmHg.

**Table 2b:** Diastolic blood pressure in tertiles and risk of all-cause mortality, cardiovascular events (both fatal and non-fatal) and cardiovascular death.

	Low HR	Middle HR (95% CI)	p	High HR (95% CI)	p
<b><u>All cause mortality</u></b>					
<b>Crude</b>					
Pre-dialysis DBP (mmHg)	1	0.92 (0.69 - 1.22)	0.56	0.60 (0.44 - 0.80)	0.022
Post-dialysis DBP (mmHg)	1	0.85 (0.64 - 1.13)	0.26	0.66 (0.49 - 0.89)	0.007
Mean DBP (mmHg)	1	0.83 (0.63 - 1.09)	0.18	0.55 (0.40 - 0.75)	<0.001
<b>Adjusted</b>					
Pre-dialysis DBP (mmHg)	1	1.37 (1.02 - 1.85)	0.038	1.41 (1.03 - 2.01)	0.021
Post-dialysis DBP (mmHg)	1	1.06 (0.78 - 1.42)	0.72	1.17 (0.84 - 1.62)	0.37
Mean DBP (mmHg)	1	1.40 (1.04 - 1.90)	0.029	1.49 (1.06 - 2.10)	0.021
<b><u>Cardiovascular events</u></b>					
<b>Crude</b>					
Pre-dialysis DBP (mmHg)	1	0.88 (0.65 - 1.11)	0.39	0.55 (0.40 - 0.77)	0.001
Post-dialysis DBP (mmHg)	1	0.80 (0.59 - 1.08)	0.14	0.54 (0.39 - 0.75)	<0.001
Mean DBP (mmHg)	1	0.93 (0.69 - 1.26)	0.65	0.53 (0.38 - 0.73)	<0.001
<b>Adjusted</b>					
Pre-dialysis DBP (mmHg)	1	1.31 (0.95 - 1.82)	0.10	0.94 (0.64 - 1.38)	0.76
Post-dialysis DBP (mmHg)	1	1.09 (0.79 - 1.49)	0.62	0.93 (0.64 - 1.34)	0.69
Mean DBP (mmHg)	1	1.35 (0.97 - 1.88)	0.08	0.94 (-.64 - 1.38)	0.76
<b><u>Cardiovascular mortality</u></b>					
<b>Crude</b>					
Pre-dialysis DBP (mmHg)	1	1.12 (0.72 - 2.00)	0.49	0.73 (0.42 - 1.29)	0.28
Post-dialysis DBP (mmHg)	1	1.06 (0.65 - 1.74)	0.81	0.60 (0.34 - 1.05)	0.076
Mean DBP (mmHg)	1	1.39 (0.83 - 2.31)	0.21	0.64 (0.36 - 1.14)	0.13
<b>Adjusted</b>					
Pre-dialysis DBP (mmHg)	1	1.92 (1.13 - 3.25)	0.015	1.36 (0.71 - 2.60)	0.35
Post-dialysis DBP (mmHg)	1	1.35 (0.81 - 2.23)	0.25	0.99 (0.53 - 1.84)	0.97
Mean DBP (mmHg)	1	1.95 (1.14 - 3.34)	0.015	1.59 (0.83 - 3.05)	0.17

Tertiles for pre-dialysis DBP: <70mmHg; 70 – 82mmHg; >82mmHg.

Tertiles for post-dialysis SBP: <66mmHg; 66 – 76mmHg; >76mmHg.

Tertiles for mean SBP: <68mmHg, 68– 77mmHg; >77mmHg.

**Table 2c:** Pulse pressure in tertiles and risk of all-cause mortality, cardiovascular events (both fatal and non-fatal) and cardiovascular death.

	Low HR	Middle HR (95% CI)	p	High HR (95% CI)	p
<b><u>All cause mortality</u></b>					
<b>Crude</b>					
Pre-dialysis PP (mmHg)	1	1.01 (0.75 - 1.37)	0.94	1.33 (0.99 - 1.78)	0.056
Post-dialysis PP (mmHg)	1	1.20 (0.88 - 1.62)	0.24	1.48 (1.11 - 1.98)	0.008
Mean PP (mmHg)	1	1.25 (0.92 - 1.67)	0.15	1.41 (1.05 - 1.89)	0.022
<b>Adjusted</b>					
Pre-dialysis PP (mmHg)	1	0.81 (0.59 - 1.12)	0.20	0.88 (0.64 - 1.20)	0.42
Post-dialysis PP (mmHg)	1	0.72 (0.52 - 1.02)	0.058	0.85 (0.62 - 1.18)	0.34
Mean PP (mmHg)	1	0.79 (0.57 - 1.08)	0.14	0.85 (0.61 - 1.18)	0.32
<b><u>Cardiovascular events</u></b>					
<b>Crude</b>					
Pre-dialysis PP (mmHg)	1	1.33 (0.93 - 1.89)	0.12	2.13 (1.53 - 2.96)	<0.001
Post-dialysis PP (mmHg)	1	1.18 (0.84 - 1.65)	0.34	1.66 (1.22 - 2.28)	0.001
Mean PP (mmHg)	1	1.56 (1.10 - 2.21)	0.013	2.23 (1.60 - 3.11)	<0.001
<b>Adjusted</b>					
Pre-dialysis PP (mmHg)	1	1.06 (0.74 - 1.54)	0.74	1.42 (0.99 - 2.03)	0.059
Post-dialysis PP (mmHg)	1	0.93 (0.65 - 1.33)	0.69	1.23 (0.86 - 1.76)	0.27
Mean PP (mmHg)	1	1.14 (0.79 - 1.65)	0.48	1.85 (1.08 - 2.29)	0.019
<b><u>Cardiovascular mortality</u></b>					
<b>Crude</b>					
Pre-dialysis PP (mmHg)	1	1.33 (0.75 - 2.34)	0.33	1.84 (1.07 - 3.17)	0.028
Post-dialysis PP (mmHg)	1	1.46 (0.84 - 2.53)	0.18	1.78 (1.04 - 3.04)	0.036
Mean PP (mmHg)	1	1.88 (1.05 - 3.37)	0.035	2.39 (1.35 - 4.22)	0.003
<b>Adjusted</b>					
Pre-dialysis PP (mmHg)	1	0.97 (0.54 - 1.74)	0.91	1.17 (0.65 - 2.09)	0.60
Post-dialysis PP (mmHg)	1	0.99 (0.55 - 1.78)	0.96	1.15 (0.63 - 2.09)	0.65
Mean PP (mmHg)	1	1.32 (0.72 - 2.42)	0.38	1.64 (0.88 - 3.06)	0.12

Tertiles for pre-dialysis PP: <63mmHg; 63 – 79mmHg; >79mmHg.  
Tertiles for post-dialysis PP: <56mmHg; 56 – 70mmHg; >70mmHg.  
Tertiles for mean PP: <60mmHg, 60– 74mmHg; >74mmHg.

**Table 2d:** Mean arterial pressure in tertiles and risk of all-cause mortality, cardiovascular events (both fatal and non-fatal) and cardiovascular death.

	Low HR	Middle HR (95% CI)	p	High HR (95% CI)	p
<b><u>All cause mortality</u></b>					
<b>Crude</b>					
Pre-dialysis MAP (mmHg)	1	0.87 (0.65 - 1.17)	0.36	0.67 (0.50 - 0.90)	0.007
Post-dialysis MAP (mmHg)	1	0.81 (0.61 - 1.07)	0.14	0.68 (0.51 - 0.91)	0.010
Mean MAP (mmHg)	1	0.81 (0.61 - 1.08)	0.15	0.66 (0.49 - 0.88)	0.005
<b>Adjusted</b>					
Pre-dialysis MAP (mmHg)	1	1.25 (0.91 - 1.71)	0.17	1.18 (0.86 - 1.64)	0.31
Post-dialysis MAP (mmHg)	1	0.91 (0.68 - 1.24)	0.56	0.86 (0.62 - 1.12)	0.38
Mean MAP (mmHg)	1	1.25 (0.92 - 1.70)	0.16	1.21 (0.87 - 1.69)	0.26
<b><u>Cardiovascular events</u></b>					
<b>Crude</b>					
Pre-dialysis MAP (mmHg)	1	0.73 (0.53 - 1.01)	0.056	0.78 (0.57 - 1.06)	0.11
Post-dialysis MAP (mmHg)	1	0.78 (0.60 - 1.06)	0.11	0.69 (0.50 - 0.95)	0.022
Mean MAP (mmHg)	1	0.74 (0.54 - 1.02)	0.065	0.76 (0.56 - 1.04)	0.082
<b>Adjusted</b>					
Pre-dialysis MAP (mmHg)	1	0.86 (0.61 - 1.23)	0.42	1.04 (0.74 - 1.45)	0.83
Post-dialysis MAP (mmHg)	1	0.87 (0.62 - 1.21)	0.42	0.85 (0.60 - 1.20)	0.36
Mean MAP (mmHg)	1	0.97 (0.69 - 1.36)	0.85	1.10 (0.78 - 1.56)	0.59
<b><u>Cardiovascular mortality</u></b>					
<b>Crude</b>					
Pre-dialysis MAP (mmHg)	1	0.91 (0.54 - 1.54)	0.72	0.84 (0.49 - 1.42)	0.51
Post-dialysis MAP (mmHg)	1	1.46 (0.51 - 1.42)	0.54	0.69 (0.41 - 1.18)	0.18
Mean MAP (mmHg)	1	1.48 (0.86 - 2.56)	0.16	1.10 (0.63 - 1.93)	0.75
<b>Adjusted</b>					
Pre-dialysis MAP (mmHg)	1	1.29 (0.74 - 2.23)	0.37	1.47 (0.82 - 2.65)	0.20
Post-dialysis MAP (mmHg)	1	0.96 (0.57 - 1.63)	0.88	0.89 (0.50 - 1.59)	0.68
Mean MAP (mmHg)	1	2.11 (1.19 - 3.72)	0.010	1.78 (0.97 - 3.27)	0.065

Tertiles for pre-dialysis MAP: <93mmHg; 93 – 105mmHg; >105mmHg.

Tertiles for post-dialysis MAP: <86mmHg; 86 – 98mmHg; >98mmHg.

Tertiles for mean MAP: <90mmHg, 90– 101mmHg; >101mmHg.

**Ad Table 2a-d:**

DBP: diastolic blood pressure; HR: hazard ratio; MAP: mean arterial blood pressure; PP: pulse pressure; SBP: systolic blood pressure.

\*All-cause mortality HR adjusted for: age, gender, history of cardiovascular disease, diabetes, residual kidney function, estimated glomerular filtration ratio, serum albumin, serum phosphate, serum creatinine, calcium antagonist use, renine angiotensin aldosterone system inhibitor use, beta-blocker use and dialysis modality (intervention).

Cardiovascular event HR adjusted for: age, body mass index, history of cardiovascular disease, diabetes, estimated glomerular filtration ratio,  $\text{spKt/V}_{\text{urea}}$ , hematocrit, serum phosphate, serum creatinine, calcium antagonist use and renine angiotensin aldosterone system inhibitor use and dialysis modality (intervention).

Cardiovascular death HR adjusted for: age, history of cardiovascular disease, diabetes, dialysis vintage, residual kidney function, serum albumin, calcium antagonist use and renine angiotensin aldosterone system inhibitor use and dialysis modality (intervention).

As shown in the supplementary table 2c, results were similar when PP was examined as a continuous variable.

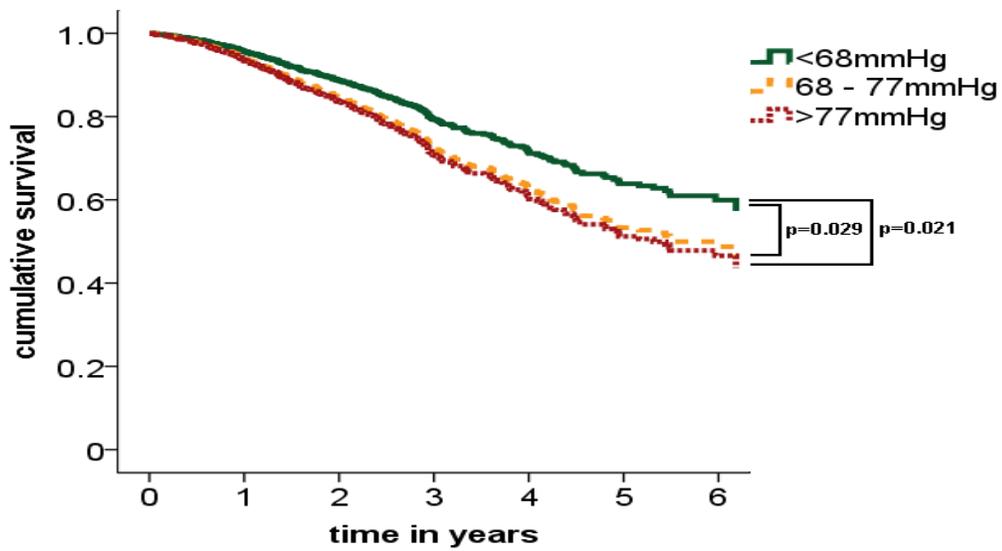
**Mean arterial pressure**

A significant inverse relation was found between MAP and risk of all-cause mortality and risk of cardiovascular events in the crude analysis (table 2d). After adjustment for confounders, this relations were no longer significant.

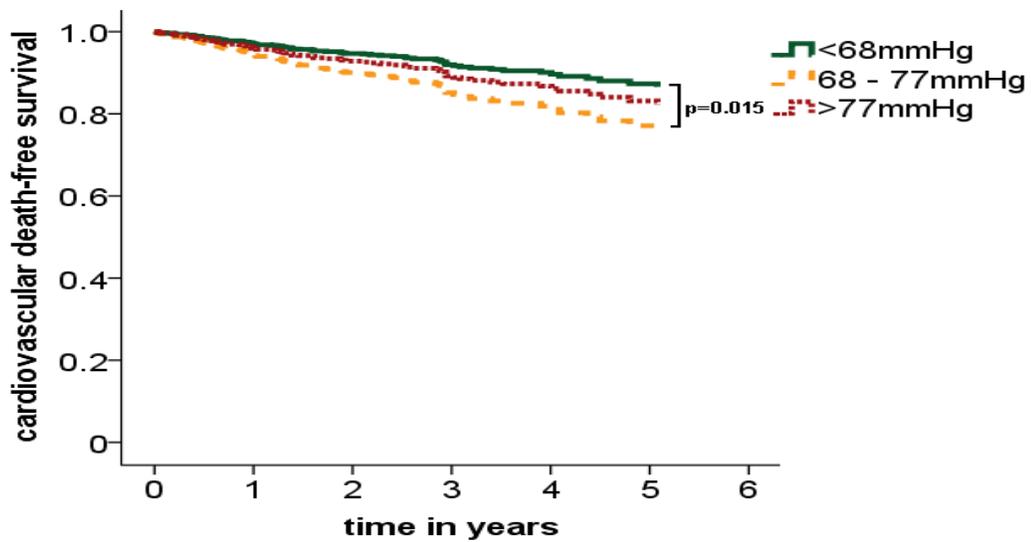
The relation between MAP and cardiovascular death was not significant in crude analysis: HR 1.48 (95% CI 0.86 – 2.56) for mean MAP 90 – 101mmHg and HR 1.10 (0.63 – 1.93) for mean MAP >101mmHg, as compared to patients with mean MAP <90mmHg. After adjustment for confounders patients in the middle tertile of mean MAP had an increased risk of cardiovascular death, while the positive relation between MAP in the highest tertile and cardiovascular death was borderline significant: HR 2.11 (95% CI 1.19 – 3.72) for mean MAP 90 – 101mmHg and HR 1.78 (0.97 – 3.27) for mean MAP >101mmHg, as compared to patients with mean MAP <90mmHg (figure 4). The model with mean MAP (as compared to pre-dialysis and post-dialysis MAP) was deemed to have the best fit .

As shown in the supplementary table 2d, results were similar when MAP was examined as a continuous variable.

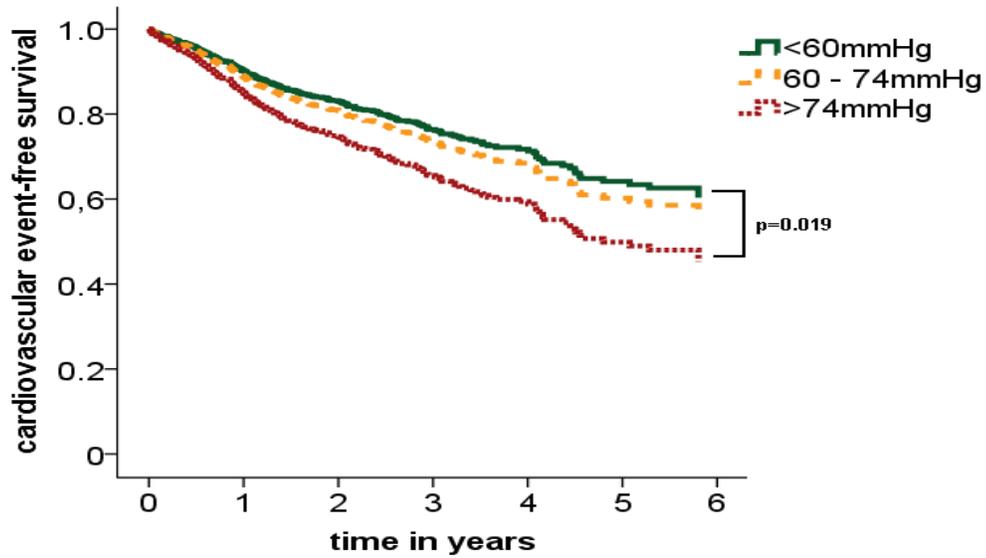
**Figure 1:** Survival curve for time to death from any cause stratified by mean diastolic blood pressure tertiles and adjusted for confounders.



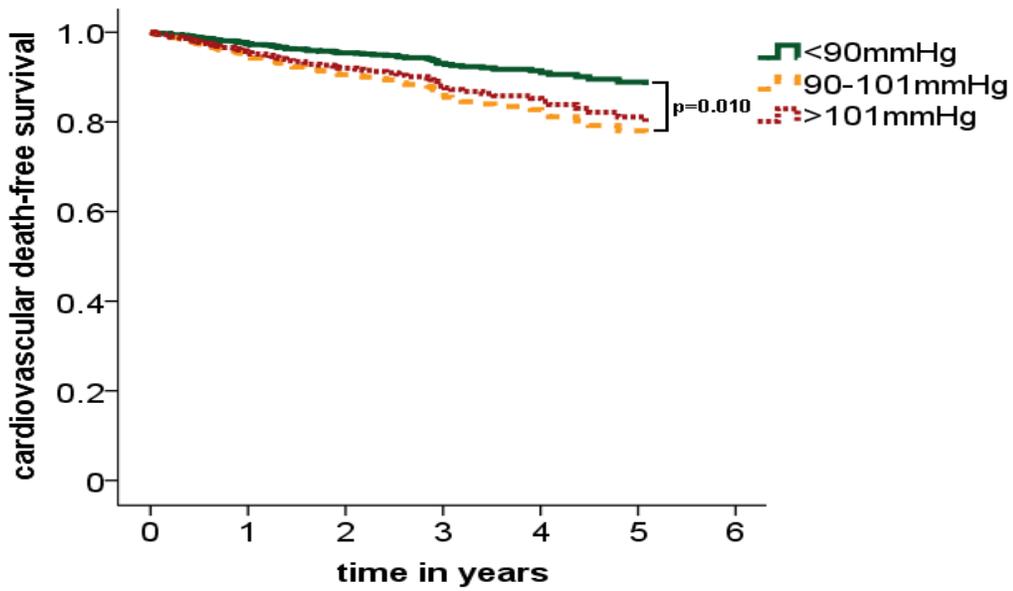
**Figure 2:** Survival curve for time to death from a cardiovascular cause stratified by mean diastolic blood pressure tertiles and adjusted for confounders.



**Figure 3:** Survival curve for time to cardiovascular event (both fatal and non-fatal) stratified by mean pulse pressure tertiles and adjusted for confounders.



**Figure 4:** Survival curve for time to death from a cardiovascular cause stratified by mean 'mean arterial pressure' tertiles and adjusted for confounders.



## **Discussion**

In the present study we have shown that DBP values are significantly related to risk of all-cause mortality (positive relation) and cardiovascular death (“U-shaped” relation). PP was positively related to risk of cardiovascular events. No relation was found between SBP and risk of all-cause mortality, cardiovascular mortality and cardiovascular events (both fatal and non-fatal) after adjustment for confounders.

Regarding the fit of the risk models, we found that overall the models using the mean of pre- and post-dialysis blood pressures had the best fit to the data.

### **Systolic blood pressure and clinical events**

In our study we found no significant relation between SBP and mortality, cardiovascular events or cardiovascular mortality. When looking at our tertiles of SBP we do see a (non-significant) “U-curve”-trend: patients in the middle tertile of SBP have a slightly lower risk of mortality / cardiovascular events / cardiovascular death, when compared to the lowest tertile; while patients in the highest tertile had a slightly increased risk. Since most studies describing this “U-curve” relation previously had more participants (4 000 to 56 000 patients), (10-12;14;22) it is possible that the magnitude of the potential relation is underestimated in our population.

### **Diastolic blood pressure and clinical events**

In contrast to similar studies, where SBP is found to be the best predictor for mortality (10;14), DBP was the best type BP-measurements to predict mortality and cardiovascular mortality risk in our population. However Klassen et al in an observational study in 37 069 dialysis patients also described an inverse univariate relation between DBP and mortality.(13)

### **Pulse pressure and clinical events**

In our study PP was positively related to risk of cardiovascular events (both fatal and non-fatal). PP is high in our population, with only 12% of patients having a PP below 50mmHg, the mean value found in population-based samples. PP reflects dynamic stress that is

caused by large-artery stiffness and early reflected arterial pressure waves from the periphery back to central conduit vessels. The mechanisms underlying the high arterial stiffness in ESKD patients include hypertension, hypervolemia, lipid abnormalities and aberrant inflammatory responses. (23-25) Earlier studies in non-ESRD populations have described that pulsatile vessel stress may be more related to cardiac disease than steady state stress. (26) Our paper confirms these findings in ESKD patients.

Klassen et al have demonstrated in a retrospective cohort study in 37 069 dialysis patients, followed for 1 year, a relation between PP and death risk, after adjusting PP for the SBP values. However, the relation between PP and cardiovascular events was not described in this paper. (13) Due to multi-collinearity issues (the fact that PP and SBP have an approximate linear relationship) we could not repeat the adjustments for SBP in our own population to confirm the results of Klassen et al.

#### **Mean arterial pressure and clinical events**

We found a U-shaped relation between MAP and risk of cardiovascular death. However, the predictive value of this model is not significantly better than the model with DBP predicting cardiovascular death risk.

MAP is a combination of DBP and SBP, and it's relation to mortality and cardiovascular events has not been elaborately described in earlier literature. Since MAP does not predict mortality or cardiovascular events better than DBP or SBP separately, there is little additive value to using MAP for these predictions.

#### **Pre-dialysis versus post-dialysis blood pressure**

Most studies in dialysis patients looking into the relation between blood pressure and mortality and/or cardiovascular events emphasize pre-dialysis blood pressure (11;12;15;22), while others find a stronger association between post-dialysis blood pressure and mortality. (13) Pre-dialysis BP measurements could be seen as a proxy for the actual BP and the intradialytic BP-change due to fluid excess combined, both risk factors for mortality. (1;10) Hence this would be a plausible explanation why pre-dialysis BPs would predict mortality and other clinical events better than post-dialysis BPs.

We are among the first to systematically explore our data with the goal to test whether the pre- post- or mean BP value is most predictive for mortality and cardiovascular events. Since the models with mean blood pressure seem to have the best fit overall, we can conclude that the average of pre- and post-dialysis BP can best be used to predict risk of mortality, cardiovascular events and cardiovascular death in particular.

### **Strengths and limitations**

The strengths of this study are the concise and prospective data collection and the independent review of source documentation for all primary and secondary outcomes . Also, in contrast to large international database cohort studies, we were able to correct for more potential confounders such as antihypertensive medication use and laboratory values.

This study had several limitations. First, BP measurements were collected before and after three dialysis session during one week at the beginning of the study. Hence these measurements may not be as precise as for example home BP measurements or continuous ambulatory blood pressure measurements. Imprecise measurements may lead to an insignificant result, even when a relation exists. Also, the magnitude of a potential relation could be underestimated. Hence, the observations that lack statistical significance, (as is the case for SBP) do not entirely disqualify the predictive value of that variable, especially if that variable has been proven to be a relevant predictor in earlier literature. Conversely, the statistically significant results that were observed are therefore likely to be valid. Second, our study population was relatively small, so we did not have the power to stratify our patients in a large amount of groups, to demonstrate the nature of the relation between BP and clinical events with more precision.

### **Conclusion**

To conclude, DBP is a strong predictor of all-cause mortality and cardiovascular mortality in ESKD patients. PP is a predictor of cardiovascular events (both fatal and non-fatal). The average of pre- and post-dialysis BP measurements predict risk of clinical events better than pre-dialysis or post-dialysis measurements alone.

## Supplementary Tables

**Supplementary Table 1:** Determinants of mortality, cardiovascular events (both fatal and non-fatal) and cardiovascular death.

	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
<b>All-cause mortality</b>						
Age (year)	1.06	1.05 - 1.07	<0.001	1.05	1.03 - 1.06	<0.001
Male gender	1.56	1.20 - 2.03	0.001	1.82	1.33 - 2.46	<0.001
History of cardiovascular disease	2.09	1.64 - 2.66	<0.001	1.23	0.93 - 1.63	0.14
Diabetes	1.34	1.02 - 1.75	0.040	1.36	1.02 - 1.83	0.039
Residual kidney function	0.83	0.66 - 1.06	0.14	0.69	0.49 - 0.98	0.034
eGFR (mL/min/1.73m <sup>2</sup> )	0.99	0.96 - 1.03	0.79	0.95	0.90 - 1.01	0.079
Serum albumin (g/L)	0.88	0.86 - 0.91	<0.001	0.91	0.88 - 0.94	<0.001
Serum phosphate (mmol/L)	0.73	0.57 - 0.94	0.014	1.36	1.01 - 1.82	0.044
Serum creatinin, predialysis (μmol/L)	0.99	0.99 - 0.99	<0.001	0.99	0.99 - 0.99	<0.001
Calcium antagonist use	0.87	0.67 - 1.14	0.31	1.48	1.08 - 2.04	0.016
Beta-blocker use	0.82	0.81 - 1.31	0.82	0.83	0.63 - 1.09	0.18
RAAS-inhibitor use	0.59	0.46 - 0.75	<0.001	0.57	0.43 - 0.76	<0.001
<b>Cardiovascular events</b>						
Age (year)	1.03	1.02 - 1.04	<0.001	1.02	1.01 - 1.03	0.009
Body Mass Index (kg /m <sup>2</sup> )	1.01	0.98 - 1.04	0.45	0.97	0.94 - 1.01	0.10
History of cardiovascular disease	3.02	2.30 - 3.06	<0.001	2.26	1.66 - 3.08	<0.001
Diabetes	2.22	1.69 - 2.92	<0.001	2.13	1.56 - 2.91	<0.001
eGFR (mL/min/1.73m <sup>2</sup> )	0.98	0.94 - 1.02	0.31	0.94	0.89 - 0.99	0.032
spKt/V <sub>urea</sub>	0.60	0.32 - 1.13	0.11	0.51	0.26 - 1.03	0.060
Hematocrit (%)	0.99	0.53 - 1.90	0.96	0.022	0.01 - 1.06	0.054
Serum phosphate (mmol/L)	1.16	0.90 - 1.49	0.25	1.54	1.14 - 2.08	0.005
Serum creatinin, predialysis (μmol/L)	0.99	0.99 - 0.99	0.002	0.99	0.99 - 0.99	0.044
Calcium antagonist use	1.04	0.79 - 1.38	0.77	1.39	0.99 - 1.93	0.054
RAAS-inhibitor use	0.77	0.59 - 0.99	0.045	0.62	0.45 - 0.84	0.002
<b>Cardiovascular death</b>						
Age (year)	1.04	1.02 - 1.06	<0.001	1.03	1.01 - 1.06	0.004
History of cardiovascular disease	3.25	2.06 - 5.11	<0.001	2.12	1.29 - 3.50	0.003
Diabetes	1.48	0.91 - 2.42	0.12	1.47	0.86 - 2.50	0.16
Dialysis vintage (year)	0.94	0.86 - 1.02	0.15	0.92	0.82 - 1.03	0.15
Residual kidney function	0.78	0.51 - 1.12	0.25	0.69	0.41 - 1.14	0.14
Serum albumin (g/L)	0.90	0.85 - 0.95	<0.001	0.92	0.86 - 0.98	0.008
Calcium antagonist use	1.23	0.79 - 1.93	0.36	1.78	1.03 - 3.06	0.038
RAAS-inhibitor use	0.79	0.52 - 1.22	0.30	0.66	0.39 - 1.12	0.13

eGFR: estimated glomerular filtration rate; RAAS: renin angiotensin aldosterone system.

**Supplementary table 2a:** Systolic blood pressure as a continuous variable and risk of all-cause mortality, cardiovascular events (both fatal and non-fatal) and cardiovascular death. HR are shown per 1 standard deviation increase in systolic blood pressure.

	HR	95% CI	p-value
<b><u>All cause mortality</u></b>			
<i>Crude</i>			
Pre-dialysis SBP (mmHg)	0.99	0.87 - 1.12	0.87
Post-dialysis SBP (mmHg)	0.99	0.87 - 1.11	0.80
Mean SBP (mmHg)	0.99	0.93 - 1.06	0.81
<i>Adjusted*</i>			
Pre-dialysis SBP (mmHg)	0.98	0.88 - 1.16	0.70
Post-dialysis SBP (mmHg)	0.98	0.89 - 1.07	0.65
Mean SBP (mmHg)	0.99	0.93 - 1.04	0.77
<b><u>Cardiovascular events</u></b>			
<i>Crude</i>			
Pre-dialysis SBP (mmHg)	1.14	0.98 - 1.29	0.18
Post-dialysis SBP (mmHg)	1.05	0.97 - 1.13	0.23
Mean SBP (mmHg)	1.00	0.99 - 1.01	0.23
<i>Adjusted*</i>			
Pre-dialysis SBP (mmHg)	1.10	0.93 - 1.16	0.29
Post-dialysis SBP (mmHg)	1.08	0.98 - 1.11	0.16
Mean SBP (mmHg)	1.01	0.99 - 1.01	0.21
<b><u>Cardiovascular mortality</u></b>			
<i>Crude</i>			
Pre-dialysis SBP (mmHg)	1.06	0.78 - 1.43	0.73
Post-dialysis SBP (mmHg)	1.01	0.74 - 1.36	0.97
Mean SBP (mmHg)	1.06	0.94 - 1.19	0.38
<i>Adjusted*</i>			
Pre-dialysis SBP (mmHg)	1.04	0.89 - 1.25	0.62
Post-dialysis SBP (mmHg)	1.03	0.71 - 1.74	0.78
Mean SBP (mmHg)	1.07	0.95 - 1.09	0.19

**Supplementary table 2b:** Diastolic blood pressure as a continuous variable and risk of all-cause mortality, cardiovascular events (both fatal and non-fatal) and cardiovascular death. HR are shown per 1 standard deviation increase in diastolic blood pressure.

	HR	95% CI	p-value
<b><u>All cause mortality</u></b>			
<b><i>Crude</i></b>			
Pre-dialysis DBP (mmHg)	0.76	0.75 – 1.14	<0.001
Post-dialysis DBP (mmHg)	0.79	0.70 – 0.89	<0.001
Mean DBP (mmHg)	0.64	0.53 – 0.78	<0.001
<b><i>Adjusted*</i></b>			
Pre-dialysis DBP (mmHg)	1.08	0.95 – 1.21	0.088
Post-dialysis DBP (mmHg)	1.09	0.98 – 1.25	0.059
Mean DBP (mmHg)	1.19	1.03 – 1.42	0.031
<b><u>Cardiovascular events</u></b>			
<b><i>Crude</i></b>			
Pre-dialysis DBP (mmHg)	0.77	0.66 – 0.85	<0.001
Post-dialysis DBP (mmHg)	0.75	0.66 – 0.86	<0.001
Mean DBP (mmHg)	0.63	0.51 – 0.77	<0.001
<b><i>Adjusted*</i></b>			
Pre-dialysis DBP (mmHg)	0.87	0.75 – 1.01	0.064
Post-dialysis DBP (mmHg)	0.84	0.72 – 0.96	0.014
Mean DBP (mmHg)	0.74	0.60 – 0.94	0.012
<b><u>Cardiovascular mortality</u></b>			
<b><i>Crude</i></b>			
Pre-dialysis DBP (mmHg)	0.81	0.65 – 1.01	0.063
Post-dialysis DBP (mmHg)	0.77	0.91 – 0.96	0.019
Mean DBP (mmHg)	0.68	0.48 – 0.95	0.022
<b><i>Adjusted*</i></b>			
Pre-dialysis DBP (mmHg)	1.01	0.79 – 1.29	0.94
Post-dialysis DBP (mmHg)	0.89	0.94 – 0.99	0.09
Mean DBP (mmHg)	0.94	0.78 – 1.02	0.059

**Supplementary table 2c:** Pulse pressure as a continuous variable and risk of all-cause mortality, cardiovascular events (both fatal and non-fatal) and cardiovascular death. HR are shown per 1 standard deviation increase in pulse pressure.

	HR	95% CI	p-value
<b><u>All cause mortality</u></b>			
<b><i>Crude</i></b>			
Pre-dialysis PP (mmHg)	1.18	1.05 – 1.32	0.006
Post-dialysis PP (mmHg)	1.14	1.02 – 1.29	0.023
Mean PP (mmHg)	1.30	1.08 – 1.57	0.006
<b><i>Adjusted*</i></b>			
Pre-dialysis PP (mmHg)	0.96	0.85 – 1.09	0.55
Post-dialysis PP (mmHg)	0.92	0.81 – 1.05	0.20
Mean PP (mmHg)	0.90	0.73 – 1.11	0.32
<b><u>Cardiovascular events</u></b>			
<b><i>Crude</i></b>			
Pre-dialysis PP (mmHg)	1.35	1.20 – 1.53	<0.001
Post-dialysis PP (mmHg)	1.23	1.09 – 1.39	0.001
Mean PP (mmHg)	1.56	1.28 – 1.90	<0.001
<b><i>Adjusted*</i></b>			
Pre-dialysis PP (mmHg)	1.33	1.08 – 1.64	0.008
Post-dialysis PP (mmHg)	1.12	0.98 – 1.27	0.099
Mean PP (mmHg)	1.24	1.09 – 1.41	0.001
<b><u>Cardiovascular mortality</u></b>			
<b><i>Crude</i></b>			
Pre-dialysis PP (mmHg)	1.29	1.05 – 1.58	0.017
Post-dialysis PP (mmHg)	1.26	1.04 – 1.54	0.022
Mean PP (mmHg)	1.53	1.10 – 2.12	0.011
<b><i>Adjusted*</i></b>			
Pre-dialysis PP (mmHg)	1.11	0.89 – 1.38	0.84
Post-dialysis PP (mmHg)	1.09	0.88 – 1.35	0.42
Mean PP (mmHg)	1.19	0.84 – 1.69	0.33

**Supplementary table 2d:** Mean arterial pressure as a continuous variable and risk of all-cause mortality, cardiovascular events (both fatal and non-fatal) and cardiovascular death. HR are shown per 1 standard deviation increase in mean arterial pressure.

	HR	95% CI	p-value
<b><u>All cause mortality</u></b>			
<b><i>Crude</i></b>			
Pre-dialysis MAP (mmHg)	0.84	0.74 – 0.95	0.006
Post-dialysis MAP (mmHg)	0.86	0.77 – 0.98	0.019
Mean MAP (mmHg)	0.84	0.74 – 0.94	0.004
<b><i>Adjusted*</i></b>			
Pre-dialysis MAP (mmHg)	0.98	0.87 – 1.11	0.78
Post-dialysis MAP (mmHg)	0.97	0.86 – 1.10	0.64
Mean MAP (mmHg)	0.97	0.86 – 1.11	0.66
<b><u>Cardiovascular events</u></b>			
<b><i>Crude</i></b>			
Pre-dialysis MAP (mmHg)	0.91	0.80 – 1.04	0.17
Post-dialysis MAP (mmHg)	0.86	0.75 – 0.98	0.025
Mean MAP (mmHg)	0.87	0.76 – 0.99	0.035
<b><i>Adjusted*</i></b>			
Pre-dialysis MAP (mmHg)	0.99	0.87 – 1.14	0.91
Post-dialysis MAP (mmHg)	0.91	0.80 – 1.05	0.19
Mean MAP (mmHg)	0.94	0.82 – 1.08	0.37
<b><u>Cardiovascular mortality</u></b>			
<b><i>Crude</i></b>			
Pre-dialysis MAP (mmHg)	0.93	0.75 – 1.16	0.53
Post-dialysis MAP (mmHg)	0.89	0.71 – 1.10	0.28
Mean MAP (mmHg)	0.90	0.72 – 1.12	0.35
<b><i>Adjusted*</i></b>			
Pre-dialysis MAP (mmHg)	1.06	0.85 – 1.33	0.61
Post-dialysis MAP (mmHg)	0.97	0.77 – 1.12	0.35
Mean MAP (mmHg)	1.02	0.81 – 1.28	0.87

**Ad Supplementary Table 2a-d:** DBP: diastolic blood pressure; HR: hazard ratio; MAP: mean arterial blood pressure; PP: pulse pressure; SBP: systolic blood pressure.

\*All-cause mortality HR adjusted for: age, gender, history of cardiovascular disease, diabetes, residual kidney function, estimated glomerular filtration ratio, serum albumin, serum phosphate, serum creatinine, calcium antagonist use, renine angiotensin aldosterone system inhibitor use, beta-blocker use and dialysis modality (intervention).

Cardiovascular event HR adjusted for: age, body mass index, history of cardiovascular disease, diabetes, estimated glomerular filtration ratio,  $\text{spKt/V}_{\text{urea}}$ , hematocrit, serum phosphate, serum creatinine, calcium antagonist use and renine angiotensin aldosterone system inhibitor use and dialysis modality (intervention).

Cardiovascular death HR adjusted for: age, history of cardiovascular disease, diabetes, dialysis vintage, residual kidney function, serum albumin, calcium antagonist use and renine angiotensin aldosterone system inhibitor use and dialysis modality (intervention).

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## Chapter 6

**Blood pressure and antihypertensive use over time in end stage kidney disease patients.**

**Results from the CONvective TRANsport Study (CONTRAST).**

*Submitted for publication*

Ira M. Mostovaya,<sup>1</sup> Michiel L. Bots,<sup>2</sup> Marinus A. van den Dorpel,<sup>3</sup> Muriel P.C. Grooteman,<sup>4,5</sup> Otto Kamp,<sup>6</sup> Renée Levesque,<sup>7</sup> Piet M. ter Wee,<sup>4,5</sup> Menso J. Nubé,<sup>4,5</sup> Peter J. Blankestijn.<sup>1</sup>

<sup>1</sup>Department of Nephrology, University Medical Center Utrecht, Utrecht

<sup>2</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht

<sup>3</sup>Department of Internal Medicine, Maastad Hospital, Rotterdam

<sup>4</sup>Department of Nephrology, VU Medical Center, Amsterdam

<sup>5</sup>Institute for Cardiovascular Research VU Medical Center (ICaR-VU), VU Medical Center, Amsterdam, the Netherlands

<sup>6</sup>Department of Cardiology, VU Medical Center, Amsterdam

<sup>7</sup>Department of Nephrology, Centre Hospitalier de l'Université de Montréal, St. Luc Hospital, Montréal, Canada

**Abstract****Background**

An elevated blood pressure represents an important burden of morbidity and mortality in end stage kidney disease (ESKD) patients. The aim of this study is to assess changes over time in blood pressure (BP) in ESKD patients and evaluate the impact of age, sex, medical history, antihypertensive use and dialysis-treatment related characteristics on these changes.

**Methods**

Data from all 714 patients from the CONvective TRANsport STudy (CONTRAST), a randomized trial comparing online hemodiafiltration and low-flux hemodialysis, were used for this analysis. Blood pressure was measured at baseline and every 3 months up to 6 years, three times pre-, and three times post-dialysis. The means of these pre- and post-dialysis measurements were computed, as well as the mean of all six blood pressure measurements. The rate of change over time of blood pressures was estimated using linear mixed effects models.

**Results**

At baseline mean age was  $64 \pm 14$  years, and 445 (62%) of patients were male. Systolic BP (SBP), diastolic BP (DBP), mean arterial pressure (MAP) and pulse pressure (PP) all declined over time. Males and older patients (>67 years) experienced a greater decline in SBP and PP, when compared to females and patients <67 respectively. A dialysis vintage >2 years was related to a higher rate of decline in SBP and DBP, when compared to patients with a vintage < 2 years. Patients with a history of cardiovascular disease (CVD) experienced a greater decline in DBP. Patients with a BMI  $>25 \text{ kg/m}^2$  had a smaller decline in SBP and PP over time.

**Conclusion**

SBP, DBP, PP and MAP all decline over time in dialysis patients. Age, gender, BMI, a history of CVD and dialysis vintage are important determinants of rate of decline of blood pressure.

## **Introduction**

A high blood pressure (BP) represents a large burden of morbidity and mortality in the end stage kidney disease (ESKD) population. (1-3) Approximately two thirds of all ESKD patients have a blood pressure that would be considered high in the overall population. (4;5) The relation between mortality risk and blood pressure in ESKD is most often described as a “U-shaped” curve: patients with a high and a very low BP have an increased mortality risk (1;6;7), while the risk is lowest for patients in the mid-range BP. An increase in BP over time has been associated with increased cardiovascular damage. (8)

The physiology of elevated blood pressure is multifactorial. Apart from the ‘standard’ physiological processes that determine BP in healthy individuals, enhanced activation of the renin-angiotensin-aldosterone system (RAAS) through primary vascular scarring, increased sympathetic activity, reduced arterial compliance and calcification, increased intracellular calcium due to parathyroid hormone excess, erythropoietin administration and volume excess all contribute to the BP of dialysis patients. (3;9-13)

Little is known about how blood pressure changes over time in patients undergoing chronic intermittent dialysis. In the general population systolic blood pressure (SBP) increases over time. Diastolic blood pressure (DBP) increases until age of 50 years, but afterwards a decrease occurs. Pulse pressure (PP) tends to slowly increase over time in the general population. (14;15) Furthermore, it is not clear whether blood pressure changes differ across strata of conventional cardiovascular risk factors in dialysis patients. Changes in blood pressure over time could be influenced by several patient characteristics. For example, changes in administered dose of antihypertensive medication could influence change in blood pressure. However, changes in intrinsic patient factors, such as cardiovascular function, residual renal function and blood volume could affect BP changes also. (3)

The aim of this study is to assess changes over time in BP in patients undergoing chronic intermittent dialysis and evaluate the impact of age, gender, medical history characteristics, and dialysis modality on these changes. Furthermore, we will study the influence of changes in dose of antihypertensive medication and cardiac function on the rate of change of BP parameters.

## **Materials and methods**

### **Patients**

Analysis was performed with data from all 714 participants of the CONvective TRANsport Study (CONTRAST). CONTRAST has been designed to investigate the effects of increased convective transport by online HDF as compared with low-flux HD on all-cause mortality and cardiovascular morbidity and mortality (ISRCTN38365125). (16;17)

Patients were eligible if treated with haemodialysis two or three times a week, for at least 2 months, with a minimum dialysis urea Kt/V  $\geq 1.2$ . Furthermore, patients had to be able to understand the study procedures. Exclusion criteria were age  $< 18$  years, treatment by HDF or high flux HD in the 6 months preceding randomization, severe incompletion defined as non-adherence to the dialysis prescription, a life expectancy  $< 3$  months due to non-kidney disease and participation in another clinical intervention trial evaluating cardiovascular outcomes. Randomization was stratified by participating center. From June 2004 until January 2010 a total of 714 patients were enrolled in CONTRAST.

CONTRAST was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating dialysis centres. Written informed consent was obtained from all patients prior to enrolment.

### **Dialysis procedures**

Before randomization, all patients had to be stable with a minimum dialysis single-pool Kt/V for urea ( $spKt/V_{urea}$ ) of 1.2. Treatment times were fixed during follow-up in both treatment arms unless  $spKt/V_{urea}$  was less than 1.2. Online HDF was performed in the post-dilution mode; target volume was 6L/hour. Blood flow rates could be increased in the HDF arm to improve convection volumes. Synthetic high-flux dialyzers were used for HDF. (FX80: 35%, FX100: 18% and Optiflux F200NR: 8% [Fresenius Medical Care, Bad Homburg, Germany]; Polyflux 170H: 24% and Polyflux 210H: 8% [Gambro AB, Stockholm, Sweden] or other dialyzers: 2%) HD patients were treated with synthetic low-flux dialyzers. (F6HPS: 9%, F8HPS: 36% and Optiflux 18NR: 7% [Fresenius]; Polyflux 14L: 7%, Polyflux 17L: 29% and Polyflux 21L: 1% [Gambro]; or other: 2%) All patients were treated with ultrapure dialysis fluid, defined as less than 0.1 colony forming units per mL and less than 0.03

endotoxin units per mL. Routine patient care was performed according to the guidelines of the Quality of Care Committee of the Dutch Federation of Nephrology.

### **Data collection**

At baseline standardized forms were used to collect demographical, clinical and laboratory data. Type of vascular access, duration of dialysis (dialysis vintage), medication use and medical history: presence of diabetes mellitus (DM), history of kidney transplantation and previous cardiovascular disease (CVD) were also assessed. A history of cardiovascular disease was defined as a confirmative answer on any of the questions regarding a previous acute myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, angina pectoris, stroke, transient ischemic attack, intermittent claudication, amputation, percutaneous transluminal angioplasty, peripheral bypass surgery and renal percutaneous transluminal angioplasty. Dialysis vintage was determined as the sum of time patients were treated with HD or PD before inclusion in CONTRAST. The mean of three consecutive post-dialysis weights was used to calculate weight at baseline. Patients' height was determined once at inclusion in the study. Body mass index (BMI) was computed as the quotient of weight by height squared.

Antihypertensive drugs were defined as diuretics, renin-angiotensin-aldosterone system inhibitors, beta-blockers, alpha-blockers, calcium channel blockers, peripheral anti-adrenergics, centrally working antihypertensives, nitrates and other antihypertensives (bosentan).

Patients with a urinary production of less than 100mL per day were considered anuric. In patients with residual diuresis of more than 100mL per day, interdialytic 24 hour urinary samples were collected.

At each three-monthly visit, data on clinical events, clinical characteristics, dialysis treatment, medication, and standard laboratory values were recorded. Standard laboratory samples were analysed in the local laboratories of the participating hospitals by standard laboratory techniques.

**Table 1:** Baseline characteristics of the CONTRAST participants.

Variable	CONTRAST participants (n=714)
<b>Demographic data</b>	
Male gender	445 (62%)
Race, caucasian	600 (84%)
Age (year)	64.1 ± 13.7
Smoking	133 (19%)
Region	
Netherlands	597 (84%)
Norway	15 (2%)
Canada	102 (14%)
<b>Anthropometrics</b>	
Length (cm)	1.69 ± 0.10
Weight, postdialysis (kg)	72.4 ± 14.4
Body Mass Index (kg/m <sup>2</sup> )	25.4 ± 4.8
Body Surface Area (m <sup>2</sup> )	1.85 ± 0.21
<b>Dialysis Properties</b>	
Hemodiafiltration	358 (50%)
Duration of dialysis (minutes)	226 ± 23
Blood flow (mL/minute)	308 ± 39
spKt/Vurea	1.40 ± 0.22
Vascular access	
Arterio-venous fistula	567 (80%)
Graft	100 (14%)
Central venous catheter	47 (6%)
<b>Comorbidities</b>	
Cardiovascular disease	313 (44%)
Diabetes	170 (24%)
Previous kidney transplant	78 (11%)
Dialysis vintage (years)	2.0 (1.0 - 4.0)*
Patients with residual kidney function	376 (53%)
<b>Laboratory parameters</b>	
Hemoglobin (g/dL)	7.3 ± 7.8
Hematocrit (%)	37 ± 4
Phosphate (mmol/L)	1.64 ± 0.49
Albumin (g/L)	40.4 ± 3.8

Creatinine, pre-dialysis ( $\mu\text{mol/L}$ )	861 $\pm$ 225
Beta-2-microglobulin (mg/L)	31.5 $\pm$ 14.0
eGFR (mL/min/1.73m <sup>2</sup> )	3.2 (1.3 - 5.5)*
<b>Medication</b>	
Erythropoietin	633 (89%)
Diuretic	185 (26%)
Alpha blocker	69 (10%)
Beta-blocker	378 (53%)
Angiotensin converting enzyme -inhibitor	206 (29%)
Angiotensin-2 antagonist	167 (24%)
Calcium antagonist	221 (31%)
Other antihypertensives	51 (7%)
Nitrates	79 (11%)
Lipid lowering therapy	367 (51%)
Platelet aggregation inhibitor therapy	238 (33%)
<b>Hemodynamic measurements</b>	
Pre-dialysis systolic blood pressure (mmHg)	148 $\pm$ 22
Pre-dialysis diastolic blood pressure (mmHg)	76 $\pm$ 12
Pre-dialysis pulse pressure (mmHg)	72 $\pm$ 18
Pre-dialysis mean arterial pressure (mmHg)	100 $\pm$ 13
Post-dialysis systolic blood pressure (mmHg)	135 $\pm$ 21
Post-dialysis diastolic blood pressure (mmHg)	71 $\pm$ 12
Post-dialysis pulse pressure (mmHg)	64 $\pm$ 17
Post-dialysis mean arterial pressure (mmHg)	92 $\pm$ 13
Mean systolic blood pressure (mmHg)	141 $\pm$ 19
Mean diastolic blood pressure (mmHg)	73 $\pm$ 11
Mean pulse pressure (mmHg)	68 $\pm$ 16
Mean mean arterial pressure (mmHg)	96 $\pm$ 12

\* medians and interquartile ranges (P25 - P75) are shown

eGFR: estimated glomerular filtration rate

To convert hemoglobin from mmol/L to g/dL divide by 0.62; phosphorous in mmol/L to mg/dL, divide by 0.323; albumin in g/L to g/dL, divide by 10; creatinine in  $\mu\text{mol/L}$  to mg/dL divide by 88.4.

### Blood pressure measurements

Systolic and diastolic blood pressure (SBP and DBP) was measured using a standard electronic sphygmomanometer. SBP and DBP were recorded before and after three consecutive dialysis sessions. The mean of the pre-dialysis measurements was considered

the pre-dialysis SBP and DBP. The mean of the three post-dialysis measurements was considered the post-dialysis SBP and DBP. The mean of the pre-dialysis SBP and DBP and the post-dialysis SBP and DBP was defined as the mean SBP and mean DBP. Pulse pressure (PP) was computed as the difference between systolic and diastolic blood pressure, for pre-dialysis, post-dialysis and the mean. Mean arterial pressure (MAP) was computed as  $(SBP \cdot 1/3 + DBP \cdot 2/3)$  for pre-dialysis, post-dialysis and the mean thereof.

Blood pressure measurements were collected at baseline and during each three-monthly follow-up visit.

### **Echocardiography measurements**

Participants in 15 centres (n=327) were requested to undergo echocardiography next to the standard CONTRAST data collection at baseline, after 6 months, after 12 months and annually thereafter.

Transthoracic M-mode echocardiography studies were performed on a non-dialysis day by an echocardiographer at the participating local hospital. From the parasternal long axis position the left ventricular end-diastolic diameter (LVEDD), end-systolic diameter (LVESD) as well as the posterior and septal wall thickness were determined. The ultrasound investigations were then assessed by an independent experienced echocardiographer at the core laboratory (Vrije Universiteit Medisch Centrum, Amsterdam, the Netherlands), who was blinded for all other patient data. EF was computed automatically by the echocardiography software.

### **Outcome**

The primary study aim in the present analysis was the rate of change per year of SBP, DBP, PP and MAP.

The secondary study outcome was the effect of patient characteristics (age, gender, medical history, antihypertensive medication and dialysis-treatment related characteristics) on the rate of change over time of SBP, DBP, PP and MAP.

### Data analysis

Data were reported as means with standard deviations, medians with ranges, or proportions when appropriate.

Prescribed dosages of antihypertensive drugs were converted to daily defined doses (DDD) using conversion factors as provided by the World Health Organization (WHO) Drug Classification (<http://www.whooc.no/atcddd/>). Using DDDs and the total prescribed dosages, daily use (DU) of all antihypertensive drugs was calculated.

Linear mixed effect models were performed with a random intercept and random slope or a random intercept alone (depending on the lowest Aikake's information criterion value) to model changes over time of SBP, DBP, PP and MAP. Subsequently, the changes over time were modelled with a linear mixed effect model in strata of the conventional risk factors. Each model was adjusted for dialysis modality as well as the other baseline risk factors by adding them as fixed effects to the model. To explore if rates of change differed depending on follow-up time, we calculated rates of change from baseline to 12 months, and baseline to end of follow-up of measurements. Differences between these strata were tested with the interaction term of the concerning conventional risk factor with time. For continuous variables such as age and dialysis vintage the interaction terms age\*time and vintage\*time were tested, with age and vintage as continuous variables. Continuous variables were also stratified below or above the median for the patient group under study, to show differences between young and old patients, patients with a short and long dialysis vintage and so on. Age, gender, medical history, dialysis modality and type of vascular access were entered into the model as time-independent covariates, while body mass index, laboratory variables and antihypertensive medication use and DDDs were entered as time-varying covariates.

Results were considered statistically significant when  $p < 0.05$  (two-sided). All calculations were made by use of a standard statistical package (SPSS for Windows Version 20.0.1; SPSS Inc. Headquarters, Chicago, Illinois, US).

## **Results**

The baseline patient characteristics of the 714 participants of CONTRAST are shown in Table 1. Mean age was  $64.1 \pm 14.7$  years, 445 were male (62%) and the median dialysis vintage was 2.0 (P25-P75: 1.0 – 4.0) years. After inclusion patients were followed for an average of 3.04 years (range, 0.4–6.6 years; median 2.9 years). The participant flowchart of the blood pressure measurements is shown in the supplementary Figure 1.

### **Blood pressure changes over time**

As shown in table 2, SBP, DBP, MAP and PP all decreased significantly over time. This applies to both the pre-dialysis and the post-dialysis measurements. Mean SBP decreased by

2.4 mmHg per year (95% CI: -3.2 to -1.6,  $p < 0.001$ ), while DBP decreased by 1.5 mmHg per year (95% CI: -1.9 to -1.2,  $p < 0.001$ ), PP decreased by 0.9 mmHg per year (95% CI: -1.4 to -0.5,  $p = 0.002$ ), and MAP decreased by 1.8 mmHg per year (95% CI: -2.3 to -1.4,  $p < 0.001$ ). Intradialytic weight change did not change significantly over time:  $\Delta -0.01$  kg per year (95% CI: -0.04 to 0.01,  $p = 0.33$ ).

### **Blood pressure and age**

Tables 3a, 3b, 3c and 3d show the rate of change of mean SBP, DBP, PP and MAP respectively for strata of conventional risk factors. Older patients experienced a greater decline in SBP (and consequently MAP) as well as PP. For SBP, patients who were older than the median age of 66.8 years, declined by an excess 1.2 mmHg per year (95% CI: 0.1 to 2.5,  $p = 0.048$ ). When age was modelled as a continuous variable, patients declined by an extra 0.05 mmHg per year (95% CI: 0.01 to 0.09,  $p = 0.046$ ) in SBP for every excess year of age. Consequently, patients declined by an excess 0.03 mmHg per year (95% CI -0.01 to 0.05,  $p = 0.079$ ) in MAP for every extra year of age. PP also declined faster in older patients: patients older than 66.8 years experienced an excess decline in PP of 0.92 mmHg per year (95% CI: -0.02 to 1.56,  $p = 0.053$ ), when compared to those younger than 66.8 years. When age was modelled as a continuous variable, patients declined by an extra 0.03 mmHg per year (95% CI: 0.01 to 0.07,  $p = 0.046$ ) in PP for every extra year of age.

**Blood pressure and sex**

Men experienced a greater decline in SBP and PP over time, when compared to women. For SBP, men declined by an excess of 1.30mmHg per year (95% CI 0.09 to 2.61,  $p=0.037$ ) when compared to women. Also, men declined by 0.99mmHg per year (95% CI: 0.03 to 1.94,  $p=0.044$ ) in PP more than women. In fact, the rate of change of PP was not significantly negative in females:  $\Delta=-0.01$  (95% CI: -0.78 to 0.76,  $p=0.99$ ), while a significant decrease in PP was observed in males:  $\Delta=-0.98$  (95% CI: -1.60 to -0.40,  $p<0.001$ ).

**Blood pressure and body mass index**

Patients with a higher BMI experienced a smaller decline in SBP (and consequently MAP) and PP, when compared to those with a lower BMI. Per point increase of BMI, the decrease in SBP was 0.23mmHg/year (95% CI: 0.10 to 0.37,  $p=0.001$ ) smaller. For PP, when BMI increased by one  $\text{kg/m}^2$ , PP decline was 0.18mmHg/year smaller (95% CI: 0.08 to 0.28,  $p<0.001$ ). Per point increase of BMI, the decrease in MAP was 0.13mmHg/year (95% CI: 0.02 to 0.19,  $p=0.011$ ) smaller.

**Blood pressure and dialysis vintage**

Patients with a high dialysis vintage experienced a greater decline in SBP, DBP and, consequently MAP. An excess decline of 2.00mmHg per year (95% CI: 0.06 to 3.05,  $p=0.005$ ) in SBP occurred in patients with a dialysis vintage above 2 years, when compared to those who had a dialysis vintage of less than 2 years. Per year of dialysis vintage, an excess decline of 0.02mmHg per year (95% CI: -0.01 to 0.05,  $p=0.12$ ) was observed in SBP. Regarding DBP, patients with a dialysis vintage above 2 years declined by an excess 1.1mmHg per year (95% CI: 0.5 to 1.8,  $p=0.001$ ) when compared to those who had a dialysis vintage of less than 2 years. Per year of dialysis vintage, an extra decline of 0.13mmHg per year (95% CI: 0.01 to 0.25,  $p=0.032$ ) was observed for DBP. Consequently, patients with a higher dialysis vintage experienced a greater decrease in MAP: an excess 1.44mmHg per year (95% CI: 0.60 to 2.30,  $p=0.001$ ) for patients with a dialysis vintage above 2 years, or an excess decrease of 0.16mmHg per year (95% CI: 0.01 to 0.32,  $p=0.049$ ) per year of dialysis vintage.

**Table 2:** Changes in blood pressure (pre-dialysis, post-dialysis and mean) over time, over different lengths of follow-up.

	$\Delta$ (mmHg/year)	95% CI of $\Delta$	p-value
<b>Pre-dialysis SBP (mmHg)</b>			
0 - 1 years	-2.08	-4.08 to -0.07	0.042
0 - 3 years	-2.96	-3.92 to -1.99	<0.001
0 - 6.6 years (maximum follow-up)	-2.95	-3.80 to -2.10	<0.001
<b>Pre-dialysis DBP (mmHg)</b>			
0 - 1 years	-1.47	-2.55 to -0.38	0.008
0 - 3 years	-1.65	-2.12 to -1.19	<0.001
0 - 6.6 years (maximum follow-up)	-1.66	-2.06 to -1.29	<0.001
<b>Pre-dialysis PP (mmHg)</b>			
0 - 1 years	-0.70	-2.12 to 0.71	0.33
0 - 3 years	-1.34	-2.02 to -0.67	<0.001
0 - 6.6 years (maximum follow-up)	-1.30	-1.90 to -0.70	<0.001
<b>Pre-dialysis MAP (mmHg)</b>			
0 - 1 years	-1.60	-2.88 to -0.33	0.014
0 - 3 years	-2.08	-2.67 to -1.48	<0.001
0 - 6.6 years (maximum follow-up)	-2.10	-2.61 to -1.56	<0.001
<b>Post-dialysis SBP (mmHg)</b>			
0 - 1 years	-1.65	-2.93 to -0.37	0.011
0 - 3 years	-2.00	-2.60 to -1.41	<0.001
0 - 6.6 years (maximum follow-up)	-2.03	-2.55 to -1.52	<0.001
<b>Post-dialysis DBP (mmHg)</b>			
0 - 1 years	-1.50	-2.60 to -0.40	0.008
0 - 3 years	-1.38	-1.81 to -0.94	<0.001
0 - 6.6 years (maximum follow-up)	-1.29	-1.65 to -0.93	<0.001
<b>Post-dialysis PP (mmHg)</b>			
0 - 1 years	-0.61	-1.40 to -0.03	0.047
0 - 3 years	-0.43	-1.13 to 0.27	0.23
0 - 6.6 years (maximum follow-up)	-0.46	-1.05 to 0.13	0.13
<b>Post-dialysis MAP (mmHg)</b>			
0 - 1 years	-2.03	-3.38 to -0.67	0.004
0 - 3 years	-1.49	-2.07 to -0.92	<0.001
0 - 6.6 years (maximum follow-up)	-1.43	-1.91 to -0.96	<0.001

<b>Mean SBP (mmHg)</b>			
0 - 1 years	-2.55	-4.41 to -0.69	0.007
0 - 3 years	-2.38	-3.28 to -1.49	<0.001
0 - 6.6 years (maximum follow-up)	-2.37	-3.15 to -1.60	<0.001
<b>Mean DBP (mmHg)</b>			
0 - 1 years	-1.49	-2.43 to -0.55	0.002
0 - 3 years	-1.54	-1.95 to -1.14	<0.001
0 - 6.6 years (maximum follow-up)	-1.51	-1.85 to -1.17	<0.001
<b>Mean PP (mmHg)</b>			
0 - 1 years	-0.57	-1.35 to 0.22	0.10
0 - 3 years	-0.87	-1.51 to -0.24	0.007
0 - 6.6 years (maximum follow-up)	-0.88	-1.44 to -0.52	0.002
<b>Mean MAP (mmHg)</b>			
0 - 1 years	-1.85	-3.02 to -0.77	0.002
0 - 3 years	-1.83	-2.37 to -1.29	<0.001
0 - 6.6 years (maximum follow-up)	-1.80	-2.26 to -1.35	<0.001

DBP: diastolic blood pressure; MAP: mean arterial pressure; PP: pulse pressure; SBP: systolic blood pressure.

#### **Blood pressure and a history of cardiovascular disease**

Patients with a history of CVD experienced a greater decline in DBP over time when compared to patients without a history of CVD. The decline of DBP was 0.70mmHg per year (95% CI: 0.01 to 1.3,  $p=0.050$ ) greater in patients with a history of CVD than those without such a history.

#### **Antihypertensive medication over time**

In CONTRAST 582 (82%) of all patients used one or more oral anti-hypertensive drug, with a median DU of 2.00 DDD (95% CI: 0.74 - 3.67) at baseline (supplementary table 1). Over time, dosage of total antihypertensive medication declined by 0.16 DDD per year (95% CI: 0.07 to 0.25,  $p=0.001$ ), despite the fact that total DU of diuretics increased over time:

**Table 3a:** Systolic blood pressure changes over time in various strata of conventional risk factors.

	Estimate slope (mmHg / year)	95% CI	p-value slope	p-value interaction term
Age < 66.8 years	-1.66	-2.5 to -0.78	<0.001	0.048
Age > 66.8 years	-2.8	-3.8 to -1.8	<0.001	0.046*
Men	-2.7	-3.5 to -1.9	<0.001	0.037
Women	-1.4	-2.6 to -0.2	0.018	
Body mass index <24.7 (kg/m <sup>2</sup> )	-1.9	-2.9 to -0.9	<0.001	0.12
Body mass index > 24.7 (kg/m <sup>2</sup> )	-1.7	-2.6 to -0.8	<0.001	0.001*
Residual kidney function	-2.5	-3.4 to -1.6	<0.001	0.44
No residual kidney function	-2.0	-2.9 to -1.0	<0.001	
Cardiovascular disease	-2.8	-3.9 to -1.7	<0.001	0.22
No cardiovascular disease	-1.8	-2.8 to -0.8	<0.001	
Diabetes mellitus	-1.5	-2.8 to -0.2	0.023	0.30
No diabetes mellitus	-2.5	-3.4 to -1.6	<0.001	
Dialysis vintage < 2 years	-1.2	-2.2 to -0.3	0.012	0.005
Dialysis vintage > 2 years	-3.4	-3.4 to -2.3	<0.001	0.12*
Hemodiafiltration	-2.2	-3.2 to -1.3	<0.001	0.97
Hemodialysis	-2.3	-3.4 to -1.1	<0.001	

\*p-value of interaction term when age / body mass index / dialysis vintage are modelled as a continuous variable

**Table 3b:** Diastolic blood pressure changes over time in various strata of conventional risk factors.

	Estimate slope (mmHg / year)	95% CI	p-value slope	p-value interaction term
Age < 66.8 years	-1.4	-1.9 to -0.9	<0.001	0.25
Age > 66.8 years	-1.8	-2.2 to -1.3	<0.001	0.18*
Men	-1.7	-2.1 to -1.3	<0.001	0.62
Women	-1.5	-2.1 to -0.9	<0.001	
Body mass index <24.7 (kg/m <sup>2</sup> )	-1.4	-1.9 to -1.0	<0.001	0.31
Body mass index > 24.7 (kg/m <sup>2</sup> )	-1.2	-1.7 to -0.8	<0.001	0.21*
Residual kidney function	-1.3	-2.4 to -1.0	<0.001	0.36
No residual kidney function	-1.5	-2.6 to -1.1	<0.001	
Cardiovascular disease	-2.0	-2.4 to -1.5	<0.001	0.050
No cardiovascular disease	-1.3	-1.7 to -0.8	<0.001	
Diabetes mellitus	-1.5	-2.1 to -0.9	<0.001	0.84
No diabetes mellitus	-1.6	-2.0 to -1.2	<0.001	
Dialysis vintage < 2 years	-1.1	-1.5 to -0.6	<0.001	0.001
Dialysis vintage > 2 years	-2.2	-2.6 to -1.7	<0.001	0.032*
Hemodiafiltration	-1.7	-2.2 to -1.3	<0.001	0.44
Hemodialysis	-1.5	-1.9 to -1.0	<0.001	

\*p-value of interaction term when age / body mass index / dialysis vintage are modelled as a continuous variable

**Table 3c:** Pulse pressure changes over time in various strata of conventional risk factors.

	Estimate slope		p-value slope	p-value interaction term
	(mmHg / year)	95% CI		
Age < 66.8 years	-0.18	-0.76 to 0.40	0.54	0.053
Age > 66.8 years	-1.07	-1.80 to -0.34	0.004	0.046*
Men	-0.98	-1.60 to -0.40	0.001	0.044
Women	-0.01	-0.78 to 0.76	0.99	
Body mass index <24.7 (kg/m <sup>2</sup> )	-0.5	-1.2 to 0.3	0.21	0.16
Body mass index > 24.7 (kg/m <sup>2</sup> )	-0.4	-1.0 to 0.2	0.21	<0.001*
Residual kidney function	-0.7	-1.4 to -0.1	0.03	0.51
No residual kidney function	-0.3	-0.6 to 0.2	0.22	
Cardiovascular disease	-0.76	-1.51 to -0.01	0.048	0.54
No cardiovascular disease	-0.48	-1.07 to 0.11	0.11	
Diabetes mellitus	-0.04	-1.01 to 0.93	0.93	0.22
No diabetes mellitus	-0.78	-1.32 to -0.24	0.005	
Dialysis vintage < 2 years	-0.27	-0.92 to 0.38	0.42	0.47
Dialysis vintage > 2 years	-0.97	-1.64 to -0.30	0.005	
Hemodiafiltration	-0.48	-1.10 to 0.14	0.13	0.54
Hemodialysis	-0.75	-1.46 to -0.05	0.037	

\*p-value of interaction term when age / body mass index / dialysis vintage are modelled as a continuous variable

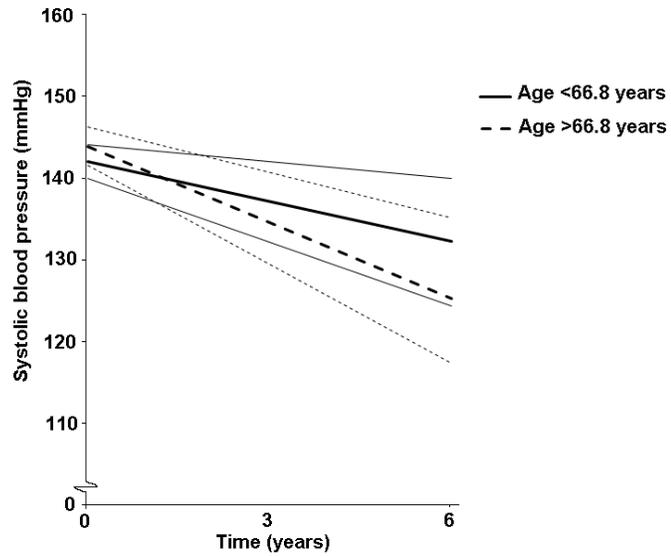
**Table 3d:** Mean arterial pressure changes over time in various strata of conventional risk factors.

	Estimate slope (mmHg / year)	95% CI	p-value slope	p-value interaction term
Age < 66.8 years	-1.5	-2.1 to -0.9	<0.001	0.17
Age > 66.8 years	-2.2	-2.8 to -1.5	<0.01	0.079*
Men	-2.0	-2.5 to -1.4	<0.001	0.33
Women	-1.6	-2.3 to -0.8	<0.001	
Body mass index <24.7 (kg/m <sup>2</sup> )	-1.7	-2.2 to -1.0	<0.001	0.13
Body mass index > 24.7 (kg/m <sup>2</sup> )	-1.4	-2.0 to -1.0	<0.001	0.011*
Residual kidney function	-1.3	-2.4 to -1.0	<0.001	0.24
No residual kidney function	-1.4	-2.4 to -1.1	<0.001	
Cardiovascular disease	-2.3	-2.87 to -1.65	<0.001	0.091
No cardiovascular disease	-1.4	-2.04 to -0.83	<0.001	
Diabetes mellitus	-1.5	-2.30 to -0.76	<0.001	0.51
No diabetes mellitus	-1.9	-2.45 to -1.46	<0.001	
Dialysis vintage < 2 years	-1.1	-1.71 to -0.55	<0.001	0.001
Dialysis vintage > 2 years	-2.6	-3.23 to -1.96	<0.001	0.049*
Hemodiafiltration	-1.9	-2.52 to -1.45	<0.001	0.39
Hemodialysis	-1.6	-2.24 to -1.03	<0.001	

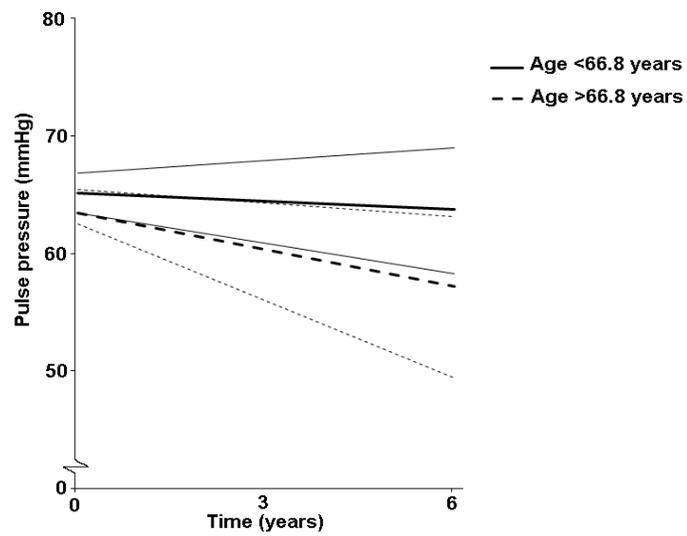
\*p-value of interaction term when age / body mass index / dialysis vintage are modelled as a continuous variable

**Figure 1:** Change in systolic blood pressure (1a) and pulse pressure (1b) over time stratified by age groups.

1a: Systolic blood pressure over time (with 95% confidence intervals) stratified by age.

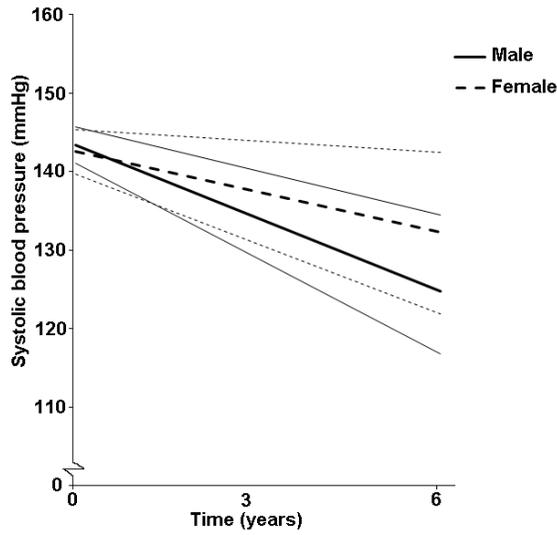


1b: Pulse pressure over time (with 95% confidence intervals) stratified by age.

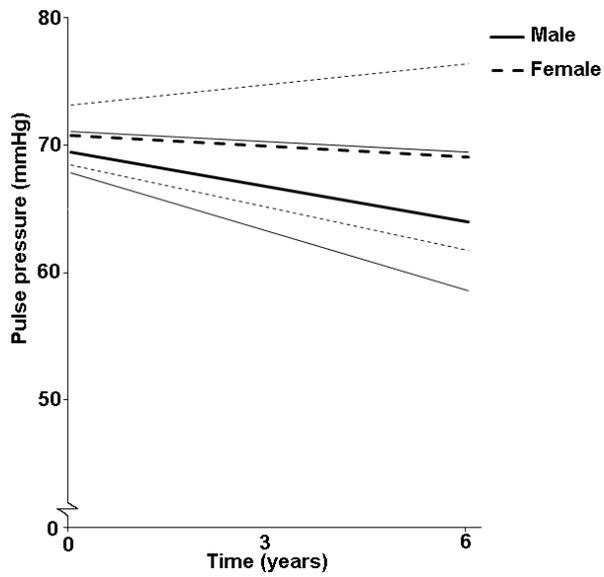


**Figure 2:** Change in systolic blood pressure (2a) and pulse pressure (2b) over time stratified by gender.

2a: Systolic blood pressure over time (with 95% confidence intervals) stratified by gender.

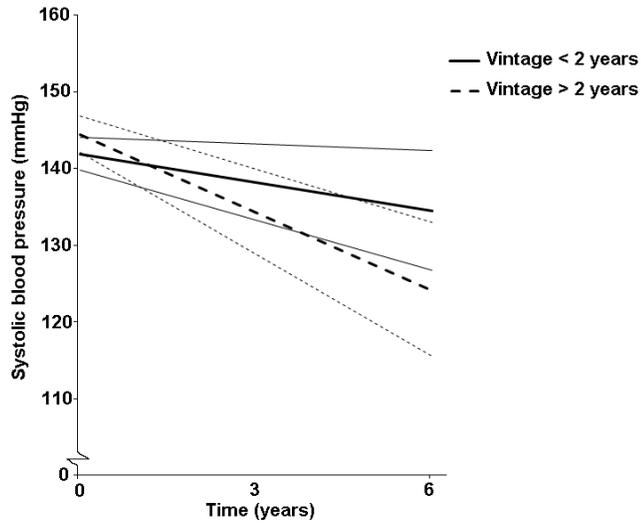


2b: Pulse pressure over time (with 95% confidence intervals) stratified by gender.

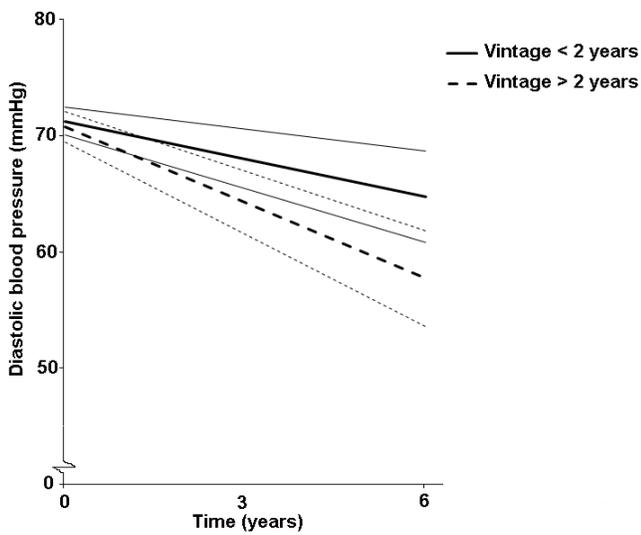


**Figure 3:** Change in systolic blood pressure (3a) and diastolic blood pressure (3b) over time stratified by dialysis vintage.

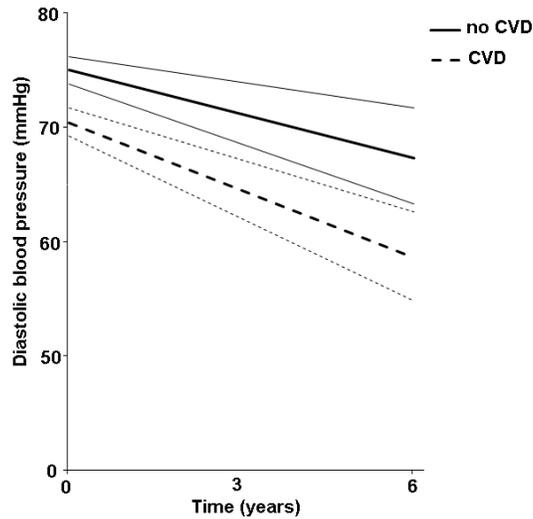
3a: Systolic blood pressure over time (with 95% confidence intervals) stratified by dialysis vintage.



3b: Diastolic blood pressure over time (with 95% confidence intervals) stratified by dialysis vintage.



**Figure 4:** Change in diastolic blood pressure over time (with 95% confidence intervals) stratified by history of cardiovascular disease.



CVD: cardiovascular disease

$\Delta$ : 1.05 (95% CI: 0.66 to 1.56,  $p < 0.001$ ), as shown in supplementary table 2. A DDD of 0.16 would be comparable to, for example, 8mg of losartan, 24mg of metoprolol or 0.8mg amlodipine, while a DDD of 1.05 would be comparable to 42mg of furosemide or 79mg of spironolactone. As described earlier in the Methods section, all rate of changes of BPs were corrected for the DDDs of anti-hypertensives as time-varying covariates.

#### Ejection fraction and rate of change of blood pressure

In a subgroup of CONTRAST, consisting of 342 patients in total, 327 measurements at baseline, echocardiography was performed and ejection fraction was measured. At baseline, the median EF was 65% (P25-P75: 55-72%). When EF was stratified into tertiles and rate of change of BP was computed per tertile, patients in the lowest tertile of EF (<59%) experienced a greater decline in SBP ( $p=0.038$ ) and DBP ( $p=0.026$ ), and consequently, MAP( $p=0.014$ ), than patients in the highest tertile of EF (>69%), as shown in table 4.

**Discussion**

In this paper we have shown that SBP, DBP, PP and MAP all slowly decline over time in the dialysis population. Age, gender, BMI, a history of cardiovascular disease and dialysis vintage are important determinants of rate of decline of blood pressure in ESKD patients. Since rate of SBP and DBP decline is more pronounced in patients with a low EF, and antihypertensive medication use decreases over time, it is probable that this BP decline can at least partly be attributed to deterioration in cardiac function.

**Blood pressure changes over time**

We are among the first to study blood pressure changes over a long follow-up time in dialysis patients, and in particular, characteristics that might influence these changes.

Usvyat et al have shown recently in a large intercontinental study in 52 130 ESKD patients that pre-dialysis SBP declines slowly over time and shows a sharper decline in the 20 weeks before death. However, rate of decline of SBP was not adjusted for use of antihypertensive medication, other BP parameters were not reported and characteristics that could influence rate of change were not studied. (18) Another large observational study in 15 056 ESKD patients showed that seasonal variation occurs in pre-dialysis SBP, namely, a higher SBP in the winter and a lower SBP in the summer. When looking at SBP over 5 years an overall gradual decline could also be observed from the figures, although this was not explicitly described in the manuscript. (19) BP changes in the general population differ from our findings in this dialysis cohort. For example, SBP tends to increase over time and with older age, as does PP, while DBP increases until the age of 50, but slowly declines afterwards. (14;15) Conversely, in our dialysis cohort we see a decrease in SBP, DBP and PP. Since in our population only 125 (18%) patients are younger than 50, it is possible that the DBP decline we find is similar to the DBP decline in the general population. Also, in the general population a high BMI and increase in BMI is related to an increase in SBP and DBP, (20) while we find that a high BMI is related to a smaller BP decline.

**Table 4:** Rate of change of blood pressure stratified by tertiles of ejection fraction.

	$\Delta$ SBP (mmHg per year)	p	p for interaction
EF<59% (n=113)	-3.9 (-6.0 to 01.8)	<0.001	0.038
EF: 59 - 69% (n=105)	-4.2 (-6.9 to -1.6)	0.003	0.024
EF>69% (n=107)	-0.44 (-2.7 to 1.8)	0.24	
	$\Delta$ DBP (mmHg per year)	p	p for interaction
EF<59% (n=113)	-3.2 (-4.2 to -2.2)	<0.001	0.026
EF: 59 - 69% (n=105)	-2.7 (-4.2 to -1.2)	0.001	0.20
EF>69% (n=107)	-0.9 (-2.3 to 0.44)	0.18	
	$\Delta$ PP (mmHg per year)	p	p for interaction
EF<59% (n=113)	-1.8 (-2.6 to 1.0)	0.40	0.26
EF: 59 - 69% (n=105)	-2.1 (-4.8 to 0.1)	0.054	0.09
EF>69% (n=107)	0.8 (-1.0 to 2.6)	0.40	
	$\Delta$ MAP (mmHg per year)	p	p for interaction
EF<59% (n=113)	-3.3 (-4.4 to -2.1)	<0.001	0.014
EF: 59 - 69% (n=105)	-3.1 (-4.8 to -1.4)	0.001	0.068
EF>69% (n=107)	-0.7 (-2.2 to 0.9)	0.39	

DBP: diastolic blood pressure; EF: ejection fraction; MAP: mean arterial pressure; PP: pulse pressure; SBP: systolic blood pressure

### Blood pressure change differences in subgroups

In our analysis older age was associated with a greater decline in SBP and PP. Since older age has been associated with an increased risk of systolic dysfunction and other echocardiographic abnormalities (21), a decline in (mainly systolic) BP which is related to decrease in cardiac function would appear logical.

Patients with a dialysis vintage >2 years were found to have a bigger decline in SBP and DBP, than patients with a vintage < 2 years. Patients with a higher vintage, have been exposed to end stage kidney disease-related damage to the cardiovascular system (such as accumulation of uremic toxins, an increased extracellular volume and increased intracellular calcium due to parathyroid hormone excess) for a longer period of time.

(3;10;11) Hence it is probable that decline of BP related to cardiovascular function is greater in patients with a higher dialysis vintage. Furthermore, it is possible that increasing atrophy of the non-functioning kidneys would lead to a decrease in activation of the RAAS system by the kidneys, thus leading to a decrease in sympathetic nerve activity and a BP decline.

A history of CVD is related to a larger DBP decrease. Naturally, when a patient has shown obvious signs of cardiovascular damage by developing CVD, it seems plausible that a larger decrease in cardiovascular function would occur in such a patient over time.

Male gender has been related to an increased risk of echocardiographic abnormalities such as left ventricular dilatation in dialysis patients. (21) We found that male gender was related to a bigger decrease in SBP and DBP. Our findings further support the hypothesis that cardiovascular pathology is worse in male dialysis patients.

In dialysis patients a 'reverse epidemiology' has been observed between BMI and risk of death and cardiovascular events: in contrast to the normal population a higher BMI is associated with a better survival and a smaller risk of cardiovascular events. (22;23) It is plausible that a higher BMI is a sign of a better general disease condition, which in turn affects the cardiac function in a more favourable manner and thus induces less BP decline.

#### **Heart function and blood pressure changes**

In our population more than 70% of the patients had a normal EF ranging 55-75%. (24) Notably, only the patients in the higher ranges of normal EF (>69%) experienced no significant change in BP over time, while dialysis patients in the slightly lower but normal range of EF, as well as the patients with suboptimal EF experienced BP decline. EF was modelled as a time-dependent co-variable, which means that the patients that maintained an optimal EF were the ones who remained stable in BP. Hence it is probable that deterioration in cardiovascular function is a relevant contributor to the BP decline. (25)

#### **Antihypertensive medication use**

We are among the first to extensively study use of antihypertensive medication 'in daily clinical practice' in a large population of dialysis patients over a long period of follow-up

time. Also, we are among the first to adjust BP rates of changes for use of antihypertensive medication in a standardized manner. We found an overall decline in DU of antihypertensive medication. It is likely that the prescription of antihypertensive medication was restricted over time by the attending nephrologist, because of a decreasing BP in the patients.

Although diuretic use increases over time, a decrease of residual renal function occurs simultaneously. (26) Therefore, it is questionable whether the overall effect of the diuretic medication increases over time also, or that the dose of diuretics increases to maintain the same effect. Furthermore, we included nitrates in the overall model, although these are not strictly speaking antihypertensives, since they have a BP lowering effect. When the rate of change of DU of antihypertensives is modelled, excluding the nitrate and diuretic use, we see an even larger decline of DU: -0.46DDD per year (95% CI: -0.76 to -0.17,  $p=0.002$ ).

Theoretically, BP decline could be attributed to an increased use of antihypertensive medication. However, the above described analyses show that this is highly improbable in our population.

### **Strengths and limitations**

The strengths of our study are the concise and prospective data collection over a long follow-up period. In addition, all measurements were taken into account with the linear mixed models, where time-dependent co-variables were modelled adequately. Also, BP rates of changes were adjusted for use of antihypertensive medication in a standardized manner.

A limitation of this study is that a relevant proportion of patients dropped out (mainly due to death or transplantation) or missed examinations during the follow-up period. Although mixed effect models can calculate rate of change well, with some missing data, the precision of the estimates decreases. Another potential limitation is that an intervention, namely HDF, was performed in this study. Therefore, changes over time might be affected by the intervention. However, we did not find differences in BP changes over time when we adjusted for treatment modality in our analyses. Finally, although we could provide

information on the relation between BP decline and EF as a surrogate marker for cardiac function, we could not provide information on other potential explanations for BP decline, such as a decrease in RAAS activation and intracellular calcium levels.

**Conclusion**

In conclusion, SBP, DBP and PP all decrease over time in dialysis patients. Age, gender, BMI, a history of cardiovascular disease and dialysis vintage are important determinants of rate of decline of blood pressure in ESKD patients. Since BP decline is bigger in patients with a low EF, and antihypertensive medication use decreases over time, it is probable that this BP decline can at least partly be attributed to deterioration in cardiovascular function.

## Supplementary Tables

**Supplementary table 1:** Prevalence and daily use (as dialy defined dose) of anti-hypertensive medication at baseline.

	DU (DDD)	prevalence
Diuretic	8.0 (5.0 - 12.5)*	185 (26%)
Alpha blocker	0.5 (0.5 - 1.0)*	69 (10%)
Beta-blocker	0.6 (0.3 - 1.0)*	378 (53%)
Angiotensin converting enzyme -inhibitor	1.0 (0.5 - 2.0)*	206 (29%)
Angiotensin-2 antagonist	2.0 (1.0 - 2.0)*	167 (24%)
Calcium antagonist	2.0 (1.0 - 2.0)	221 (31%)
Other antihypertensives	1.0 (1.0 - 2.0)	51 (7%)
Nitrates	1.25 (0.8 - 1.5)*	79 (11%)
All antihypertensives	4.00 (1.31 - 10.00)*	582 (82%)
All antihypertensives minus nitrates and diuretics	1.67 (0.67 - 3.33)*	532 (72%)
All antihypertensives minus nitrates	2.00 (0.74 - 3.67)*	543 (76%)

\* medians and interquartile ranges (P25 - P75) are shown  
DDD: daily defined dose; DU: daily use

**Supplementary table 2:** Changes in daily use of antihypertensive medication over time.

	<b>Estimate slope (DU in DDD per year)</b>	<b>95% CI slope</b>	<b>p-value</b>
Diuretic	1.05	0.66 to 1.56	<0.001
Alpha blocker	-0.02	-0.05 to 0.01	0.41
Beta-blocker	-0.01	-0.04 to 0.01	0.24
Angiotensin converting enzyme -inhibitor	-0.01	-0.08 to 0.07	0.85
Angiotensin-2 antagonist	-0.04	-0.10 to 0.02	0.23
Calcium antagonist	0.01	-0.05 to 0.05	0.91
Other antihypertensives	0.02	-0.13 to 0.16	0.81
Nitrates	-0.01	-0.06 to 0.04	0.65
All antihypertensives	-0.16	-0.25 to -0.07	0.001
All antihypertensives minus nitrates and diuretics	-0.46	-0.76 to -0.17	0.002
All antihypertensives minus nitrates	-0.15	-0.24 to -0.06	0.001

DDD: daily defined dose; DU: daily use

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## Chapter 7

# Peripheral resistance, cardiac output and blood pressure over time in end stage kidney disease.

## Results from the CONvective TRANsport STudy (CONTRAST).

*Submitted for publication*

Ira M. Mostovaya,<sup>1</sup> Michiel L. Bots,<sup>2</sup> Marinus A. van den Dorpel,<sup>3</sup> Muriel P.C. Grooteman,<sup>4,5</sup> Otto Kamp,<sup>5,6</sup> Renée Levesque,<sup>7</sup> Piet M. ter Wee,<sup>4,5</sup> Menso J. Nubé,<sup>4,5</sup> Peter J. Blankestijn.<sup>1</sup>

<sup>1</sup>Department of Nephrology, University Medical Center Utrecht, Utrecht

<sup>2</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht

<sup>3</sup>Department of Internal Medicine, Maastricht Hospital, Rotterdam

<sup>4</sup>Department of Nephrology, VU Medical Center, Amsterdam

<sup>5</sup>Institute for Cardiovascular Research VU Medical Center (ICaR-VU), VU Medical Center, Amsterdam, the Netherlands

<sup>6</sup>Department of Cardiology, VU Medical Center, Amsterdam

<sup>7</sup>Department of Nephrology, Centre Hospitalier de l'Université de Montréal, St. Luc Hospital, Montréal, Canada

**Abstract****Background**

Peripheral resistance is a marker of sympathetic activity in end stage kidney disease (ESKD) patients, however, data on changes over time are scarce. The aim of this study was to examine changes over time in peripheral resistance (PR), cardiac output (CO), mean arterial pressure (MAP), systolic blood pressure (SBP) and diastolic blood pressure (DBP).

**Methods**

A subpopulation of 84 patients from the CONvective TRANsport STudy (CONTRAST), a randomized trial comparing online hemodiafiltration (HDF) with low-flux hemodialysis, received echocardiography and simultaneous blood pressure measurements on a non-dialysis day at baseline, and annually thereafter. PR was computed as MAP/CO. A total of 190 measurements were thus performed over a follow-up period of 3 years. The rate of change over time of PR, CO, MAP, SBP and DBP was estimated using linear mixed effects models.

**Results**

At baseline, patients had a mean age of  $62 \pm 14$  years and 55% were male. Median PR was 17.7 (IQR 15.3 – 22.5) mmHg•min/L, mean CO was  $5.5 \pm 1.5$  L/min, mean MAP was  $97 \pm 15$  mmHg and mean SBP and DBP were  $137 \pm 29$  and  $76 \pm 12$  mmHg respectively. PR ( $\Delta$ -3.3 95%CI:-6.6 to -0.2 mmHg•min/L per year), MAP ( $\Delta$ -5.4 95%CI:-9.8 to -1.1 mmHg per year) and DBP ( $\Delta$ -5.8 95%CI:-9.3 to -2.3 mmHg per year) decreased over time, while CO ( $\Delta$ 0.2 95%CI:-0.2 to 0.7 L/min per year) and SBP ( $\Delta$ -4.3 95%CI:-12.6 to 3.9 mmHg per year) remained stable.

**Conclusion**

MAP decreases over time, mainly due to a decrease in DBP. This decline of MAP can be explained by a decrease in PR over time, but not a change in CO.

## **Introduction**

Poorly controlled blood pressure (BP) is a common health issue in ESKD patients, causing and contributing to a high cardiovascular morbidity and mortality. (1)

The regulatory mechanisms of BP in ESKD patients are even more complex than in the healthy populations. Apart from the 'standard' physiological processes that determine BP in healthy individuals, several ESKD-specific factors have an important influence. Activation of the renin-angiotensin-aldosterone system through primary vascular disease and scarring in the kidney, increased sympathetic activity, reduced arterial compliance and calcification, increased intracellular calcium due to parathyroid hormone excess, erythropoietin administration and volume excess may all contribute to the elevated BP levels that are generally observed in dialysis patients. (1-6)

An inappropriate increase in systemic vascular resistance due to the activation of the renin-angiotensin system and consequently sympathetic overactivity is seen as one of the main causes for elevated blood pressure in ESKD patients. (7) Chronic elevation of the activity of the sympathetic nervous system has repeatedly been demonstrated to be an important factor underlying the increased risk of cardiovascular disease in this population. (8;9)

Total peripheral resistance (PR), a manifestation of increased sympathetic activity, has been shown to be elevated in ESKD patients, as compared to healthy individuals. (10) PR is the sum of the resistance of all peripheral vasculature in the systemic circulation and can be estimated as the quotient of mean arterial blood pressure (MAP) and cardiac output (CO). (11) PR increases due to binding of catecholamines to  $\alpha_1$  receptors of vascular smooth muscle cells, causing vasoconstriction. (12)

Although it has been well established that both sympathetic activity and BP are elevated in ESKD patients, little is known about how PR, and consequently BP change over time in a population of prevalent ESKD patients. Thus the aim of this study was to examine changes over time in BP and to investigate whether these changes are dependent on alterations in CO and/or PR in ESKD patients.

## **Materials and methods**

### **Patients**

Analysis was performed with data of a subgroup from the CONvective TRANsport STudy (CONTRAST): a cohort of 84 patients who underwent echocardiography with simultaneous blood pressure measurements. CONTRAST was designed to investigate the effects of increased convective transport by online HDF as compared with low-flux HD on all-cause mortality and cardiovascular morbidity and mortality (ISRCTN38365125). (13;14) The present subset of the population consisted of patients who were treated in a medical center where performance of additional echocardiography with simultaneous blood pressure measurements was logistically possible. Furthermore, patients signed informed consent for the additional echocardiography measurements.

Patients were eligible for CONTRAST when treated with haemodialysis two or three times a week, for at least 2 months, with a minimum dialysis urea Kt/V  $\geq 1.2$ . Furthermore, patients had to be able to understand the study procedures. Exclusion criteria were age  $< 18$  years, treatment by HDF or high flux HD in the 6 months preceding randomization, severe non-compliance defined as non-adherence to the dialysis prescription, a life expectancy  $< 3$  months due to non-kidney disease and participation in another clinical intervention trial evaluating cardiovascular outcomes. Randomization was stratified by participating center. From June 2004 until January 2010 a total of 714 patients were enrolled in CONTRAST.

CONTRAST was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating dialysis centres. Written informed consent was obtained from all patients prior to enrolment.

### **Dialysis procedures**

Before randomization, all patients had to be stable with a minimum dialysis single-pool Kt/V for urea ( $\text{spKt}/V_{\text{urea}}$ ) of 1.2. Treatment times were fixed during follow-up in both treatment arms unless  $\text{spKt}/V_{\text{urea}}$  was less than 1.2. Online HDF was performed in the post-dilution mode; target volume was 6L/hour. Synthetic high- or low-flux dialyzers were used respectively for HDF and HD (polysulfon [Fresenius Medical Care, Bad Homburg,

Germany] or polyamide [Gambro AB, Stockholm, Sweden] ). All patients were treated with ultrapure dialysis fluid, defined as containing less than 0.1 colony forming units per mL and less than 0.03 endotoxin units per mL. Routine patient care was performed according to the guidelines of the Quality of Care Committee of the Dutch Federation of Nephrology.

### **Data collection**

At baseline standardized forms were used to collect demographical, clinical and laboratory data. Type of vascular access, duration of dialysis (dialysis vintage), and medical history (presence of diabetes mellitus (DM), history of kidney transplantation and previous cardiovascular disease (CVD)) were also assessed. A history of cardiovascular disease was defined as a confirmative answer on any of the questions regarding a previous acute myocardial infarction, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, angina pectoris, stroke, transient ischemic attack, intermittent claudication, amputation, percutaneous transluminal angioplasty, peripheral bypass surgery and renal percutaneous transluminal angioplasty. Dialysis vintage was determined as the sum of time patients were treated with HD or peritoneal dialysis before inclusion in CONTRAST. The mean of three consecutive post-dialysis weights was used to calculate weight at baseline. Patients' height was determined once at inclusion in the study.

Patients with a urinary production of less than 100mL per day were considered anuric. In patients with residual diuresis of more than 100mL per day, interdialytic 24 hour urinary samples were collected.

At each three-monthly visit, data on clinical events, clinical characteristics, dialysis treatment, medication, and standard laboratory values were recorded. Standard laboratory samples were analysed in the local laboratories of the participating hospitals by standard laboratory techniques.

Prescribed dosages of antihypertensive drugs were converted to daily defined doses (DDD) using conversion factors as provided by the World Health Organization (WHO) Drug Classification (<http://www.whooc.no/atcddd/>). Using DDDs and the total prescribed dosages, daily use (DU) of all antihypertensive drugs was calculated.

**Echocardiography measurements**

Participants in 15 centres were requested to undergo echocardiography next to the standard CONTRAST data collection at baseline, after 6 months, after 12 months and annually thereafter.

Transthoracic M-mode echocardiography studies were performed on a non-dialysis day by an echocardiographer at the participating local hospital. From the parasternal long axis position the left ventricular end-diastolic diameter (LVEDD), end-systolic diameter (LVESD) as well as the posterior and septal wall thickness were determined. The ultrasound investigations were then assessed by an independent experienced echocardiographer at the Core Laboratory (Vrije Universiteit Medisch Centrum, Amsterdam, the Netherlands), who was blinded for all other patient data. LVM was calculated using the formula of Devereux and Reicke (15), modified in accordance with the recommendations of the American Society of Echocardiography. (16) Left ventricular ejection fraction (EF) was calculated using left ventricular diameters at end systole and end diastole obtained from M-mode images. Cardiac output (CO) was estimated during echocardiography.

Systolic and diastolic blood pressure (SBP and DBP) was measured using a standard electronic sphygmomanometer during the echocardiography session. MAP, computed as  $(SBP \cdot 1/3 + DBP \cdot 2/3)$ , was recorded as the mean of the values measured before and after dialysis treatment. Peripheral resistance (PR) was computed as  $(MAP/CO)$  and expressed in mmHg-min/L.

**Outcome**

The primary study aim in the present analysis was the rate of change per year in PR, CO, MAP, SBP and DBP.

**Data analysis**

Data were reported as means with standard deviations, medians with interquartile ranges (IQR), or proportions when appropriate.

Linear mixed effect models were performed with a random intercept and random slope or a random intercept alone (depending on the lowest Aikake's information criterion value)

to model changes over time of PR, CO, MAP, SBP and DBP, EF and DU of antihypertensives. All models were adjusted for treatment modality: online post-dilution hemodiafiltration versus standard low-flux hemodialysis (intervention) as well as age, gender, body mass index, dialysis vintage, a history of cardiovascular disease, and daily use (in defined daily dose) of antihypertensive medication. Body mass index and daily use of antihypertensive medication were modelled as time-varying covariates.

Results were considered statistically significant when  $p < 0.05$  (two-sided). All calculations were made by use of a standard statistical package (SPSS for Windows Version 20.0.1; SPSS Inc. Headquarters, Chicago, Illinois, US).

## **Results**

### **Baseline characteristics**

The baseline patient characteristics of the 84 patients participating in this study are shown in Table 1. Mean age was  $62 \pm 14$  years, 46 (55%) were male and the median dialysis vintage was 1.7 (P25-P75: 0.8 – 3.1) years. After inclusion patients were followed for an average of 2.4 years (range, 0.4–5.9 years; median 2.1 years). The participant flowchart of the cardiac output and blood pressure measurements is shown in the supplementary Figure 1.

Antihypertensive medication was used by 68 (81%) participants, with a median daily use of 4.4 DDD (P25 – P75: 2.6 – 10.1). A total of 45 (53%) patients used a renin-angiotensin-aldosterone system (RAAS) inhibitor, with a median DU of 2.0 DDD (P25 – P75: 1.0 – 2.0). None of the participants used an alpha-blocker or centrally acting antihypertensives.

The baseline hemodynamic measurements of the study population are shown in Table 2. The median PR was  $17.8 \text{ mmHg} \cdot \text{min/L}$  (P25 – P75: 15.3 – 22.6), while mean CO was  $5.5 \pm 1.4 \text{ L/min}$  and mean MAP  $97 \pm 15 \text{ mmHg}$ .

### **Cardiovascular function over time**

The estimated rates of changes of the parameters of cardiovascular function are shown in table 3, both univariate and with adjustment for age, gender, BMI, dialysis vintage, history

**Table 1:** Baseline characteristics of the study participants.

<b>Demographic data</b>	
Male gender	46 (55%)
Race, caucasian	67 (80%)
Age (years)	62 ± 14
<b>Anthropometrics</b>	
Body mass index (kg/m <sup>2</sup> )	24.5 ± 4.2
Body surface area (m <sup>2</sup> )	1.82 ± 0.21
<b>Dialysis Properties</b>	
Duration of dialysis (minutes)	240 (180 - 240)*
Blood flow (mL/minute)	309 ± 37
spKt/V <sub>urea</sub>	1.31 (1.01 - 2.07)*
AV fistula	70 (83%)
Graft	14 (17%)
<b>Comorbidities</b>	
Cardiovascular disease	37 (44%)
Diabetes	22 (27%)
Previous kidney transplant	10 (18%)
Dialysis vintage (years)	1.7 (0.8 – 3.1)*
Residual renal function	38 (45%)
Smoking	14 (17%)
<b>Laboratory parameters</b>	
Hemoglobin (g/dL)	7.4 ± 0.8
Phosphate (mmol/L)	1.72 ± 0.60
Beta 2 - microglobulin (mg/L)	27.2 ± 10.1
Albumin (g/L)	39.3 ± 4.2
Creatinin (µmol/L)	912 ± 274
<b>Therapeutic parameters<sup>#</sup></b>	
Antihypertensive medication	68 (81%) / 4.4 (2.6 - 10.1)*
Diuretic	33 (39%) / 5.0 (4.8 - 10.6)*
Beta-blocker	47 (56%) / 0.6 (0.3 - 0.8)*
RAAS inhibitor	45 (53%) / 2.0 (1.0 - 2.0)*
ACE-inhibitors	28 (33%) / 2.0 (1.0 - 3.5)*
AT-2 antagonists	21 (25%) / 2.0 (1.0 - 2.0)*
Calcium channel blocker	23 (27%) / 2.0 (2.0 - 2.0)*

Data expressed as n (%) or mean  $\pm$  SD.

\* median and interquartile range (P25 – P75) are provided

# therapeutic parameters are reported as prevalence / daily use (defined daily dose) in prevalent patients

ACE: angiotensin converting enzyme; AT-2: angiotensin 2; AV: arterio-venous; RAAS: renin-angiotensin-aldosterone system.

To convert hemoglobin from mmol/L to g/dL divide by 0.62; phosphorous in mmol/L to mg/dL, divide by 0.323; albumin in g/L to g/dL, divide by 10; creatinine in  $\mu$ mol/L to mg/dL divide by 88.4.

of cardiovascular disease and daily use of antihypertensive medication. During follow-up DBP decreased significantly over time by -5.77mmHg per year (95%CI: -9.29 to -2.25,  $p=0.002$ ), while SBP tended to decrease also by -4.31mmHg per year (95% CI: -12.58 to 0.3.94,  $p=0.25$ ), although the rate of change was not significant (Figure 1). Hence MAP also decreased significantly over time by -5.43mmHg (95% CI: -9.80 to -1.06,  $p=0.018$ ). CO remained stable during follow up: 0.23 L/min per year (95% CI: -0.2 to 0.7,  $p=0.31$ ) as shown in Figure 2. Heart rate also remained stable: 0.94 beats/min per year (95% CI: -3.00 to 4.29,  $p=0.62$ ). PR decreased significantly by 2.3 mmHg•min/L per year (95% CI: -4.1 to -0.6,  $p=0.016$ ) as shown in Figure 3. EF also decreased by 3.3% per year (95% CI: -6.5 to -0.1,  $p=0.047$ ).

**Table 2:** Hemodynamic measurements at baseline.

<b>Hemodynamic measurements</b>	
Peripheral resistance (mmHg•min/l)	17.8 (15.3 – 22.6)*
Cardiac Output (L/minute)	5.5 $\pm$ 1.5
Mean arterial pressure (mmHg)	97 $\pm$ 15
Systolic blood pressure (mm Hg)	139 $\pm$ 28
Diastolic blood pressure (mm Hg)	77 $\pm$ 12
Heart rate (beats per minute)	73 $\pm$ 14
LVEDD (mm)	49 $\pm$ 7
LVESD (mm)	32 (14 - 58)*
EFLV (%)	61 $\pm$ 15

Data expressed as mean  $\pm$  SD.

\* median and interquartile range are provided

EFLV: ejection fraction of left ventricle; LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter; LVM: left ventricular mass; LVMI: left ventricular mass index.

**Table 3:** Annual rate of change of parameters of cardiovascular function.

	<b>Estimate slope (unit per year)</b>	<b>95% CI slope</b>	<b>p-value</b>
<b><i>Univariate</i></b>			
Peripheral resistance (mmHg·min/l)	-1.83	-3.15 to -0.51	0.009
Cardiac Output (L/minute)	0.70	0.24 to 1.16	0.005
Mean arterial pressure (mmHg)	-4.04	-7.35 to -0.73	0.019
Systolic blood pressure (mm Hg)	-3.80	-9.66 to 2.06	0.18
Diastolic blood pressure (mm Hg)	-4.21	-6.84 to -1.58	0.003
Heart rate (beats per second)	0.44	-2.73 to 3.60	0.78
Ejection fraction of left ventricle (%)	-2.15	-8.06 to 3.76	0.046
LVEDD (mm)	-0.44	-1.86 to 0.99	0.54
LVESD (mm)	-0.35	-2.99 to 2.28	0.78
<b><i>Corrected rate of change*</i></b>			
Periphery resistance (mmHg·min/l)	-3.30	-6.59 to -0.24	0.036
Cardiac Output (L/minute)	0.23	-0.23 to 0.68	0.31
Mean arterial pressure (mmHg)	-5.43	-9.80 to -1.06	0.018
Systolic blood pressure (mm Hg)	-4.31	-12.58 to 3.94	0.25
Diastolic blood pressure (mm Hg)	-5.77	-9.29 to -2.25	0.002
Heart rate (beats per second)	0.94	-3.00 to 4.29	0.62
Ejection fraction of left ventricle (%)	-3.25	-6.45 to -0.04	0.047
LVEDD (mm)	-0.99	-3.47 to 1.48	0.42
LVESD (mm)	-1.10	-3.29 to 2.05	0.21

\*Rate of change is corrected for age, gender, body mass index, dialysis vintage, a history of cardiovascular disease, intervention and daily use (in defined daily dose) of antihypertensive medication. Body mass index and daily use of antihypertensive medication are modelled as time-varying covariates.

LVEDD: left ventricular end diastolic diameter; LVESD: left ventricular end systolic diameter.

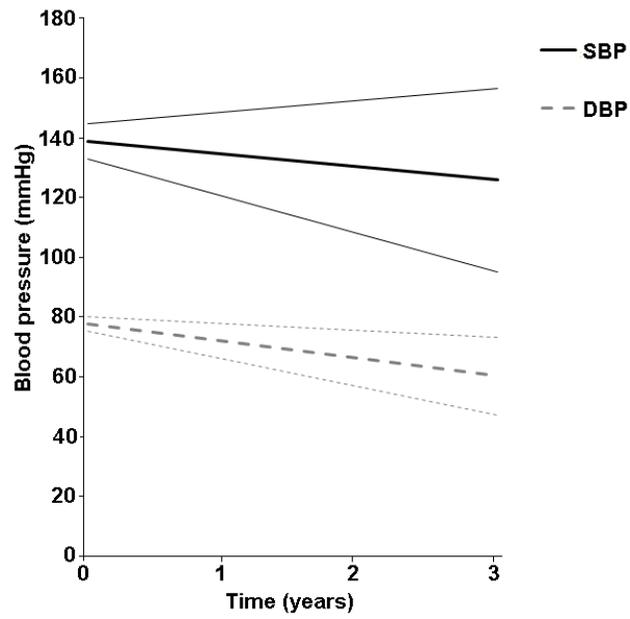
### Antihypertensive medication use over time

Daily use of antihypertensive medication decreased significantly over time by -1.09 DDD per year (95% CI: -1.78 to -0.41,  $p=0.002$ ) as shown in Table 4. For purposes of illustration, a decrease in DU of antihypertensive medication by 1.09 DDD would for example be comparable to a decrease of the dose enalapril by 11mg per day, or a decrease of the metoprolol dose by 165mg per day. (17) When rate of change of separate groups of antihypertensive medication was studied, an overall trend for a decrease of DU over time was observed, although the decreases per medication group were not significant. DU of RAAS-inhibitors did not change significantly over time: -0.14 DDD per year (95% CI: -0.62 to 0.33,  $p=0.54$ ).

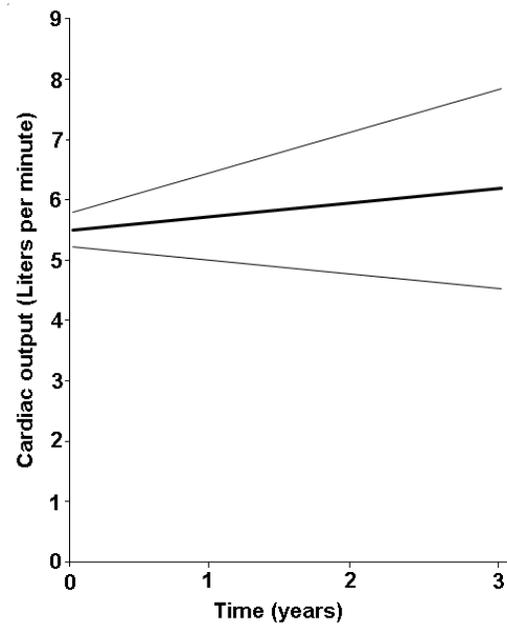
**Table 4:** Annual rate of change of daily use (in defined daily dose) of antihypertensive medication.

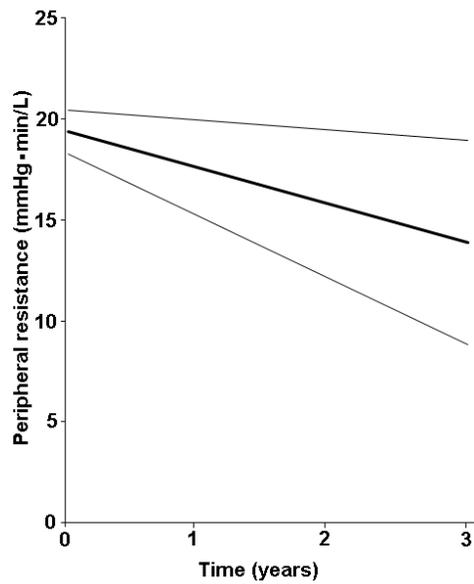
	Estimate slope (DU in DDD per year)	95% CI slope	p-value
Diuretic	-0.65	-2.56 to 1.27	0.46
Beta-blocker	-0.02	-0.16 to 0.12	0.77
RAAS-inhibitor	-0.14	-0.62 to 0.33	0.54
ACE -inhibitor	-0.30	-0.84 to 0.24	0.26
AT-2 antagonist	-0.13	-0.42 to 0.16	0.36
Calcium antagonist	-0.01	-0.09 to 0.08	0.96
All antihypertensives	-1.09	-1.78 to -0.41	0.002

ACE: angiotensin converting enzyme; AT-2: angiotensin 2; DDD: defined daily dose; DU: daily use; RAAS: renin-angiotensin-aldosterone system.

**Figure 1:** Mean changes in blood pressure over time with 95% confidence intervals.

DBP: diastolic blood pressure; SBP: systolic blood pressure.

**Figure 2:** Mean changes in cardiac output over time with 95% confidence intervals.

**Figure 3:** Mean changes in peripheral resistance over time with 95% confidence intervals.**Discussion**

We are among the first to study rate of change of PR and CO in ESKD patients over time, and how this influences the BP. From our analysis three main conclusions can be drawn. First, We have demonstrated that MAP decreases over time, which is fully explained by the decrease in DBP. As CO remained unaltered, this decline of MAP and DBP most likely results from a decrease in PR over time. Second, we clearly showed that Left ventricular EF decreases over time in our population, while heart rate (HR) tends to increase (although this change is not significant). Therefore, it is likely that a certain extent of heart failure occurs, but can be compensated by increasing HR, thus keeping the CO constant. Left ventricular EF decreases over time in our population, while heart rate (HR) tends to increase (although this change is not significant). Therefore, it is likely that a certain extent of heart failure occurs, but can be compensated by increasing HR, thus keeping the CO constant. Third, daily use of antihypertensive medication also decreases over time. Hence it is unlikely that prescription of antihypertensive medication contributes to the BP decline.

Sympathetic activity is higher in dialysis patients than in the overall population. (10;18;19) (Ischemic) kidney damage leads to activation of the RAAS system, and an increase in sympathetic nerve activity. The activated RAAS system causes an additional stimulation of the sympathetic activity, which in turn increases the peripheral resistance. (20) To illustrate, Converse et al demonstrated in an observational study in 34 patients (23 on dialysis), that sympathetic nerve activity was higher in dialysis patients compared to healthy controls. (19) Also, Araujo et al have shown in an observational study in 31 hemodialysis patients that a lower residual diuresis (ranging 0 to 2000mL/24 hours) is related to a higher total peripheral vascular resistance index. (21)

In long-term dialysis patients, kidney damage is severe, and eventually atrophy of the non-functional kidneys occurs. One can hypothesize that when the kidney is atrophic, its ability to activate the RAAS system and in the end increase the peripheral resistance also diminishes. In an earlier observational study in the entire CONTRAST population we have shown that patients with a higher dialysis vintage indeed experience a larger decline in both SBP and DBP. [ref: Mostovaya et al, 'BP over time']. Hence, it is conceivable that these larger declines in BP could be caused by a more pronounced decline in PR in the patients who have been undergoing dialysis for a longer period of time, and thus whose kidneys have undergone more atrophic changes. Furthermore, the above mentioned study by Converse et al also demonstrated that when dialysis patients had undergone a bilateral nephrectomy their sympathetic nervous activity levels were similar to those of the healthy controls. (19)

#### **Antihypertensive medication use**

We have systematically reported DU of antihypertensive medication in dialysis patients over several years of follow-up. DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDD provide a fixed unit of measurement independent of price and dosage form enabling the researcher to assess trends in drug consumption and to perform comparisons between population groups. (17) Both a decrease in DU of antihypertensive medication (of -1.1 DDD per year, a seemingly

clinically relevant difference) and a decrease of BP occurs over time. Thus it is improbable that the BP decrease may be caused by changes in antihypertensive medication use.

Since an increased use in RAAS inhibitor use could in theory also lead to a decrease in PR over time, we have studied the changes in DDD specifically for this medication group. However, no significant changes were found in DDD dose of RAAS inhibitors. Thus, it is improbable that PR decrease is caused by a change in RAAS-inhibitor use.

Most likely, use of antihypertensive medication was restricted over time by the attending nephrologists because of a decreasing BP in these patients.

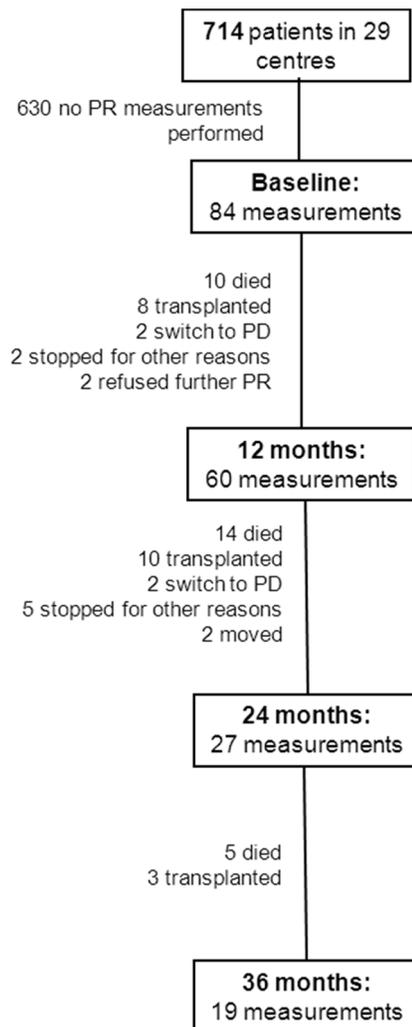
### **Strengths and limitations**

The strengths of our study are the concise and prospective data collection over a long follow-up period. In addition, all measurements were taken into account with the linear mixed models, where time-dependent co-variables were modelled adequately.

A limitation of this study is that CO and simultaneous BP measurements were not available for all patients included in CONTRAST, since it was not logistically feasible to perform these measurements in the entire study population. Therefore, we might not have the power to demonstrate significant rates of changes for some parameters (such as CO), while these could in fact exist. Furthermore, a relevant proportion of patients dropped out (mainly due to death or transplantation) or missed examinations during the follow-up period. Although mixed effect models can calculate rate of change well, with some missing data, the precision of the estimates decreases. Another potential limitation is that an intervention, namely HDF, was performed in this study. Therefore, changes over time might be affected by the intervention. However, we did not find differences in BP changes over time when we adjusted for treatment modality in our analyses. Lastly, we did not record blood flow in the vascular access of the patients in our population, nor if and how vascular access type changed over time. Theoretically, an arterio-venous fistula could expand over time, leading to an increase in CO and a decrease in PR; alternatively a stenosis may develop in a graft, leading to a decrease in CO and an increase in PR.

**Conclusion**

In a cohort of chronic hemodialysis patients, MAP decreases over the course of 3 years, mainly due a decrease in DBP. This decline of MAP can be explained by a decrease in PR over time, but not a change in CO. Decrease in BP cannot be explained by prescription of antihypertensives, since the prescribed doses of antihypertensive medication also decrease over time. Precise mechanisms were not investigated, but a decrease in renin-angiotensin-aldosteron system activation and renal sympathetic nerve activity as a consequence of a further deteriorating kidney function over time could be a plausible explanation

**Supplementary Figure****Supplementary Figure 1:** Flowchart of CONTRAST participants undergoing echocardiography measurements with simultaneous blood pressure measurements.

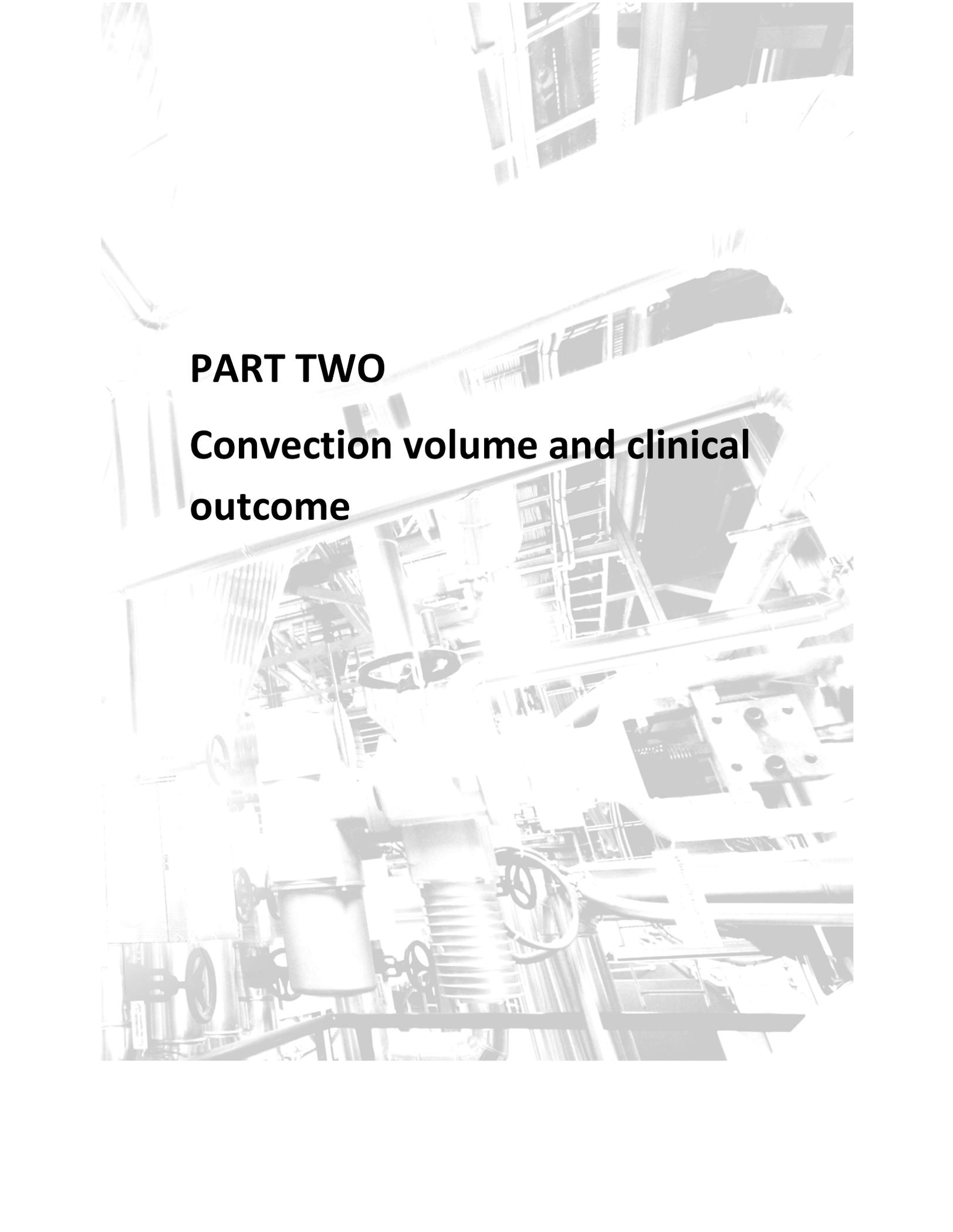
PD: peritoneal dialysis; PR: peripheral resistance

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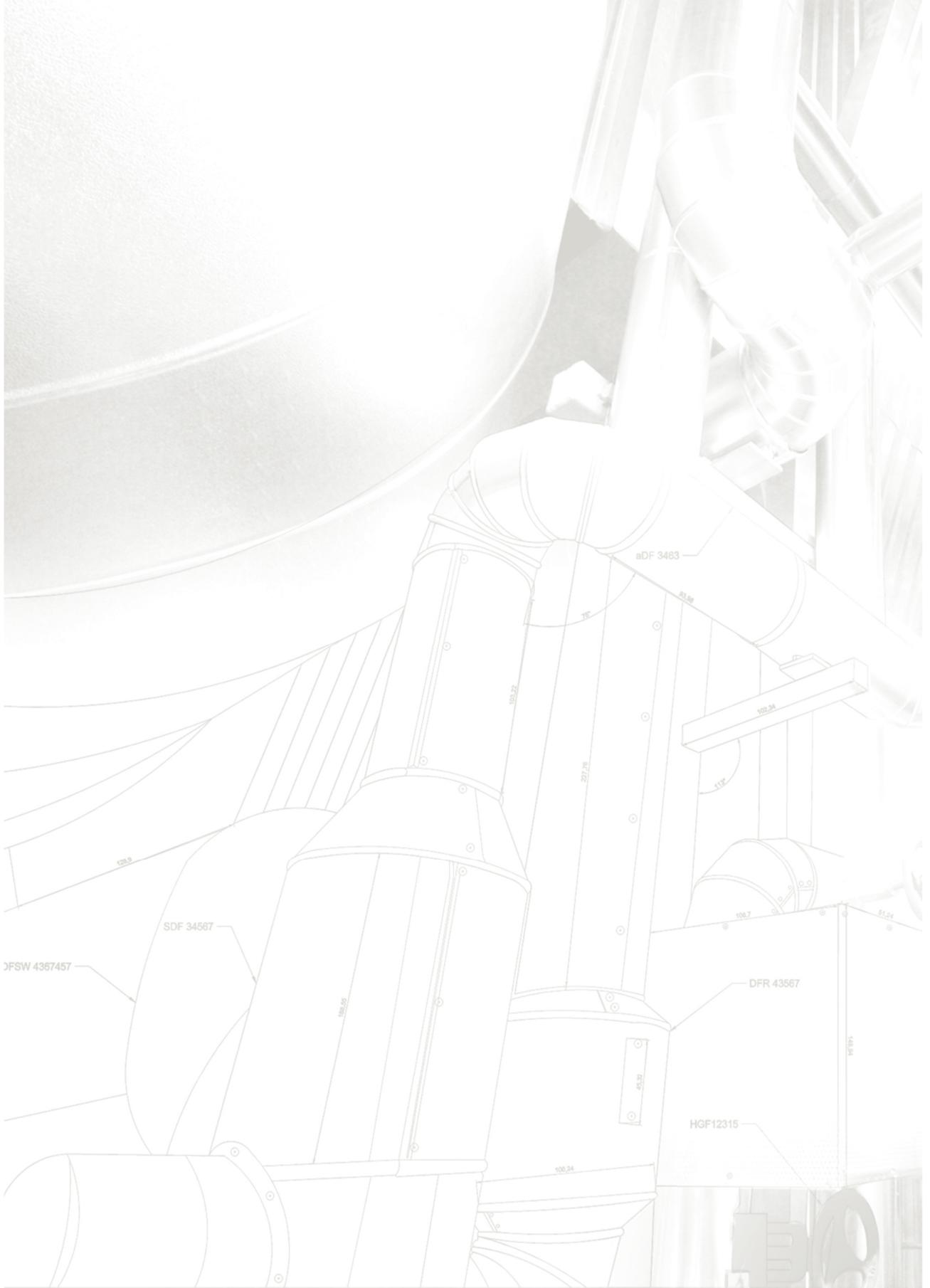






## **PART TWO**

# **Convection volume and clinical outcome**



## Chapter 8

# Clinical evidence on hemodiafiltration: a systematic review and meta-analysis.

*Seminars in Dialysis, 27: 119–127*

Ira M. Mostovaya,<sup>1</sup> Peter J. Blankestijn,<sup>1</sup> Michiel L. Bots,<sup>2</sup> Adrian Covic,<sup>3</sup> Andrew Davenport,<sup>4</sup> Muriel P.C. Grooteman,<sup>5,6</sup> Jörgen Hegbrant,<sup>7</sup> Francesco Locatelli,<sup>8</sup> Raymond Vanholder,<sup>9</sup> Menso J. Nubé.<sup>5,6</sup> on behalf of the EUDIAL, an official ERA-EDTA Working Group

<sup>1</sup>Department of Nephrology, University Medical Center Utrecht, Utrecht, the Netherlands

<sup>2</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

<sup>3</sup>Nephrology Clinic, Dialysis and Renal Transplant Center, C.I. Parhon University Hospital, Gr. T. Popa University of Medicine and Pharmacy, Iasi, Romania

<sup>4</sup>UCL Centre for Nephrology, Royal Free Hospital, University College London Medical School, London, United Kingdom

<sup>5</sup>Department of Nephrology, VU University Medical Center, Amsterdam, the Netherlands

<sup>6</sup>Institute for Cardiovascular Research VU Medical Center (ICaR-VU), VU University Medical Center, Amsterdam, the Netherlands

<sup>7</sup>Diaverum Renal Services Group, Lund, Sweden

<sup>8</sup>Department of Nephrology Dialysis and Renal Transplantation, Alessandro Manzoni Hospital, Lecco, Italy

<sup>9</sup>Nephrology Section, Department of Internal Medicine, University Hospital, Ghent, Belgium

**Abstract**

In this review, a systematic literature search and meta-analysis were performed to assess the effects of hemodiafiltration (HDF) on clinical outcome, if compared to hemodialysis (HD). Furthermore, the relation between the convection volume in HDF and clinical outcome was studied. The literature search identified six randomized controlled trials (RCTs). In a meta-analysis of these RCTs, HDF treatment was related to a decreased risk of mortality (RR: 0.84; 95% CI 0.73–0.96) and cardiovascular death (RR: 0.73; 95% CI 0.57–0.92). *Post hoc* analyses of the three largest RCTs suggested an inverse relation between the magnitude of convection volume and mortality risk. The evidence presented in this analysis supports a wider acceptance of HDF.

**EUDIAL OBJECTIVE**

The general objective assigned to the European DIALysis (EUDIAL) Working Group by the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) was to enhance the quality of dialysis therapies in Europe in the broadest possible sense. Given the increasing interest in convective therapies, the Working Group has started by focusing on hemodiafiltration (HDF) therapies. A EUDIAL consensus conference was held in Paris on 13 October 2011 to discuss definitions, safety standards, clinical outcome and educational issues. Recently, the first report of the EUDIAL group was published, revisiting the definition, dose quantification and safety of HDF. Since the meeting in Paris, new evidence has become available regarding the clinical benefits of HDF. This is the second report of the expert group, in which the relation between HDF and clinical outcomes is systematically reviewed and analyzed, with emphasis on the relation between achieved convection volume and treatment effect.

## **Introduction**

In low flux hemodialysis (HD), solutes with a molecular weight (MW) <500 dalton [D], such as urea and creatinin, are removed by diffusion. In high flux HD, diffusion is combined with convection, which enables the elimination of substances up to 40 kiloD (kD). In hemodiafiltration (HDF), diffusion is also combined with convection, but much more efficiently. Whereas the estimated amount of convective transport during high-flux HD is <10L/session, in HDF 25-60L can be reached, depending on the mode of HDF (pre- or post-dilution). Moreover, while in high-flux HD loss of plasma water is compensated by back-filtration of dialysis fluid within the dialyzer, contemporary HDF equipment allows the online preparation of sterile and pyrogen-free substitution fluid which is infused directly into the circulation of patients.(1) As retention of middle MW (MMW) uremic toxins (<40 kD) has been associated with an adverse clinical outcome in patients with chronic kidney disease (CKD), it has been suggested that removal of these substances by HDF may lead to a reduction in morbidity and mortality. (2)

Several observational studies have reported a lower mortality and less morbidity when subjects, who were treated with HDF, were compared with HD patients. (3-8) In these studies, however, the level of adjustment for potential confounders varied. In general, observational, non-experimental results are subject to residual confounding, leading to either an overestimation or an underestimation of the true benefit, despite adjustments. Three randomized controlled trials (RCT), also reported on a better survival in patients who were treated with HDF. (9-11) However, as these studies were small (23-51 HDF patients) and not powered to detect differences in mortality between treatment arms, the issues on clinical outcome remained largely unsolved after publication of the results.

Recently, the results of three large RCTs, collectively encompassing more than 2400 participants, were published. (12-14) Against expectations, neither the CONvective TRANsport STudy (CONTRAST) (12), nor the Turkish HDF study (13) showed a significant difference in all- cause mortality or (both fatal and non-fatal) cardiovascular events between HDF and HD. By contrast, the Estudio de Supervivencia de Hemodiafiltracion On-

Line (ESHOL), the RCT with the highest achieved convection volumes, reported superiority of HDF over HD with respect to all-cause and cardiovascular mortality. (14) Interestingly, *post hoc* analyses of all three studies suggested a dose-effect relation: the higher the convection volume, the lower the mortality risk, even after adjustment for potential confounders. (12-14)

Therefore, the EUDIAL working group set out to perform a systematic search and a quantitative meta-analysis on published RCTs. The aims of this analysis are first, to assess whether treatment with HDF reduces all-cause mortality and cardiovascular events, and second, to study whether a dose-response relation exists between convection volume and clinical outcome.

## **Materials and Methods**

### **Search strategy**

We searched the PubMed database (Ovid: 1 January 1992 to 18 February 2013) for potential studies. The search was limited to published data only. Documents that were written in another language than English were excluded. The literature search strategy included title, abstract and keywords, combining the terms hemodiafiltration, hemodialysis, clinical events and mortality (table 1). Next, titles and abstracts were obtained and assessed for inclusion. Included studies were RCTs that compared HDF with (low-flux or high flux) HD and had at least all-cause mortality or cardiovascular mortality or cardiovascular events or hospitalizations as outcome measures. After title and abstract screening, full papers were retrieved for more detailed information. We excluded reviews, studies without clinical events and those where patients who were treated with HDF were not considered as a separate group (for example, where HDF patients were combined with patients treated by another convective modality). Additional citations were deduced from the reference lists of papers and review articles produced by the search.

Studies selected by the search to address the first objective were further examined. We checked whether convection volume or infusion/substitution volume was mentioned and defined, and if so, whether the relationship between convection volume and clinical outcome was described.

**Outline of terminology**

For the present study the following terms were applied. When the inter-dialytic weight gain in kilograms was mentioned, this was considered equal to the amount of fluid in liters that was removed by ultrafiltration during treatment. The sterile replacement fluid given as replenishment for the removal of extra fluid during HDF, was called 'substitution fluid'. The sum of the net ultrafiltration volume and the amount of substitution fluid was termed 'convection volume'.

**Methodological evaluation of the retrieved articles**

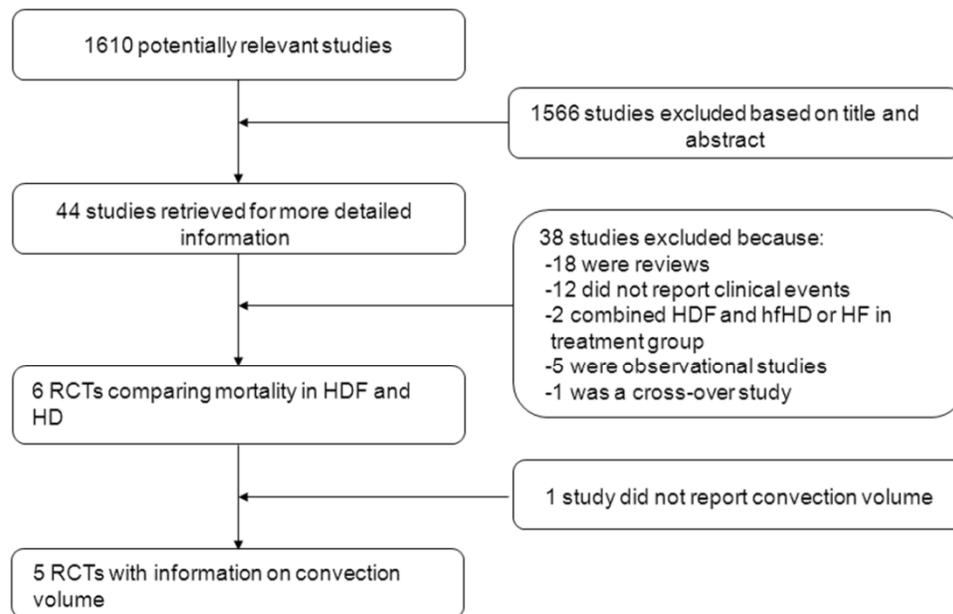
All papers were thoroughly evaluated using the checklist developed by the Cochrane Renal Group. (15;16) Emphasis was placed on the risk of bias with respect to the relation between HDF and mortality and/or morbidity. Bias refers to a systematic deviation from the truth, i.e., the reported relative risk is either overestimated or underestimated. Aspects that were specifically addressed in the present evaluation dealt with the adequacy of randomization in trials, intention-to-treat approach, exclusion of patients after randomization, blinding of the outcome assessment, completeness of follow-up after randomization, and the selective censoring after non-fatal events.

**Data analysis**

Effect measures were reported first, as described in the quoted articles (relative risks (RR), relative *rates*, hazard ratios (HR) and cumulative mortality data). If possible, the absolute number of deaths, or cumulative survival at 1, 2 and 3 years was used to calculate the RR (proportion of deaths in HDF group / proportion of deaths in HD group) for mortality. Probability values were considered significant at a two sided  $p < 0.05$ .

For the meta-analysis of mortality risks, only RCTs reporting crude mortality were included. The overall numbers of participants and deaths per treatment group were used to calculate the RR for each study and its 95% confidence interval (CI). Studies were assigned weights according to the inverse variance method, which means that both the size and number of events in the study positively affects the allocated weight. (17) The

**Figure 1:** Flow chart of selection of articles. Search strategy to identify studies into the relation of HDF with clinical outcome.



HD: hemodialysis, HDF: hemodiafiltration, HF: hemofiltration; hfHD: high flux hemodialysis; RCT: randomized controlled trial

method of Mantel-Haenszel was used to calculate the relative risk for the pooled data in a fixed-effects model and the DerSimonian-Laird method was used for the pooled relative risk in a random-effects model. (18) In a fixed effects model the assumption is made that there is one true effect size, which underlies all studies in the analysis and that differences in observed effects are due to sampling error. A random effects model assumes that the true effect varies from study to study, which makes the estimate of the pooled effect size be adequate. However, one might argue that since study populations and intensity of HDF differed, a random effects model would be considered more appropriate. For these more conservative. As p-values for homogeneity were  $>0.10$ , a fixed effects model would

**Table 1:** Search strategy to identify RCTs into the relation between HDF and clinical outcome .

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Database:	PubMed on 18 February 2013
General:	Only English language
Domain :	#1 ( <b>hemodialysis</b> OR haemodialysis OR (renal AND replacement AND therapy))
Determinant:	#2 ( <b>hemodiafiltration</b> OR haemodiafiltration OR hemofiltration OR haemofiltration OR ultrafiltration)
Outcome: #3	(( <b>mortality</b> OR survival OR death OR dying OR (loss AND of AND life) OR fatality OR decease OR deceased OR died OR ( <b>cardiovascular</b> AND <b>events</b> ) OR (cardiovascular AND disease) OR (heart AND disease) OR (clinical AND events) OR (clinical AND event))
Search results:	#1: 117 778 #2: 21 732 #3: 2 117 223 #1 AND #2 AND #3: 1775 #1 AND #2 and #3 after 1 Jan 1992: 1610

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reasons we have chosen to display both options. A Forest plot was formatted to illustrate the relative strengths of treatment effects and their pooled results.

Next, we repeated the meta-analysis for all-cause mortality rates and RCTs mentioning cardiovascular mortality risks and mortality *rates* to allow for differences in person years of follow-up across the trials.

## **Results**

### **Results from search findings**

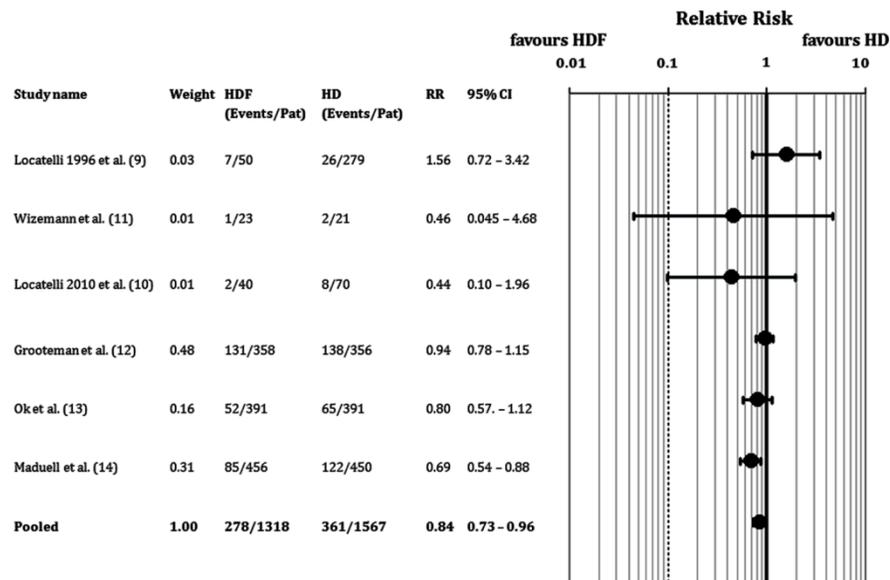
The literature search resulted in 1610 hits. After screening for title and abstract, 44 manuscripts remained. Eighteen articles were reviews and therefore excluded. Twelve publications were excluded after examination of the full text, since they did not report clinical events, and two manuscripts compared a combination of HDF and high flux HD or hemofiltration respectively with a control group, and were therefore excluded. Five studies were excluded because they were observational trials, and one study was excluded because it was a cross-over study. Finally, 6 RCTs were left for critical appraisal (figure 1). Cross referencing yielded no further studies. Several characteristics and mortality results are summarized in table 2.

In four RCTs, the substitution volume was administered as post-dilution (9;12-14), in one as mid-dilution (11) and in one as pre-dilution HDF (10). The type of HD in the reference group varied. In three studies, low-flux HD was used for comparison (10-12), in one high-flux HD (13) and in two both low-flux and high-flux HD.(9;14) Follow-up time varied from 2-3 years in the RCTs.

### HDF and fatal and non-fatal outcomes: evidence from RCTs

The potential risks of bias in the RCTs reporting on all-cause and cause specific mortality are described in the supplementary table 1. The most frequent type of potential risk of bias was “incomplete follow-up” (ranging from 18% to 47%). Incomplete follow up means that individuals were censored at a non-fatal event, mostly kidney transplantation, and therefore not followed afterwards for death. This type of bias may influence the hazard

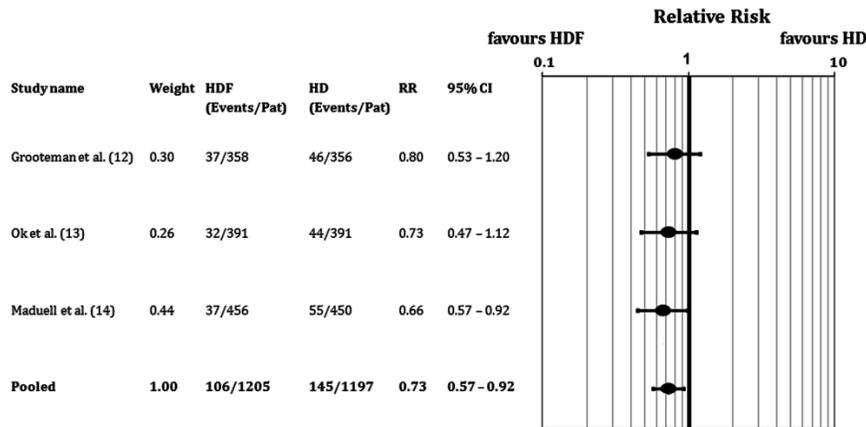
**Figure 2:** Meta-analysis of all RCTs comparing *mortality* in patients treated with HD or HDF using patient numbers. A fixed effects model was used for the meta-analysis of survival data in the RCTs ( $p$  for homogeneity = 0.19).



ratio, if censoring differs across treatment modalities. Other potential risks of bias were the non-availability of information on blinding for the assessment of both treatment allocation and outcome. Out of the six RCTs only three (12-14) were designed with cause specific or all-cause mortality as primary outcome.

Figure 2 shows a Forest plot of the mortality data in a fixed-effect model ( $p$  for homogeneity: 0.19). Overall, mortality was significantly lower in the HDF group (RR: 0.84; 95% CI 0.73–0.96). When a random effects model was applied a similar risk reduction was observed, albeit with wider confidence intervals (RR: 0.83; 95% CI 0.68–1.02). When the meta-analysis was restricted to those trials that had been designed to study mortality as primary outcome (CONTRAST, Turkish HDF study and ESHOL), results were similar (fixed effects model: RR: 0.83; 95% CI: 0.67–0.95;  $p$  for homogeneity: 0.14; in a random effects

**Figure 3:** Meta-analysis of all RCTs comparing *cardiovascular mortality* in patients treated with HD or HDF using patient numbers. A fixed effects model was used for the meta-analysis of cardiovascular death free survival data in the RCTs ( $p$  for homogeneity = 0.88).



model RR: 0.81; 95% CI 0.66–0.99). When, instead of cumulative risks (% per time interval), mortality *rates* (person years) were studied (available in CONTRAST, Turkish HDF study and ESHOL), all-cause mortality was significantly lower in the HDF group (fixed effect model relative *rate*: 0.83; 95% CI 0.71–0.98, p for homogeneity: 0.26; random effects model relative *rate*: 0.83; 95% CI 0.68–1.00).

Figure 3 shows a Forest plot of cardiovascular mortality in the three RCTs that compared this outcome parameter between HDF and HD patients. Overall, cardiovascular mortality was significantly lower in the HDF group (fixed effects model: RR: 0.73; 95% CI 0.57–0.92; p for homogeneity: 0.88; random effects model RR: 0.73; 95% CI 0.58 – 0.92). Similar results were obtained when cardiovascular *rates* were used instead of cumulative risks (fixed effects model relative *rate*: 0.74; 95% CI 0.57–0.95, p for homogeneity: 0.87; random effects model relative *rate*: 0.74; 95% CI 0.57–0.95).

With respect to combined fatal and non-fatal cardiovascular events, CONTRAST (HR: 1.07; 95% CI 0.83 – 1.39) showed no difference in incidence between HD and HDF. (12) The Turkish HDF study did not report difference in primary outcome, which was a combination of mortality and both fatal and non-fatal cardiovascular events (HR: 0.81; 95% CI 0.58 – 1.14). (13)

As for hospitalizations, ESHOL reported a relative risk reduction in favour of the HDF group (*rate* ratio 0.78; 95% CI: 0.67–0.90), while the Turkish HDF study reported no difference between treatment arms (20.4 versus 18.6 per 100 patient years in the HDF and HD groups, respectively). (14) CONTRAST only reported on the risk of hospital admission due to infection and found no difference between HDF and HD patients (HR: 1.21, 95% CI: 0.94–1.56). (12)

### **Convection volume and fatal and non-fatal outcome**

In five out of six articles information was available on the average volume of convection or substitution fluid and varied from 8 to 24 litres in post-dilution HDF and up to 60 litres in pre-dilution HDF (table 2). The achieved convection or substitution volume was reported in only three of these studies (12-14), while two provided the target volume (9;11).

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**Table 2:** Studies describing the relation between HDF versus HD and mortality.

Reference	Intervention	Patient number	Outcome	CV*	SV*	IDWL*	1yr RR	2yr RR	3 yr RR	HR	95% CI of HR
ESHOL 2012 (14)	hfHD vs olHDF	906 456 = olHDF	improved survival in olHDF (by 30%)	23.7	20.8 - 21.8 <sup>#</sup>	1.9 - 2.9 <sup>#</sup>	0.70	0.71	0.71	0.70	0.53 – 0.92
Turkish HDF study 2012 (13)	hfHD vs olHDF	782 391=olHDF	no difference in mortality	19.5	17.1	2.4	0.55	0.78	0.84	0.82	0.59 – 1.16
CONTRAST 2012 (12)	lfHD vs olHDF	714 358 = HDF	no difference in mortality	20.7	18.8	1.9	0.67	0.87	0.99	0.95	0.75 – 1.20
Locatelli et al. 2010 (10)	HD vs HDF & HF	146 36 = HF, 40 = HDF	no difference in mortality	-	-	-	-	0.44	-	-	-
Wizemann 2001 (11)	HD vs HDF	44 23 = HDF	no difference in mortality	-	60	-	-	0.45	-	-	-
Locatelli et al. 1996 (9)	HD vs hfHD & HDF	380 51=hfHD, 50=HDF	no difference in mortality	8-12	-	-	-	hfHD: 0.46 HDF: 2.92	-	-	-

\*:In Liters per session.

<sup>#</sup>: Average SV and IDWL per 6 months were reported in the manuscript. The lowest and highest average volume (range) are shown in the table.

CONTRAST: Convective Transport Study; ESHOL: Estudio de Supervivencia de Hemodiafiltracion On-Line;

CI: confidence interval; CV: convective volume; HD: hemodialysis; HDF: hemodiafiltration; HF: hemofiltration; hfHD: high flux hemodialysis; HR: hazard ratio; IDWL: inter dialytic weight loss; lfHD: low flux hemodialysis; olHDF: online hemodiafiltration; RCT: randomized controlled trial; RR: relative risk; SV: substitution volume.

**Table 3:** Mortality rates in CONTRAST and Turkish HDF Study stratified and arranged by convection volume, on-treatment analyses.

Reference	CV (L/treatment)	SV (L/treatment)	IDWL (L/treatment)	HR	95% CI of HR
ESHOL	<23.1	-	-	0.90	0.61 to 1.31
2012 (14)	23.1 - 25.4	-	-	0.60	0.39 to 0.90
	>25.4	-	-	0.55	0.34 to 0.84
Turkish HDF study	18.8	16.2	2.6	1.10	0.68 – 1.76
2012 (13)	20.3	18.1	2.2	0.54	0.31 – 0.93
CONTRAST	<18.18	-	-	0.80	0.52 – 1.24
2012 (12)	18.18 - 21.95	-	-	0.84	0.54 – 1.29
	>21.95	-	-	0.61	0.38 – 0.98

\*In ESHOL and CONTRAST, survival risks were reported by tertiles of convection volume. Ranges of the tertiles are reported.

\*\*In the Turkish study, survival risks were reported for patients above and below the median ultrafiltration fluid. Means of convection volume per group are shown. In the 'low CV group', the mean ultrafiltration fluid was 16.2L, while in the 'high CV group' the mean ultrafiltration fluid was 18.1L.

CI: confidence interval; CV: convection volume, HR : hazard ratio; IDWL: interdialytic weight loss; SV: substitution volume.

*Post hoc* analyses of three RCTs provided information on a potential dose-response relation between convection volume and mortality. These *post hoc* analyses must be viewed as cohort analyses and therefore, adequate multivariable adjustments should be made in order to reduce potential confounding. In CONTRAST, mortality risk in HDF patients with a convection volume >22L (the highest tertile) was significantly lower than in HD patients (HR: 0.61 (95% CI: 0.38 – 0.98)). (12) The Turkish HDF trial reported on a reduced mortality in HDF patients who received >17.4 L substitution fluid per session, which is equivalent to a convection volume of approximately 19.5 L. (HR: 0.54; 95% CI: 0.31 – 0.93). (13) In ESHOL, mortality risk in HDF patients with convection volumes between 23.1-25.4 L and >25.4 L (two upper tertiles) was considerably lower than in HD patients (HR: 0.60 (95% CI 0.39 – 0.90) and HR: 0.55 (95% CI 0.34 – 0.84), respectively). (14) An overview of convection volumes and corresponding mortality risks is shown in table 3

**Table 4:** Patient characteristics at baseline of three large RCTs comparing overall mortality in HDF versus HD.

	<i>CONTRAST (12)</i>		<i>Turkish HDF study (13)</i>		<i>ESHOL (14)</i>	
	<i>HDF</i>	<i>HD</i>	<i>HDF</i>	<i>HD</i>	<i>HDF</i>	<i>HD</i>
Age	64.1 ± 14.0	64.0 ± 13.4	56.4 ± 13.0	56.5 ± 14.9	64.5 ± 14.3	66.3 ± 14.3
Male gender	60%	65%	59%	58%	69%	64%
BMI post dialysis (kg/m <sup>2</sup> )	25.2 ± 5.0	25.6 ± 4.6	24.9 ± 4.9	24.8 ± 4.6	24.9 ± 4.6	24.9 ± 4.4
Cardiovascular disease	42%	46%	27%	26%	NA	NA
Diabetes	26%	22%	36%	33%	23%	27%
Dialysis Vintage (years)	2.8 ± 2.9	3.0 ± 2.8	4.8 ± 3.6	4.9 ± 3.8	2.4 (1.0 - 5.0)*	2.3 (1.0 - 4.8)*
Charlson comorbidity index	NA	NA	NA	NA	6.0 (5.0 - 8.0)*	7.0 (5.0 - 8.0)*
Vascular access						
Fistula	78%	81%	96%	95%	89%	83%
Graft	16%	12%	NA	NA	3%	4%
Catheter	6%	7%	NA	NA	8%	13%
Blood flow rate (mL/min)	302 ± 3.9	299 ± 41	294 ± 46	294 ± 44	392 (387 - 398)*	380 (374 - 387)*
eKt/V	1.41 ± 0.24	1.38 ± 0.19	1.44 ± 0.27	1.42 ± 0.25	NA	NA
Haemoglobin (g/dL)	11.9 ± 1.3	11.8 ± 1.2	11.4 ± 1.5	11.4 ± 1.4	12.0 (11.9 - 12.1)*	12.0 (11.8 - 12.1)*
Albumin (g/L)	40.2 ± 3.8	40.6 ± 3.9	38.3 ± 3.5	38.5 ± 3.8	41.1 (40.7 - 41.5)*	40.6 (40.2 - 41.1)*
Phosphate (mg/dL)	5.12 ± 1.58	5.05 ± 1.46	4.90 ± 1.42	4.88 ± 1.48	4.73 (4.60 - 4.87)*	4.58 (4.45 - 4.71)*
Creatinine (mg/dL)	9.52 ± 2.04	9.94 ± 2.83	8.0 ± 1.9	8.0 ± 2.3	8.1 (7.8 - 8.3)*	7.0 (7.8 - 8.2)*
β-2 microglobulin (mg/L)	30.7 ± 14.3	32.3 ± 13.6	26.5 ± 7.9	26.1 ± 9.7	23.9 (22.7 - 25.0)*	24.8 (23.6 - 26.1)*
Antihypertensives <sup>≈</sup>	NA	NA	13% <sup>≈</sup>	14% <sup>≈</sup>	59% <sup>≈</sup>	58% <sup>≈</sup>
Beta-blockers	51%	55%	NA	NA	NA	NA
ACE-inhibitors	50%	48%	NA	NA	NA	NA
EPO	88%	90%	56%	58%	90%	93%

\*median and (P25 - P75) are provided

<sup>≈</sup> all antihypertensive medication combined; ACE: angiotensin converting enzyme; BMI: body mass index; EPO: erythropoiesis stimulating agents, NA: not available.

**Discussion**

In this study a systematic literature search was performed first, to assess whether treatment with HDF reduces all-cause mortality and cardiovascular events in comparison to HD, and second, to study whether in HDF patients a dose-response relation exists between the magnitude of the convection volume and clinical outcome. For this purpose, only RCTs were considered appropriate. The current analysis provides evidence that HDF reduces all-cause mortality, when compared to HD. Moreover, data from the selected RCTs also suggest a beneficial effect of HDF on cardiovascular mortality. Furthermore, the current analysis supports the idea of a dose- response relationship between the magnitude of the convection volume and mortality risk, i.e. the higher the convection volume the lower the risk. Yet, the published reports contain several potential risks of bias, leading to either an over- or underestimation of the true effect. In addition, the minimal amount of convection volume to obtain clinical benefit is not readily apparent from the published data. Although none of the studies was specifically designed to address safety, none of the evaluated studies provided evidence to suggest that HDF is unsafe.

**HDF and mortality**

Results from randomized controlled trials are generally accepted as the highest level of evidence for efficacy of an intervention. Yet, also RCTs may suffer from methodological flaws leading potentially to biased results that may be responsible for differences in outcomes. Indeed, in the available RCTs there was apparently some risk of bias. In most cases, bias was caused by incomplete follow-up and censoring of participants due to non-fatal events, such as renal transplantation. In ESHOL for example, HDF patients received renal transplants more often than HD patients. When these subjects were withdrawn from follow-up, the HDF group may have been biased by 'censoring alive', which may have led to an overestimation of the treatment effect. The ESHOL study did not provide sufficient detailed information how to judge on the effect of this potential bias, (14) which might have been present in the Turkish HDF Study as well. In that study, 40 patients were

excluded from the HDF group during follow-up due to vascular access problems (censored alive) versus none in the HD group. (13)

Similarly, in ESHOL, patients on HDF who did not reach a minimum of 18L/session of replacement volume for two months, were withdrawn from the study (censoring alive).

(14) The effect of censoring alive on the reported results may be considerable. As an example, in CONTRAST, all participants have been followed for mortality, also after a non-fatal event like renal transplantation. When in CONTRAST analyses were repeated using censoring for the fatal or non-fatal first event the hazard ratio of mortality for HDF versus HD would have been 0.83 (95% CI: 0.64 – 1.08) instead of the currently reported 0.95 (personal communication CONTRAST group).

Apart from bias, variation in the main findings across RCTs may be due to differences in the success of the HDF treatment itself, i.e. the achieved convection volume, based on the assumption that a high convection volume is beneficial. Indeed, while the average convection volume per session was 20.7 L per session in CONTRAST and 19.5 L in the Turkish HDF study, this was 23.7 L in ESHOL (table 2). Finally, variability in results across studies may be a consequence of differences in the treatment of patients in the control arm (low-flux HD in CONTRAST, high-flux HD in ESHOL and the Turkish HDF Study), differences in study population (table 4), and differences in the time of follow-up (supplementary table 1).

### **Convection volume and mortality**

Regarding the magnitude of the convection volume, only 3 out of 5 studies reported the volume that was actually achieved. A large range was found between the different studies, varying between 60 and 8 litres per treatment in pre- and post-dilution HDF, respectively. As the physico-chemical conditions within the dialyser, including blood rheology and trans-membrane pressure, vary greatly between these modes of HDF treatment, in the present review we restricted ourselves to investigations in patients treated with post-dilution HD. Three large RCTs demonstrated in their HDF cohorts that a high convection volume was associated with a lower mortality risk, despite extensive adjustments for potential confounders to exclude dose targeting bias. Moreover, ESHOL, the study with

the highest mean convection volume achieved, not only showed a dose-response effect as reported in CONTRAST and the Turkish HDF study, but also a significant reduction in the overall mortality risk in the total group of HDF patients. (12-14)

Although a dose-response effect of the convection volume on survival is an attractive and plausible finding, the results should be interpreted with caution. In the studies that mentioned the magnitude of the convection volume in relation to mortality risk, the cut off points above which a reduction in risk was found varied considerably (table 3).

Moreover, these analyses differed in the extent of taking confounding into account. (12-

14) Finally, residual confounding, as could be caused by the quality of vascular access, which was not reported in any of the above-mentioned trials, cannot be entirely excluded. Theoretically, a high blood flow may permit a large convection volume at the one hand, and represent a good clinical condition at the other.

Since HDF is characterized by the infusion of large volumes of replacement fluid into the circulation, the question arises whether the chemical and microbiological safety is sufficiently guaranteed. Although the three recently performed trials ESHOL, CONTRAST and Turkish HDF study were not specifically designed to study safety issues, neither study provided any indication that HDF is an unsafe treatment modality. (12-14) On the opposite, CONTRAST investigators reported previously in an analysis of over 11 000 treatment sessions that it is possible to produce substitution fluid of adequate quality over a prolonged period of time. (19) Moreover, in ESHOL, mortality risk due to infectious complications was considerably lower in the HDF group (HR: 0.45; 95% CI 0.21 – 0.96), when compared to HD. (14) Lastly, in none of the above mentioned trials markers of inflammation differed between the HDF and control groups. (12-14)

### **Limitations**

Evidently, this systematic review has its limitations. First, since the research was restricted to PubMed only, publications dealing with the topics involved could be missed if they were not accessible to this database. Furthermore, documents might have been overlooked during the evaluation of titles and abstracts. However, since a crosscheck of the references of the full text articles did not reveal any new papers on this issue, both

aspects seem unlikely. Secondly, with respect to the convection volume, the amounts delivered by post- and pre-dilution HDF differed greatly. Comparison of the effectiveness of these volumes is complex, and therefore, in our opinion, it was neither justifiable nor feasible to compare the effects of pre- and post-dilution HDF on clinical events. Lastly, we can only draw conclusions regarding the relation between convection volume and survival for the ranges that were explored in the selected manuscripts.

### **Unsolved issues**

Several issues are still unclear. (20;21) One aspect deals with the question as to whether certain subgroups behave differently during treatment with HDF. As shown in ESHOL, a high Charlson co-morbidity index score at baseline is an independent predictor for the beneficial effect of HDF on all-cause mortality. Whether other subgroups, such as diabetics (HEMO) and/or patients with a low albumin (MPO), benefit especially from high volume HDF may be resolved in a meta-analysis with individual patient data. Since all of the retrieved studies were performed in prevalent dialysis patients with varying vintage, we cannot predict the effect of HDF in incident patients. An overlapping and leading effect of a previous dialysis modality could influence the clinical outcome. Another item is the duration of HDF treatment. From the current data it is unclear how long HDF treatment must be continued before a beneficial effect on clinical outcome becomes manifest. In ESHOL a 5% difference in mortality risk between HDF and HD was already observed after a treatment period of approximately 18 months (14)

The studies included in this review were generally based on dialysis regimes that applied HDF and HD treatments three times per week. The role of HDF in more intensified dialysis programs, such as daily and nocturnal dialysis, is as of yet unclear.

An important issue that was not addressed in our analysis is the question which factors determine the magnitude of the convection volume. In a previous report, the CONTRAST group showed that both treatment time and blood flow rate are important treatment-related determinants of convection volume. At present it is unknown if, and if so, how, the convection volume can be maximized by increasing treatment time, blood flow rate and the filtration fraction (ratio between ultrafiltration volume and blood flow rate). In

addition, it is unclear whether specific characteristics of the dialyzer, such as the membrane surface area and the ultrafiltration coefficient, or the type of vascular access affect the magnitude of convection volume. (22)

ESHOL, CONTRAST and the Turkish HDF study all had a small (<4.5-10.3%) population with central venous catheters, while patients with temporary catheters were excluded in ESHOL and the Turkish HDF study.(12-14) A common perception is that superior vascular access type (fistulas) contributes to the better survival in patients achieving high convection volumes. Indeed, since blood flow is a determinant of the magnitude of convection volume (22), it seems logical that a qualitatively good vascular access is a prerequisite to achieve high volumes. (1) In this respect it is noteworthy to mention that an extended re-analysis of previously published data from CONTRAST indicates that the type of vascular access is not related to the magnitude of the convection volume (personal communication CONTRAST group). Actually, from this study it appeared that a fistula is not a prerequisite and a CVC not a barrier for achieving high convection volumes. In ESHOL, the dialysis staff was specifically trained to achieve high convection volumes. As the convection volumes in that study were markedly higher than in both CONTRAST and the Turkish HDF Study, it is tempting to speculate that this training program increased the likelihood of obtaining high convection volumes in clinical practice. The issues regarding achieving a high convection volume were discussed in a subsequent editorial. (23) Why the outcome of dialysis patients is improved by high volume HDF is currently unknown, but results most likely from superior removal of uremic toxins, although none of the large randomized trials reported a relation between the change in beta2-microglobulin levels (a well-established marker of middle molecular weight substance clearance) and outcome. (12-14) Another explanation is a better hemodynamic stability during HDF, with fewer episodes of hypotension and consequently less cardiac stunning and gut ischemia. (10;24;25)

As the present analysis includes only studies that enrolled adults who require long term dialysis, our study does not provide evidence for children. In this category of patients HDF may reverse the delay in growth, which is commonly observed during treatment with HD. (26) Recently, an international registry has been installed to set up a uniform data

collection and follow-up, together with an aggregated statistical analysis on various important clinical outcomes in this young and vulnerable patient group.

### **Conclusion**

The current evidence suggests a beneficial effect of online post-dilution HDF over HD in reducing all-cause and cardiovascular mortality. Moreover, evidence is obtained supporting a dose-response relationship between the magnitude of the convection volume and mortality risk: the larger the convection volume, the better the outcome. Yet, published studies contain several potential risks of bias leading to either an over- or underestimation of the true effect. An individual participant data meta-analytic approach may solve several methodological problems and increase the level of evidence for a potential effect of HDF on morbidity and mortality. EuDial aims to facilitate these processes. Importantly, none of the analysed studies provides evidence that HDF is unsafe. Currently, HDF is mainly used in Europe, with a wide variation between countries, to a lesser extent in Asia and Canada, and rarely in the United States. (20) The evidence presented in this analysis supports a wider acceptance of HDF.

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## Chapter 9

# Treatment policy rather than patient characteristics determines convection volume in online post-dilution hemodiafiltration.

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Isabelle Chapdelaine MD,<sup>\*1</sup> Ira M. Mostovaya MD,<sup>\*2</sup> Michiel L. Bots MD PhD,<sup>3</sup> Marinus A. van den Dorpel MD PhD,<sup>4</sup> Renée Lévesque MD,<sup>5</sup> Piet M. ter Wee MD PhD,<sup>1,6</sup> Peter J. Blankestijn MD PhD,<sup>2</sup> Menso J. Nubé MD PhD,<sup>1,6</sup> and Muriel P.C. Grooteman MD PhD,<sup>1,6</sup> for the CONTRAST investigators

<sup>1</sup>Department of Nephrology, VU Medical Center, Amsterdam, The Netherlands

<sup>2</sup>Department of Nephrology, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>3</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>4</sup>Department of Internal Medicine, Maasstad Hospital, Rotterdam, The Netherlands

<sup>5</sup>Department of Nephrology, Centre Hospitalier de l'Université de Montréal, St. Luc Hospital, Montréal, Canada

<sup>6</sup>Institute for Cardiovascular Research VU Medical Center (ICaR-VU), VU Medical Center, Amsterdam, The Netherlands

\*Both authors contributed equally

**Abstract****Background/aims**

Sub-analyses of three large trials showed that hemodiafiltration (HDF) patients who achieved the highest convection volumes had the lowest mortality risk. The aims of this study are 1) to identify determinants of convection volume and 2) to assess whether differences exist between patients achieving high and low volumes.

**Methods**

HDF patients from the CONvective TRAnsport STudy with a complete data set at 6 months (314 out of a total of 358) were included in this post hoc analysis. Determinants of convection volume were identified by regression analysis.

**Results**

Treatment time, blood flow rate, dialysis vintage, serum albumin and hematocrit were independently related. Neither vascular access nor dialyzer characteristics showed any relation with convection volume. Except for some variation in body size, patient characteristics did not differ across tertiles of convection volume.

**Conclusion**

Treatment time and blood flow rate are major determinants of convection volume. Hence, its magnitude depends on center policy rather than individualized patient prescription.

## **Introduction**

Both mortality and morbidity remain unacceptably high in haemodialysis (HD) patients. (1) As retention of toxic middle molecular weight molecules (5-40kD) has been implicated in the pathogenesis of the uremic syndrome, (2-5) removal of these substances by convective therapies may improve prognosis. (6) However, neither the HEMO (7) nor the MPO study (8) demonstrated a clear advantage of high-flux over low-flux membranes.

Recently, hemodiafiltration (HDF) has gained renewed interest. (9) In HDF, diffusion, which is the main removal mechanism in low-flux HD, is combined with convection. Whereas the estimated amount of convective transport during high-flux HD is <10L/session, (10) in online post-dilution HDF 25L or more can be achieved.(11)

While several observational studies suggested a survival benefit of HDF, (12-15) two recent randomized controlled trials (RCT) with comparable design, namely the CONvective TRANsport STudy (CONTRAST) (16) and the Turkish OL-HDF Study (THDFS), (17) did not find an overall difference between post-dilution HDF and HD. Interestingly, *post hoc* analyses of both studies revealed that the lowest mortality risks were observed in patients with the highest convection volumes per session (mean >22.0L in CONTRAST and >19.7L in THDFS). Lately, a third large RCT (ESHOL) (18) showed that the overall mortality risk in HDF patients was 30% lower than in HD patients. In this study, mean convection volume was 23.7L. Sub-analysis of ESHOL confirmed the relation between convection volume and mortality risk. (18) Altogether, these findings support the concept of a dose-response relationship between convection volume and survival. (12)

Therefore, from a clinical point of view, it appears crucial to define patient- and treatment-related factors that restrict or facilitate the magnitude of convection volume, and their relative contribution. In a preliminary analysis, we found that blood flow and treatment time are important determinants. (19) As it is currently unclear whether the presence of an arterio-venous (AV) fistula (20) and/or use of particular dialyzers are required for high-volume HDF, in the present analysis special attention was paid to these issues. To minimize the probability of dose-targeting bias, we assessed whether subjects achieving high-volume HDF are characterized by a favourable baseline profile.

## **Materials and Methods**

### **Patients**

The present study is a cross-sectional analysis of the CONvective TRANsport STudy (CONTRAST, NCT00205556) in HDF patients who completed 6 months of follow-up. In CONTRAST, a total of 714 chronic HD patients from 29 centers (26 Dutch, 2 Canadian and 1 Norwegian) was randomly assigned to online post-dilution HDF (n=358) or low-flux HD (n=356) and compared with respect to all-cause mortality and cardiovascular events. As 44 patients did not have a recorded value of post-dilution convection volume at 6 months, 314 patients were eligible for the present analysis. A period of 6 months was chosen to ensure enough time to adapt to HDF on the one hand and to avoid potential dropouts, and hence censoring from analysis, on the other.

Details of CONTRAST are described elsewhere. (16,21) The study was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating centers. Written informed consent was obtained from all patients prior to enrolment.

### **Hemodiafiltration procedure**

Hemodiafiltration was performed in the online post-dilution mode. Patients who were temporarily treated with pre-dilution HDF were excluded from analysis (n=4). A target convection flow rate of 6 liters per hour was based on a filtration fraction (FF) between 25% and 33% of an extra-corporeal blood flow rate between 300 and 400 mL/min. As guidelines were absent when CONTRAST was started, these targets were mainly based on the operating instructions of the manufacturers.

The following dialysis machines were used: 4008S and 5008 with ONLINEplus™ (Fresenius Medical Care, Bad Homburg, Germany), AK 100/200™ ULTRA S (Gambro AB, Lund, Sweden), DBB-05™ (Nikkiso Co. Ltd, Tokyo, Japan) and Integra™ (Hospal-Gambro AB, Lund, Sweden). The following synthetic high-flux dialyzers (see supplementary Table 1) were used: FX80: 25%, FX100: 12% and Optiflux F200NR: 11% [Fresenius]; Polyflux 170H: 21% and Polyflux 210H: 29% [Gambro] and others: 2%. Ultrapure dialysis fluid, defined as <0.1 colony forming units and <0.025 endotoxin units per mL, was used for all treatments.

Treatment times were fixed at baseline and could only be increased if  $spKt/V_{urea}$  was  $<1.2$ . Routine patient care was performed according to the guidelines of the Quality of Care Committee of the Dutch Federation of Nephrology.

### Data collection

Demographics, medical history and medication were recorded at baseline, while various clinical, treatment and laboratory parameters were collected both at baseline and every 3 months afterwards. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height ( $m^2$ ). Body surface area (BSA) was calculated using the formula by Gehan and George. (22) Systolic and diastolic blood pressures were registered as the average of pre-dialysis values on three consecutive dialysis days. Blood samples for routine laboratory measurements were taken before the start of a dialysis session and analyzed in the local hospitals by standard techniques. Serum albumin measured with bromocresol purple method was converted to bromocresol green with the formula: bromocresol green = bromocresol purple + 5.5 (g/L). (23)

Convection volume, collected at 6 months, is defined as the sum of the intradialytic weight loss and the amount of substitution fluid, and reported as the mean of 3 consecutive sessions. Convective flow rate represents the convection volume in mL/minute. FF was calculated by dividing convective flow rate by blood flow rate and is reported as a percentage of blood flow.

### Data analysis

Data are reported as proportions, means with standard deviations or standard errors, or medians with interquartile ranges when appropriate. Differences between groups were examined by one-way ANOVA, Mann-Whitney test or Pearson Chi-square test. To compare differences between variables at baseline and 6 months, paired t-tests were used.

To study the independent relation between each variable (obtained at baseline for demography, medical history and type of vascular access, and at 6 months for clinical, laboratory and treatment parameters) and convection volume, both univariable and

**Table 1.** Baseline characteristics

	<b>N=314</b>
<b><i>Demographic data</i></b>	
Male gender	188 (60%)
Caucasian race	264 (84%)
Age (year)	63.7 ± 14.0
<b><i>Clinical characteristics</i></b>	
History of cardiovascular disease	133 (42%)
Diabetes mellitus	82 (26%)
History of renal transplantation	29 (9%)
Vascular cause of renal disease <sup>‡</sup>	152 (49%)
Dialysis vintage (year)	1.8 (1.0–3.7)*
Patients with RKF <sup>§</sup>	155 (50%)
Vascular access	
Fistula	248 (79%)
Graft	49 (16%)
Central venous catheter	17 (5%)
Weight (kg)	71.4 ± 14.9
BSA (m <sup>2</sup> )	1.83 ± 0.22
BMI (kg/m <sup>2</sup> )	25.2 ± 6.2
Pre-dialysis systolic blood pressure (mmHg)	147 ± 21
Pre-dialysis diastolic blood pressure (mmHg)	76 ± 12
<b><i>Laboratory parameters</i></b>	
Hemoglobin (mmol/L)	7.4 ± 0.8
Hematocrit (%)	36 ± 4
Serum albumin (g/L)	39.8 ± 3.5
Phosphate (mmol/L)	1.67 ± 0.52
β <sub>2</sub> microglobulin (mg/L)	30.6 ± 14.2

<sup>‡</sup> Diabetes, hypertension or vascular pathology as initial cause of kidney failure

\* Median and interquartile range (P25 – P75) is reported

<sup>§</sup> RKF: residual kidney function, defined as diuresis of ≥100 mL per day

BSA: body surface area; BMI: body mass index

To convert hemoglobin from mmol/L to g/dL multiply by 1.61. To convert albumin from g/L to g/dL divide by 10.

To convert phosphate from mmol/L to mg/dL, divide by 0.323.

multivariable regression analyses were used. First, all variables that showed a univariable relation with convection volume using a cut-off value of  $p < 0.20$  were entered into the multivariable model. Next, a backward regression analysis with a cut-off  $p$ -value of 0.20

was performed adding the variables hematocrit, blood flow rate and treatment time up front. Sensitivity analyses were performed in two ways: first by re-running the model with exclusion of patients from one center at a time and second, by re-running the analysis using data on variables and convection volume at months three and twelve. In all models the magnitude, direction and significance of the relation with convection volume remained stable.

To assess whether patients who achieved the highest convection volumes represented a favourable group at baseline, patients were stratified into tertiles of convection volume. The three groups were compared in terms of patient- and treatment-related characteristics. In addition, the Cardiac Risk Score (CRS) was applied. In this score system, the hazard ratios of previous cardiac disease, BMI, dialysis vintage and phosphate are summed. (24)

Results were considered statistically significant when  $p < 0.05$  (two-sided). Adjustment for multiple comparisons was made using the Holm-Bonferroni method. All calculations were made by use of a standard statistical package (SPSS for Windows Version 18.0.1; SPSS Inc. Headquarters, Chicago, Illinois, US).

## **Results**

### **Patient characteristics**

Data at baseline are presented in table 1.

### **Treatment-related parameters**

Data are shown in table 2. Mean convection volume per patient was  $19.7 \pm 4.4$  L per treatment (range 6.7 to 32.6) and mean FF was  $26 \pm 4\%$  (range 8 to 37). The pre-defined target convection flow rate of 6L/hour was reached in 74 patients (24%). Mean convection volume per center ranged from  $12.9 \pm 0.9$  to  $25.6 \pm 0.6$  ( $\pm$ SE) L per treatment. In 11 of the 29 centers, target convection flow rate was reached in none of the patients. Figures 1a and 1b show the convection volumes and FFs per center. In figure 1c and 1d the variation of blood flow and treatment time within and between centers is depicted. The absence of a

**Table 2.** Treatment parameters at baseline (low-flux hemodialysis) and after 6 months (HDF patients divided in tertiles of convection volume). Means with standard deviations are shown.

	All N=314	Convection volume			p-value corrected
		<17.9L (n=104)	17.9 to 21.8L (n=105)	>21.8L (n=105)	
<b>Baseline (low-flux HD)</b>					
spKt/V <sub>urea</sub>	1.37 ± 0.21	1.37 ± 0.24	1.34 ± 0.17	1.42 ± 0.19	<0.001
Treatment time (minute)	227 ± 24	214 ± 26	227 ± 19	240 ± 16	<0.001
Blood flow rate (mL/min)*	302 ± 39	294 ± 39	303 ± 37	313 ± 40	>0.99
Intradialytic weight loss (L per treatment)	1.94 ± 1.34	1.61 ± 0.85	2.10 ± 0.86	2.13 ± 1.02	0.15
<b>At 6 months (online HDF)</b>					
spKt/V <sub>urea</sub>	1.63 ± 0.33	1.55 ± 0.34	1.58 ± 0.28	1.75 ± 0.33	<0.001
Treatment time (minute)	226 ± 23	214 ± 26	229 ± 21	235 ± 16	<0.001
Blood flow rate (mL/min)	339 ± 48	311 ± 40	329 ± 36	374 ± 42	<0.001
Intradialytic weight loss (L per treatment)	1.89 ± 0.96	1.55 ± 0.95	1.92 ± 0.83	2.20 ± 0.98	<0.001
Substitution volume (L per treatment)	17.8 ± 4.2	13.5 ± 2.4	17.6 ± 1.2	22.4 ± 2.4	<0.001

p-value: for comparison between tertiles of convection volume

p-value corrected: p-value as corrected for multiple comparisons (both in tables 2 and 4) using the Holm-Bonferroni method

\*measured in 143 patients

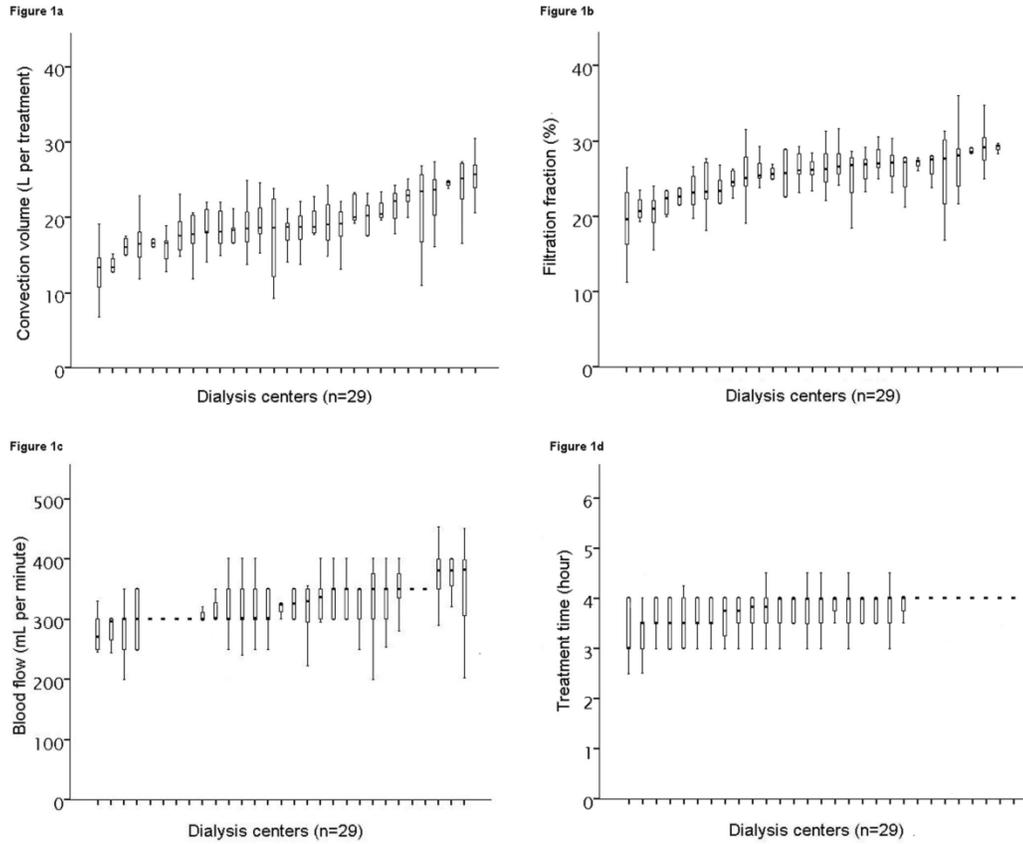
**Table 3.** Determinants of convection volume: univariable and multivariable linear regression analyses

	B	Univariable model 95% CI	R <sup>2</sup>	B	Multivariable model 95% CI	Std. B
<b>Demographic data</b>						
Male gender	1.97	0.99 to 2.94	0.004			
Caucasian race	-1.72	-3.04 to -0.39	0.020			
Age (year)	-0.02	-0.05 to 0.02	0.048			
<b>Clinical characteristics</b>						
History of cardiovascular disease	-0.37	-1.36 to 0.62	0.002			
Diabetes mellitus	0.24	-0.87 to 1.34	0.001			
Dialysis vintage (year)	0.19	0.03 to 0.95	0.017	0.14	0.03 to 0.25	0.10
BSA (dm <sup>2</sup> )	0.04	0.02 to 0.06	0.025	0.01	-0.01 to 0.03	0.07
Pre-dialysis systolic blood pressure (mmHg)	-0.01	-0.02 to 0.02	<0.001			
Residual kidney function*	-0.77	-1.74 to 0.21	0.004			
Fistula (versus all other access types)	-0.26	-1.46 to 0.94	0.001			
<b>Laboratory parameters</b>						
Hematocrit (%)	-0.19	-0.30 to -0.08	0.033	-0.13	-0.21 to -0.05	-0.13
Serum albumin (g/L)	0.27	0.13 to 0.40	0.046	0.13	0.03 to 0.22	0.10
<b>Treatment characteristics</b>						
Treatment time (minute)	0.08	0.06 to 0.10	0.177	0.08	0.07 to 0.10	0.43
Blood flow rate (mL/min)	0.06	0.05 to 0.07	0.371	0.05	0.05 to 0.06	0.58

\*Residual kidney function defined as diuresis of  $\geq 100$  mL/day.

BSA: body surface area; 95% CI: 95% confidence interval; Std. B: standardized beta. The B reflects the change of the total convection volume (in L per treatment) related with one unit increment of the determinant. Standardized B expresses how much convection volume changes when that independent variable changes by one SD and thus it conveys the relative importance of the different variables. R<sup>2</sup> of multivariable model is 0.59.

**Figure 1:** Treatment values in different participating center, ranged according to increasing median value. Median values, boxes represent 25 and 75 percentiles, whiskers minimum and maximum. (a) Convection volume (b) Filtration fraction (c) Blood flow (d) treatment time



**Table 4:** Patient characteristics at baseline divided by tertiles of convection volume

	Convection volume			p-value corrected
	<17.9L (n=104)	17.9-21.8L (n=105)	>21.8L (n=105)	
<b>Demographic data</b>				
Male gender	47 (45%)	69 (66%)	72 (69%)	0.07
Caucasian race	93 (89%)	90 (86%)	81 (77%)	0.14
Age (year)	63.9 ± 15.1	63.9 ± 13.4	63.4 ± 13.4	>0.99
<b>Clinical characteristics</b>				
Cardiac Risk Score	41.3 ± 8.0	43.3 ± 7.5	44.6 ± 8.2	0.20
History of cardiovascular disease	46 (44%)	45 (43%)	42 (40%)	>0.99
Diabetes mellitus	28 (28%)	27 (26%)	27 (27%)	>0.99
History of renal transplantation	8 (8%)	10 (10%)	11 (11%)	>0.99
Vascular cause of renal disease <sup>‡</sup>	50 (49%)	51 (50%)	51 (50%)	>0.99
Dialysis vintage (year)	1.8 (0.9–3.2)*	2.0 (1.1–3.8)*	1.7 (0.9–5.3)*	>0.99
Patients with RKF <sup>§</sup>	62 (60%)	49 (47%)	57 (54%)	>0.99
Vascular access				
Fistula	85 (82%)	80 (76%)	83 (79%)	>0.99
Graft	17 (16%)	18 (17%)	14 (13%)	>0.99
Central venous catheter	2 (2%)	7 (7%)	8 (8%)	>0.99
Weight (kg)	67.4 ± 13.3	72.3 ± 14.2	74.5 ± 16.2	0.060
BSA (m <sup>2</sup> )	1.77 ± 0.21	1.85 ± 0.21	1.88 ± 0.24	<b>0.025</b>
BMI (kg/m <sup>2</sup> )	24.3 ± 4.4	25.2 ± 4.9	26.1 ± 5.1	0.52
Pre-dialysis SBP (mmHg)	146 ± 23	146 ± 19	149 ± 22	>0.99
Pre-dialysis DBP (mmHg)	73 ± 13	76 ± 12	77 ± 12	0.57
<b>Laboratory parameters</b>				
Hemoglobin (mmol/L)	7.4 ± 0.9	7.4 ± 0.7	7.3 ± 0.8	>0.99
Hematocrit (%)	36 ± 5	36 ± 4	36 ± 4	>0.99
Serum albumin (g/L)	39.4 ± 3.8	40.6 ± 3.4	41.3 ± 3.7	0.25
Phosphate (mmol/L)	1.63 ± 0.44	1.68 ± 0.57	1.66 ± 0.52	>0.99
β <sub>2</sub> microglobulin (mg/L)	28.9 ± 16.1	29.2 ± 12.3	33.5 ± 13.9	0.61

<sup>‡</sup> Diabetes, hypertension or vascular pathology as initial cause of kidney failure

\*Medians and interquartile ranges (P25 – P75) are reported

<sup>§</sup> RKF: residual kidney function, defined as diuresis of ≥100 mL per day; BSA: body surface area; BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure

p-value: for comparison between tertiles of convection volume

p-value corrected: p-value as corrected for multiple comparisons (both in tables 2 and 4) using the Holm-Bonferroni method

box-and-whisker plot in 6 centers in figure 1c and 8 centers in figure 1d suggests that blood flow and treatment time, respectively, were fixed in these facilities.

#### **Relation between patient-related factors and convection volume**

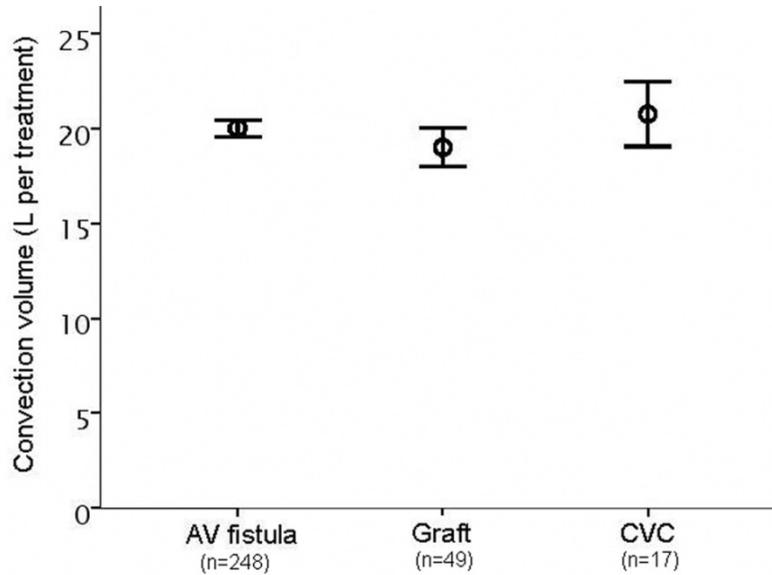
As depicted in table 3, univariate regression analysis showed that male gender, non-Caucasian race, BSA, dialysis vintage, hematocrit and albumin were related to convection volume. In the multivariable regression model dialysis vintage, BSA (borderline significant,  $p=0.07$ ) and albumin remained positively related, while an inverse relation was found with hematocrit. No marked differences were found between patients with an AV fistula, graft or CVC. Figure 2 shows the distribution of convection volume per type of vascular access, adjusted for confounders. When the crude relation between convection volume and vascular access type was studied, results were similar: AV fistula:  $19.7 \pm 4.4$  L/treatment; graft:  $19.3 \pm 4.4$  L/treatment; CVC:  $21.9 \pm 4.2$  L/treatment;  $p$  for difference between groups = 0.10.

#### **Relation between treatment-related factors and convection volume**

As depicted in table 3, univariate and multivariate regression analyses showed that blood flow rate ( $B=0.05$ L per mL/min [95%CI 0.05 to 0.06]) and treatment time ( $B=0.08$ L per min [95%CI 0.07 to 0.10]) were positively related to convection volume (Supplementary Figure 1). Neither the membrane surface area (range 1.7–2.2m<sup>2</sup>) nor the ultrafiltration coefficient (range 56–85 mL/h/mmHg) of the dialyzers showed a linear relationship with convection volume (Supplementary Figure 2a and 2b) or FF (Supplementary Figure 2c and 2d).

#### **Comparison of groups by tertiles of convection volume**

Characteristics of the HDF population stratified by tertiles of convection volume are depicted in table 4. Neither age, nor gender, history of cardiovascular disease, diabetes, type of vascular access and Cardiac Risk Score differed across tertiles. Of the clinical characteristics at baseline, only BSA was greater in the group of patients with high convection volumes. Medication use (antihypertensives, phosphate binders, lipid lowering drugs, erythropoietin and anti-coagulants) did not differ (data not shown).

**Figure 2:** Vacular access and convection volume.

Convection volume is adjusted for albumin, hematocrit, dialysis vintage, body surface area, blood flow and treatment time.

AV: arterio-venous; CVC: central venous catheter.

### **Discussion**

Increasing evidence indicates that the magnitude of convection volume is related to the clinical outcome in HDF patients. (16-18) The present analysis was performed to assess whether convection volume depends on individual patient characteristics, such as body size and cardiovascular risk profile, rather than center-specific treatment policies, such as fixed treatment times.

### **Demographic, clinical and laboratory determinants of convection volume**

Apart from BSA and dialysis vintage, none of the demographic or clinical variables was related to convection volume. In this respect it should be mentioned that the clinical effect of BSA on convection volume is limited: an increase of 10% ( $18 \text{ dm}^2$  at a mean of  $1.83 \text{ m}^2$ ) would yield only  $18 \times 0.01 = 0.18 \text{ L}$  extra (table 3).

In line with both observational (25) and prospective studies (17-19) hematocrit was negatively and albumin positively linked to convection volume, albeit to a limited extent. During post-dilution HDF, ultrafiltration favors hemoconcentration, which alters intradialyzer blood rheology. These changes may impede convective transport capacity by increasing in- and post-filter viscosity, leading to fiber clotting and pressure alarms. (26) A high serum albumin may promote plasma refilling during treatment, thus allowing higher ultrafiltration rates.

Most investigations in HDF excluded patients with CVCs or malfunctioning shunts. (17,18,27) In the present study, no relation was found between the magnitude of convection volume and the type of vascular access. In this respect, it should be mentioned that many patients with a high convection volume came from a single facility with a high CVC use, but also a higher mean blood flow. Nevertheless, it appears that the presence of an AV fistula, as recently advocated by the EuDial group, (20) is not a prerequisite for high-volume HDF. Moreover, the presence of a CVC appears neither a contra-indication for HDF nor a drawback for obtaining high convection volumes.

#### **Treatment-related determinants of convection volume**

Treatment time and blood flow rate appeared by far the most powerful predictors of the magnitude of convection volume. According to the present model, a 30-minute increase in time or a 50mL/min increase in blood flow would raise the convection volume with approximately 2.5L per treatment, provided that these parameters are within the range of our study. As the above-mentioned parameters BSA, hematocrit and albumin were only mildly related to convection volume, prescription of adequate blood flow and treatment time appears of paramount importance for obtaining high-volume HDF. As time was fixed at the beginning of the study, dose-targeting bias seems unlikely. (28) The finding that the within-center variation of both blood flow and treatment time was often very low or even nil supports the idea that center policy rather than individualized patient prescription determined convection volume in this population.

The type of dialyzer could also theoretically influence the magnitude of convection volume. Yet, within the range of dialyzers used, neither membrane surface area nor

ultrafiltration coefficient showed a linear relationship with the achieved convection volumes. At this point, however, it should be mentioned that the heterogeneity of the dialyzers used, their co-aggregation within centers and the non-standardized operating conditions prevent solid conclusions.

Finally, filtration fraction may greatly influence the magnitude of the convection volume, as it quantifies the relation between convective flow rate and blood flow rate. However, as FF was most often not a pre-set parameter, it was calculated afterwards and considered not appropriate to analyze its relation with convection volume. Nonetheless, FF varied markedly within and between centers. Although a FF of 25% is considered safe in post-dilution HDF, (20) this value was not reached in 106 patients (34%). Theoretically, it is conceivable that individual patients would have tolerated and benefited from an optimized, pre-targeted higher FF, as demonstrated in studies using automatic pressure-control. (29) When CONTRAST was designed however, maximization of convection volume was not a pre-specified goal.

#### **Comparison of patient characteristics between tertiles of convection volume**

Proportions of traditional cardio-vascular risk factors, including diabetes and previous cardio-vascular disease, and uraemia-related issues, such as vascular access type and uremic markers, were not different between tertiles of convection volume. To further assess whether patients in the highest tertile had a more favourable clinical profile than patients in the other groups, the Cardiac Risk Score (CRS) was applied, which, in fact, was similar. (24) Together with data from the regression analysis, our results suggest that the magnitude of convection volume is largely independent of individual patient characteristics. Hence, confounding by indication seems highly unlikely.

#### **Strengths and limitations**

The large sample size, the prospective follow-up and the concise data collection are important strengths of this study. Patients who were temporarily treated with pre-dilution HDF were meticulously traced and excluded from analysis. Albumin assays were rechecked and if measured by bromcresol purple converted to bromcresol green. This

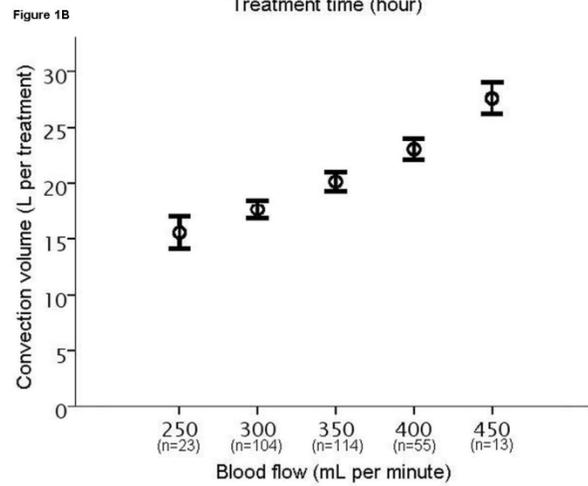
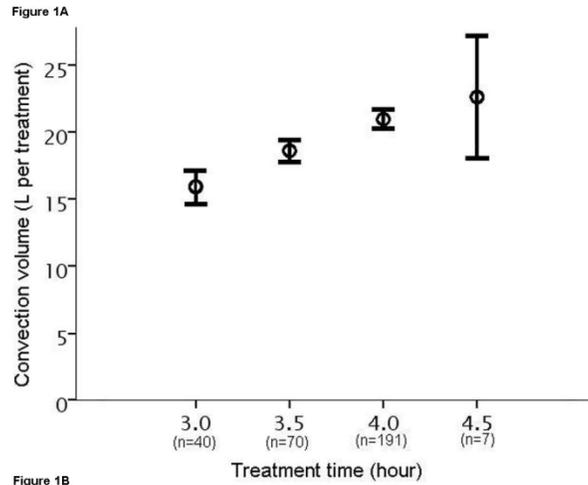
study also has limitations. First, the *post hoc* character of the analyses allows only inferences on relationships, not on causality. Second, vascular access was recorded at baseline and may have changed during follow-up. Third, determinants of convection volume at 6 months may not be representative for a longer period of time. However, as the model was consistent at different time points and a close relation was found between convection volumes at 3 and 12 months (data not shown), the chosen time point appears appropriate. Finally, as the CRS used in our study takes only the cardiac risk profile into account, non-registered clinical conditions, such as malignancies and chronic obstructive lung disease, may differ between groups.

### **Summary and conclusions**

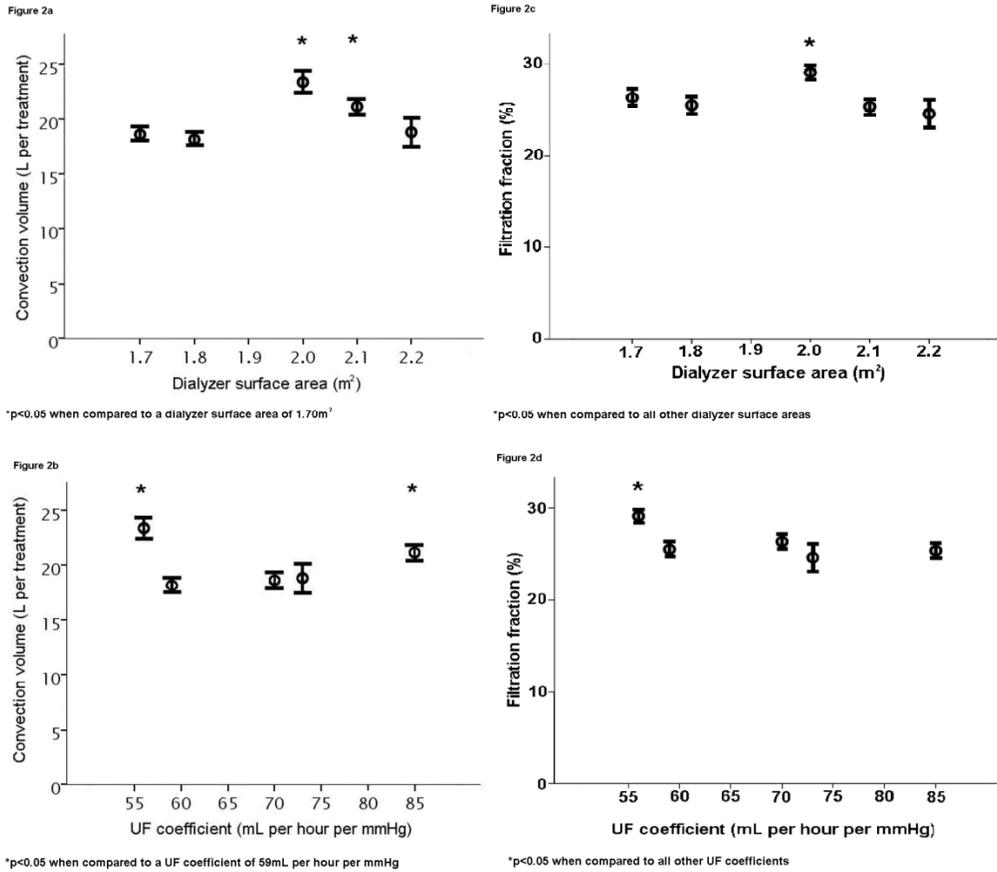
Among the various patient- and treatment-related parameters that may influence convection volume in post-dilution HDF, treatment time and blood flow rate are by far the most powerful determinants. Patient characteristics, such as BSA, hematocrit and albumin, play only a minor role in this respect. As both demographic and clinical variables, as well as prognostic markers, did not differ across tertiles of convection volume, our data do not support the idea that the beneficial effect of high-volume HDF (16) is due to a more favourable clinical profile beforehand. Hence, center policy rather than patient characteristics appears to be most decisive for the amount of convection volume achieved. An AV fistula does not seem to be a prerequisite and a CVC not a drawback for achieving high convection volumes. Although the type of dialyzer was not related to the magnitude of convection volume, its co-aggregation within centers and the non-standardized operating conditions prevent solid conclusions. Whether filtration fraction can be recommended as a prescription tool to maximize the convection volume is currently under investigation in the Feasibility Study (NCT01877499).

**Supplementary Tables and Figures**

**Supplementary Figure 1:** (a) Treatment time and convection volume (b) blood flow and convection volume. Convection volume is adjusted for dialysis vintage, BSA, hematocrit, albumin, blood flow and treatment time.



**Supplementary Figure 2:** Dialyzer characteristics and convection volume: (a) dialyzer surface area in  $m^2$ , (b) ultrafiltration (UF) coefficient in mL/h per mmHg. Dialyzer characteristics and filtration fraction: (c) dialyzer surface area in  $m^2$ , (d) ultrafiltration (UF) coefficient in mL/h per mmHg. Convection volume is adjusted for dialysis vintage, BSA, hematocrit, albumin, blood flow and treatment time.



**Supplementary Table 1:** Dialyzer characteristics.

Dialyzer	Membrane material	Effective surface area (m <sup>2</sup> )	Fiber inner diameter (µm)	Ultrafiltration coefficient (mL/h per mmHg) <sup>§</sup>	Effective fiber length (mm)	Company
FX80	Polysulfone	1.8	185	59	225	Fresenius Medical Care
FX100	Polysulfone	2.2	185	73	225	Fresenius Medical Care
Optiflux F200NR*	Polysulfone	2.0	200	56	280	Fresenius Medical Care
Polyflux 170H	Polyarylethersulfone/ polyamide	1.7	215	70	270	Gambro AB
Polyflux 210H	Polyarylethersulfone/ polyamide	2.1	215	85	270	Gambro AB

\*Used in one single Canadian facility

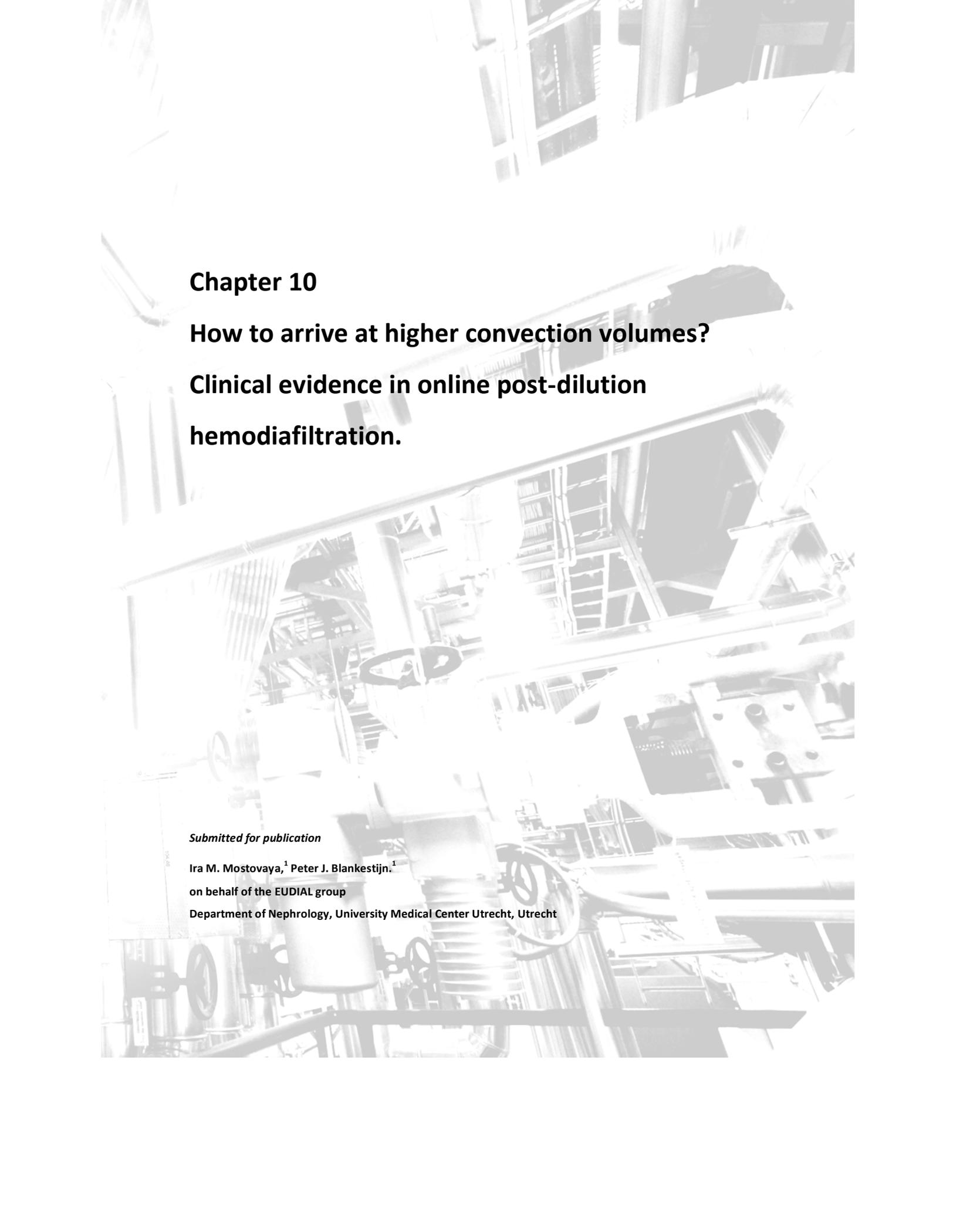
<sup>§</sup>As given by the manufacturer, measured *in vitro* at 37°C with bovine blood (Ht = 32% and protein = 60 g/L)

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## Chapter 10

**How to arrive at higher convection volumes?**

**Clinical evidence in online post-dilution  
hemodiafiltration.**

*Submitted for publication*

Ira M. Mostovaya,<sup>1</sup> Peter J. Blankestijn,<sup>1</sup>

on behalf of the EUDIAL group

Department of Nephrology, University Medical Center Utrecht, Utrecht

**Abstract**

Hemodiafiltration (HDF), is advocated as a superior renal replacement therapy for patients with end-stage-renal disease (ESRD). Convection volume is currently considered the best and easiest quantifier of HDF efficiency. *Post hoc* analyses of observational studies and randomized controlled trials (RCT) suggest that the risk on mortality and clinical events is significantly lower in HDF patients who are treated with high convection volumes. In this review we describe the available clinical evidence and overall expert opinion on how convection volumes can be increased in patients undergoing online post-dilution HDF.

## **Introduction**

Hemodiafiltration (HDF), which combines diffusive and convective transport, is advocated as a superior renal replacement therapy for patients with end-stage-renal disease (ESRD). Over the past decennium several clinical studies were published comparing the clinical outcome in HDF versus hemodialysis (HD). These studies have also examined the relation between convection volume/substitution volume and all-cause mortality.

In this review we will first describe the available evidence for a possible dose-response relation between convection volume and survival. Subsequently we will explore the relationship between the achieved convection volume and potential determining factors as described in current literature and use this information to speculate how higher convection volumes could be achieved in everyday clinical practice. Since the vast majority of literature on convection volume concerns post-dilution HDF, the review will focus on this treatment modality.

### **Why should we try to increase convection volume?**

In the past decennium two large observational studies, and recently, three large randomized controlled trials (RCTs) have provided evidence on the importance of convection volume.

In the observational DOPPS study, published in 2006, patients were stratified into 4 groups: low flux HD (n=1366), high flux HD (n=546) and two HDF groups classified according to the amount of replacement fluid per treatment: 5-14.9 litres was considered low-efficiency HDF (n=156) and 15-24.9 litres high-efficiency HDF (n=97). In this study, the mortality risk in the group of patients treated with low efficiency HDF was not significantly different from the HD group (RR 0.93, p=0.68), while it was significantly lower in the high efficiency HDF group (RR 0.65, p=0.01). (1)

In the observational RISCAVID study published in 2008, mortality was compared between 424 HD patients, 204 treated with HDF performed with bags and 129 treated with online post-dilution HDF. In the HD group, mortality was 13% and 21% after 1 and 2 years, respectively. The average substitution volume in the HDF group with bags was 14±3 litres, and the mortality rates of the patients 9% and 16% after 1 and 2 years, respectively. The

average substitution volume in the online HDF group was  $23 \pm 3$  litres, and the mortality rates of the patients 6% and 16% after 1 and 2 years, respectively. All-cause mortality was significantly lower in both HDF groups, if compared to HD (RR=0.78,  $p=0.01$ ). Cardiovascular mortality was significantly lower in the online HDF group, if compared to both HD and HDF with bags (RR=0.78,  $p=0.001$ ). (2) As weight loss or the amount of ultrafiltration during HD was not taken into account in both RISCAVID and DOPPS, the real convection volumes obtained in both studies were definitely higher.

Over the past two years, the results of three large randomized controlled trials, the CONvective TRANsport STudy (CONTRAST) ( $n=714$ , HDF:  $n=358$ ), the Turkish HDF Study ( $n=782$ , HDF:  $n=391$ ) and the Estudio de Supervivencia de Hemodiafiltracion On-Line (ESHOL) ( $n=906$ , HDF:  $n=456$ ), have been published. All three RCTs studied whether risk of mortality and cardiovascular events was lower in patients treated with online post-dilution HDF as compared to HD. (3-5) CONTRAST and the Turkish HDF study did not find such a difference between patients treated with HDF and HD. However ESHOL, the trial with the highest mean achieved convection volume, showed superiority of HDF over hemodialysis (HD) with respect to overall mortality and cardiovascular morbidity and mortality. A recently published meta-analysis combining the results of RCTs comparing post-dilution HDF to HD in terms of mortality and cardiovascular events showed a significantly better overall survival (HR: 0.74, 95% CI 0.73 – 0.96) and cardiovascular survival (HR: 0.73, 95% CI 0.57 – 0.92) in HDF. (6) The results of this meta-analysis should be interpreted with some caution, since several risks of bias (mainly due to incomplete follow-up and censoring of participants after non-fatal events) were present in the included RCTs. (6) Yet, the current evidence suggests a beneficial effect of online post-dilution HDF over HD.

Interestingly, *post hoc* analyses in all three of the above-mentioned RCTs demonstrated that HDF patients with the highest convection volumes had a lower mortality and a decreased risk of cardiovascular events compared to those treated with HD. Note that these *post hoc* analyses should be viewed as cohort analyses. Therefore, adequate multivariable adjustments need to be made in order to reduce potential confounding. In the multivariable adjusted analyses from CONTRAST, patients with an achieved convection volume above 22L (the highest tertile) had a lower mortality risk as compared to HD

**Table 1:** Mortality rates in randomized controlled trials and observational studies stratified and arranged by convection volumes, on-treatment analyses.

Reference	CV (L/treatment)	SV (L/treatment)	IDWL (L/treatment)	HR	95% CI of HR
ESHOL *	<23.1	-	-	0.90	0.61 to 1.31
2013 (7)	23.1 - 25.4	-	-	0.60	0.39 to 0.90
	>25.4	-	-	0.55	0.34 to 0.84
Turkish HDF study**	18.8	16.2	2.6	1.10	0.68 – 1.76
2013 (6)	20.3	18.1	2.2	0.54	0.31 – 0.93
CONTRAST*	<18.18	-	-	0.80	0.52 – 1.24
2012 (5)	18.18 - 21.95	-	-	0.84	0.54 – 1.29
	>21.95	-	-	0.61	0.38 – 0.98
RISCAVID <sup>§</sup>	-	14	-	0.69	-
2008 (9)	-	23	-	0.46	-
DOPPS <sup>#</sup>	-	5.0 – 14.9	-	0.93	-
2006 (8)	-	15.0 – 24.9	-	0.65	-

\*In ESHOL and CONTRAST, survival risks were reported by tertiles of convection volume. Ranges of the tertiles are reported.

\*\*In the Turkish study, survival risks were reported for patients above and below the median ultrafiltration fluid. Means of convection volume per group are shown. In the 'low CV group', the mean ultrafiltration fluid was 16.2L, while in the 'high CV group' the mean ultrafiltration fluid was 18.1L.

<sup>§</sup>In RISCAVID, *Relative Risks* (and not HRs!) after 1 year of treatment were reported for HDF treatment with fluid bags (mean SV per treatment: 14L) and online HDF (mean SV per treatment: 23L)

<sup>#</sup>In DOPPS, patients who received 5.0 – 14.9L of substitution fluid per treatment were classified as 'low-efficiency HDF' and those receiving 15.0 – 24.9 of substitution fluid per treatment were classified as 'high-efficiency HDF'.  
CI: confidence interval; CV: convection volume, HR : hazard ratio; IDWL: interdialytic weight loss; SV: substitution volume.

patients: HR: 0.61 (95% CI: 0.38 – 0.98). (3) The Turkish HDF trial reported a reduced mortality in patients receiving 17.4 L (the median of achieved volume) or more of substitution fluid per session, which was equivalent to approximately 19.5 L of convection volume per session (HR: 0.54; 95% CI: 0.31 – 0.93) as compared to HD patients. (5) In the ESHOL study, a lower mortality risk was observed in patients receiving 23.1-25.4 L and 25.4 L or more as compared to HD patients (HR: 0.60 (95% CI 0.39 – 0.90) and HR: 0.55 (95% CI 0.34 – 0.84), respectively). (4) The relations between convection volume and mortality risk found in observational studies and RCTs are summarized in Table 1.

Although the studies described above contain limitations, the overall finding is that a higher convection volume is associated with a better survival. A dose-response relation

between and convection volume and survival seems a plausible explanation for these results. Thus it would be interesting to explore how high convection volumes could be achieved.

#### **How can we arrive at higher convection volumes?**

Limited information is available on factors that determine convection volume in clinical practice.

Recently the CONTRAST group has studied determinants of the magnitude of convection volume in a subpopulation of CONTRAST: 314 online post-dilution HDF patients who had completed 6 months of follow-up. This study demonstrated that the magnitude of convection volume in online post-dilution HDF is determined by both patient characteristics and dialysis treatment characteristics. The patient characteristics serum albumin, dialysis vintage and body surface area were positively related to convection volume, while hematocrit was inversely related. The treatment characteristics blood flow and treatment time (per dialysis session) were both positively related to convection volume. Furthermore, the relation between treatment characteristics and convection volume was much stronger than the relation between convection volume and the patient characteristics. To assess the probability of dose-targeting bias, it was studied whether subjects achieving high-volume HDF were characterized by a favourable baseline profile. Except for some variation in body size, patient characteristics did not differ across tertiles of convection volume. Furthermore, a considerable difference in convection volumes was found between participating dialysis facilities. All these findings support the hypothesis that center policy rather than patient characteristics appears to be most decisive for the amount of convection volume achieved. (7) A preliminary analysis of CONTRAST data performed by Penne et al showed similar results. (8) In accordance with these data Joyeux et al. found an inverse relationship between the hematocrit and the ratio of the convection volume and the total blood volume that flowed through the extra-corporeal system during HDF treatment. (9) However, even in patients with high hematocrit levels (>35%) their impact on the solute clearance appears to be small, as described by Spalding et al. (10)

Several clinical studies and expert-reviews have defined other aspects that may influence the magnitude of convection volume.

The Filtration fraction (FF) represents the ratio of the amount of water crossing the dialysis membrane per unit of time and blood water flow passing through the hemodiafilter per same time unit, reported as a percentage of blood flow. In clinical practice FF is often approximated as the ratio between the convective flow rate and the blood flow rate. FF is an important component of HDF prescription, as it quantifies the relation between convection and blood flow rates. The operator's user manual for FX-class dialyzers (Fresenius Medical Care, Bad Homburg, Germany) recommends that 25% of the blood flow should be substitution flow. In expert reviews, a target FF of 25-35% is recommended as optimal to achieve high convection volumes, if dialysis machinery can be set by filtration fraction. (11;12)

An adequate vascular access has repeatedly been described as a pre-requisite for performing online hemodiafiltration. (11;13) Vascular access is defined as inadequate when it does not permit a blood flow rate of 300 ml/min to be reached. (14) When looking at RCTs showing a relation between convection volume and survival, the Turkish HDF study excluded patients with a temporary catheter as vascular access, or patients who could not reach a blood flow <250mL/minute. (15) ESHOL also excluded patients with a temporary non-tunnelized catheter (16), while CONTRAST did not exclude patients based on vascular access type. (3) On note, in the CONTRAST population no significant relation between vascular access type and convection volume was found nor in a univariable analysis, nor after adjustment for confounders. (7;8) In fact, it seemed that practice patterns in centres play a more important role in determining convection volume than vascular access type. (7;8) However, the fact that vascular access needs to be adequate to reach a certain minimal blood flow seems self-evident.

To achieve a high extracorporeal blood flow with an arterio-venous fistula or a graft, not only the quality of the vascular access is relevant, but also the size of the needle used for puncture. A needle with a wider lumen gives rise to a lower resistance at a given blood pump speed, thus limiting shear-stress and ensuing cell activation and possible hemolysis. (17) Despite the importance of this aspect of cannulation, the choice of a needle is most

often not made by the attending nephrologist but by the dialysis nurses, based on various factors such as type, size and vintage of vascular access, bleeding tendency, and pain and preference expressed by the patient. (17) With the exception of initial cannulation, in most guidelines no value for needle gauge (the outer diameter of a needle) is precisely recommended and the sole statement is made that 'needle size should match the blood flow rate'. (18;19) Only in the Fistula First Initiative a 15 gauge needle is recommended for a desired blood flow between 350 and 450 mL/min. (19)

Specific qualities of dialyzers have been described in expert-reviews, deemed most suitable to optimize ultrafiltration flows. Naturally dialyzers should be equipped with highly permeable membranes, appropriate for HDF. Other preferred dialyzer features should favor low blood flow resistance (large lumen diameter of fibers 200  $\mu\text{m}$ , short length of dialyzer housing and increase number of fibers per sectional surface area) in order to reduce internal convective processes. (11;20)

To summarize, patient characteristics related to convection volume are albumin (positive relation), hematocrit (inverse relation) and quality of vascular access. Dialysis prescription characteristics related to convection volume are blood flow, length of treatment and filtration fraction (all positively related). Needle size, relevant in determining blood flow in arterio-venous fistulas and grafts, most likely also indirectly plays a role in determining convection volume, but this prescription characteristic has not been extensively studied. Dialyzer characteristics such as surface area, inner fiber diameter, fiber length and membrane material could also be relevant determinants of convection volume. However, the role of dialyzer characteristics has not yet been systematically evaluated.

#### **How do we achieve high convection volumes?**

Table 2 summarizes steps suggested to maximize convection volume in online post-dilution HDF. (11;12;17) With this strategy, convection volumes of at least 20 L per session will be achieved in most cases.

As shown in table 1, data from observational studies and post-hoc analyses of RCTs does not provide a clear cut-off point what convection volume is needed to reduce mortality risk. In expert-opinion reviews and editorials a convection volume of >20-22 L per

treatment is mentioned as the presumed volume associated with likely improvement in clinical outcome variables in post-dilution HDF. (11;21)

Whether convection volume dose should be normalized for body-size related factors (such as body mass index or body surface area) has not yet been studied extensively. However, it seems plausible to assume that body size will influence the amount of large solute removal by HDF and thus such a correction is recommended by the EUDIAL group. (22)

**Table 2:** Suggested steps to maximize convection volume in online post-dilution hemodiafiltration.

1. Ascertain the presence of a vascular access allowing extracorporeal blood flows of at least 300mL/minute.
  - A minimal access flow of double that rate (600mL/minute) is considered necessary to allow treatment sessions without too many alarms
  - Central venous catheter is not automatically contra-indicated
2. Choose a relatively large dialyzer: a dialyzer with a large surface area, short fibers with a large internal radius and a high hydraulic permeability.
3. Set treatment time to 4 hours or more.
4. Optimize blood flow (>300mL/minute) and filtration fraction (>25%)
  - Specifically instruct nursing staff on how to achieve these targets
  - Tailor the needle size to the desired blood flow rate

**Is hemodiafiltration safe?**

Although the three recently performed trials ESHOL, CONTRAST and Turkish HDF study were not specifically designed to study safety issues, neither study provided any indication that HDF is an unsafe treatment modality.

The higher the convection volume, the higher the volumes of replacement fluid infused into the circulation. Since sterile substitution fluid is currently prepared online the question arises whether the chemical and microbiological safety of patients is sufficiently guaranteed. However, CONTRAST investigators reported previously in an analysis of over 11 000 treatment sessions that it is possible to produce substitution fluid of adequate quality over a prolonged period of time. (23) Also, levels of inflammatory parameters and rates of changes of these parameters (high sensitivity C-reactive protein and interleukin-6) did not differ between HDF and HD in the CONTRAST population. (24) Moreover, in ESHOL, the study with the highest mean convection volume, mortality risk due to infectious complications was considerably lower in the HDF group (HR: 0.45; 95% CI 0.21 – 0.96), when compared to HD. (16)

If achieving a higher amount of replacement fluid would be attempted by increasing the filtration fraction, this will trigger pressure alarms and could lead to haemolysis, albumin loss and filter damage. (25;26) However, a sub-analysis of CONTRAST (n=714) and one observational study (n=858) have both indicated that albumin loss is similar in both HD and HDF. (24;27)

It should be taken into account that in these studies convection volumes were on average 19-23 L per treatment and the vast majority of patients did not have volumes above 30L per treatment. (5-7) Thus it is not possible to deduce whether increasing convection volumes to outside this range would be safe.

When FF is high, the hemoconcentration increases, thus increasing the risk of clotting in the dialyzer fibers. Hence, adequate anticoagulation therapy is mandatory. Since low molecular heparins belong to the middle molecular weight class molecules, which are filtered in HDF, higher doses may be required when convection volumes are high. (28;29) However, the optimal dosage of low molecular weight heparin during HDF is not known.

**Is increasing convection volume cost-effective?**

Recently several manuscripts have been published studying costs of HDF versus HD. Mazairac et al analysed costs of HDF in the CONTRAST study. In 2009 HDF was found to be approximately 3.6% more expensive than HD. The additional costs could mainly be attributed to higher expenses for disposables and a more frequent control of dialysis water purity. However, if the costs of disposables could be decreased, HDF would fit within the currently accepted standard of cost-effectiveness. (30) Creput et al compared real overcost of HDF as compared to high-flux HD in one dialysis facility in 28 000 dialysis treatments. Additional costs for HDF varied from €-1.29 to €4.58 per dialysis session, depending on type of dialysis machine and HDF modality (post-dilution being cheaper than mid- and pre-dilution). (31)

Regarding cost-effectiveness, Takura et al studied cost-effectiveness of HDF in 24 (9 HDF) Japanese patients followed for 4 weeks, and concluded that HDF could potentially be cost-effective. (32) However, Mazairac et al demonstrated that when cost-effectiveness was approached from a societal perspective, HDF was not more cost-effective than HD. (30)

If HDF can be applied with approximately no excess costs, but in a manner which would lead to a survival benefit (which hopefully can be achieved by increasing convection volumes), it is very likely to become cost-effective. In fact, Mazairac et al showed that incremental costs were lower in patients who achieved high (an average of >20.3L/treatment) convection volumes. (30) Hence it is probable that HDF with high convection volumes may be more cost-effective than HDF with low convection volumes, probably due to the survival benefit associated with high volumes.

**What information do we still need?**

Currently available data indicate that treatment with HDF may have a beneficial effect on survival, and that a dose-response relation may exist between the magnitude of convection volume and mortality risk. However, many issues are still unclear.

For instance at present it is unknown why the outcome of dialysis patients is improved by high volume HDF. Concerning the mechanisms behind this treatment modality, both

superior removal of uremic toxins and better hemodynamic stability, with fewer episodes of hypotension and consequently less cardiac stunning and gut ischemia, may play an important role.(33-35) Notably, none of the large randomized trials reported a relation between change in beta2-microglobulin levels (a well-established marker of middle molecular weight substance clearance) and outcome. (3-5)

Furthermore, limited evidence is available on whether certain subgroups behave differently during treatment with HDF. As shown in ESHOL, a high Charlson co-morbidity index score at baseline seems an independent predictor for the beneficial effect of HDF on all-cause mortality. (4)

The RCTs comparing HDF to HD in terms of mortality and cardiovascular events were generally based on dialysis regimes that applied treatment three times per week. The role of HDF in more intensified dialysis programs, such as daily and nocturnal dialysis, is as of yet unclear.

As the currently available studies only enrolled adults who require long term dialysis, no evidence is provided for children. In this category of patients HDF may reverse the delay in growth, which is commonly observed during treatment with HD. (36) Yet, this calls for an international registry to be set up with uniform data collection and follow-up, joined with aggregated statistical analysis on various important clinical outcomes in this patient group. Limited information is available on what patient-related and treatment-related factors determine the magnitude of convection volume. More information is needed as to whether these factors are consistent in different patient populations. New studies on this subject will undoubtedly lead to more trustworthy conclusions. Important to keep in mind is that the relation between convection volume and a determinant is not necessarily causal. For example, in cohorts, treatment time may be shortened in sicker patients and increased in patients with a high interdialytic weight gain. It is debatable whether dose-targeting bias plays a role in these findings. (37)

Treatment time and blood flow, both potentially modifiable dialysis-prescription characteristics, have been shown to be important determinants of convection volume. (8) Also, ESHOL, the RCT where patients achieved the highest convection volume, reported that dialysis staff was trained on how high convection volumes could be achieved. (16)

Furthermore, marked differences in means and ranges of achieved convection volumes were observed between hospitals participating in CONTRAST. (8) These findings support the hypothesis that awareness and motivation of doctors and nursing staff, might play an important role in determining the achieved convection volume.

An elaborate analysis of patient characteristics comparing patients achieving high versus patients achieving low volumes might provide insight on this issue. Such an analysis could be performed retrospectively with data from an existing study. Ideally, combined data from recent RCTs in an individual patient data (IPD) analysis would provide the most precise and reliable answer. To answer the question whether the convection volume indeed can be safely manipulated in clinical practice, a feasibility study is currently in progress (NCT01877499). If indeed convection volumes can be increased in daily clinical practice in the majority of patients, ideally, a new RCTs comparing high efficiency HDF with HD could give a definitive answer whether HDF with high convection volumes leads to a better survival in these patients.

### **Summary and conclusions**

Total convection volume is recognized as the best and easiest quantifier of HDF efficacy. The relation between a high convection volume and a smaller risk of all-cause mortality has been repeatedly demonstrated, both in observational studies and in RCTs. Blood flow and treatment time have been defined as important modifiable determinants of convection volume in online post-dilution HDF.

In future clinical studies on hemodiafiltration achieved convection volume should always be reported. Whether higher convection volumes can be achieved by consciously modifying these parameters is a subject currently under research. If indeed convection volume can be safely manipulated in clinical practice, new RCTs comparing high efficiency HDF with HD may give a definitive answer whether HDF with high convection volumes leads to a better survival in these patients.

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## Chapter 11

# Change in convection volume over time in online post-dilution hemodiafiltration patients. Results from the CONvective TRANsport Study (CONTRAST).

*Submitted for publication*

Ira M. Mostovaya,<sup>1</sup> Peter J. Blankestijn,<sup>1</sup> Michiel L. Bots,<sup>2</sup> Isabelle Chapdelaine,<sup>3</sup> Marinus A. van den Dorpel,<sup>4</sup>  
Renée Levesque,<sup>3</sup> Piet M. ter Wee,<sup>5,6</sup> Menso J. Nubé,<sup>5,6</sup> Muriel P.C. Grooteman.<sup>5,6</sup>

<sup>1</sup>Department of Nephrology, University Medical Center Utrecht, Utrecht

<sup>2</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht

<sup>3</sup>Department of Nephrology, Centre Hospitalier de l'Université de Montréal, St. Luc Hospital, Montréal, Canada

<sup>4</sup>Department of Internal Medicine, Maastricht Hospital, Rotterdam

<sup>5</sup>Department of Nephrology, VU Medical Center, Amsterdam

<sup>5</sup>Institute for Cardiovascular Research VU Medical Center (ICaR-VU), VU Medical Center, Amsterdam, the Netherlands

<sup>6</sup>Department of Cardiology, VU Medical Center, Amsterdam.

**Abstract****Background**

Recent randomized controlled trials showed a relation between a high convection volume and a low mortality risk in post hoc sub group analyses. It unclear whether an individual patient convection volume remains stable over time. If so, that would argue in favor of hospital characteristics as the main drivers for the level of received convection volume, since patient characteristics do tend to change over time. Therefore, the aim of this study is to examine the rate of change of convection volume in patients undergoing online post-dilution hemodiafiltration (HDF).

**Methods**

Data from 339 HDF patients from the CONvective TRANsport STudy (CONTRAST), who received at least one HDF treatment after baseline were used for the present analysis. Convection volume was measured every 3 months up to 6 years. The mean of three achieved convection volumes per follow-up moment were computed. The rate of change over time in convection volume and its components was estimated using linear mixed effects models.

**Results**

At baseline mean age was  $64 \pm 14.9$  years, and 192 (56%) of patients were male. Convection volume increased significantly over time by 0.34 L/treatment per year (95%CI 0.14 to 0.54,  $p=0.001$ ). Intradialytic weight change remained stable over time ( $\Delta=0.01$ L/treatment per year, 95%CI -0.04 to 0.05,  $p=0.83$ ), while the amount of substitution volume increased ( $\Delta=0.33$  L/treatment per year, 95%CI 0.13 to 0.53,  $p=0.001$ ). Rate of change of convection volume did not differ in subgroups of age, gender, body surface area and medical history. We did observe however, large differences in rate of change in convection volume between treatment facilities.

**Conclusion**

Achieved convection volume tends to increase over time, although this increase is probably not clinically relevant. Patient characteristics were not related to rate of change. However, large differences in rate of change exist between dialysis centers. This supports the hypothesis that mainly treatment characteristics determine the volume of convection.

## **Introduction**

In patients with end stage kidney disease (ESKD) the mortality and morbidity is very high when compared to the general population. (1) Many pathophysiological processes contribute to this increased risk, including retention of uremic substances with consequent oxidative stress, endothelial dysfunction and micro-inflammation. (2)

The majority of ESKD patients receiving dialysis undergo chronic intermittent hemodialysis (HD). In HD small uremic toxins are removed by diffusion, while larger solutes remain within the body. In hemodiafiltration (HDF) diffusion is combined with convection, enabling the removal of middle- and large molecular weight substances up to 40kDa. (3) During HDF, convective transport is obtained by filtering considerable amounts of plasma water through a dialyser with a large pore size (high-flux). At the same time, sterile substitution fluid is infused directly into the bloodstream of the patient to maintain fluid balance. (4) The sum of the substitution volume and the intradialytic weight loss (ultrafiltration volume) is termed as convection volume. (5) As retention of middle and large uremic toxins has been related to the adverse clinical outcome in patients with CKD, it has been suggested that removal of these substances by HDF may improve prognosis. (6)

Recently, the results of three randomized controlled trials (RCTs) comparing online post-dilution HDF to standard HD in terms of all-cause mortality and cardiovascular events have been published: the CONvective TRANsport STUDy (CONTRAST), the Turkish HDF Study and the Estudio de Supervivencia de Hemodiafiltracion On-Line (ESHOL). (7-9) ESHOL, the trial with the highest achieved convection volumes showed superiority of HDF over HD with respect to overall mortality and cardiovascular morbidity and mortality. The other two trials did not. Of relevance, *post hoc* analyses in all three RCTs demonstrated that HDF patients with the highest convection volumes had a lower mortality and a decreased risk of cardiovascular events compared to those treated with HD. (7-9) The underlying mechanisms of this relation between convection volume and survival is not yet clear. It is possible that a dose-response relation is present: the higher the convection volume, the better the removal of uremic toxins and better hemodynamic stability.(10-12) However, a dose targeting bias may also be present: patients with a superior vascular access and a

qualitatively better cardiovascular system may be the ones able to achieve higher convection volumes, and naturally also be the group who has a better prognosis. Yet, in all three trials maximal statistical adjustment were performed to overcome the potential confounding bias.

Recently we studied the determinants of the magnitude of convection volume cross-sectionally in a subpopulation of CONTRAST and showed that both patient characteristics (serum albumin, hematocrit, dialysis vintage and body surface area) as well as treatment characteristics (blood flow and treatment time) were related to convection volume. (13) However, the treatment characteristics showed a much stronger relation with convection volume. Furthermore, at baseline, patient characteristics did not differ tertiles of convection volume, except for a small variation in body size. (13) These results seem to indicate that dialysis prescription, rather than a favorable patient profile determine the achieved convection volume.

In this paper we aimed to further explore in what manner patient characteristics or treatment characteristics influence the magnitude of change of convection volume, this time by studying longitudinal data. Firstly, we studied the rate of change of convection volume and its components in patients undergoing online post-dilution HDF. Secondly we examined whether rate of change of convection volume differs in various subgroups of ESKD patients. Thirdly, we assessed how the earlier found determinants of convection volume change over time. Finally we examined whether rate of change of convection volume differs between dialysis facilities.

### **Materials and methods**

#### **Patients**

Analysis was performed with data from 339 participants of the CONvective TRANsport Study (CONTRAST), who had at least one convection volume after baseline (the convection volume was 0L/treatment at randomization) were used for this analysis. CONTRAST has been designed to investigate the effects of increased convective transport

by online HDF as compared with low-flux HD on all-cause mortality and cardiovascular morbidity and mortality (ISRCTN38365125). (7;14)

Patients were eligible if treated with haemodialysis two or three times a week, for at least 2 months, with a minimum dialysis urea Kt/V  $\geq 1.2$ . Furthermore, patients had to be able to understand the study procedures. Exclusion criteria were age  $< 18$  years, treatment by HDF or high flux HD in the 6 months preceding randomization, severe incompletion defined as non-adherence to the dialysis prescription, a life expectancy  $< 3$  months due to non-kidney disease and participation in another clinical intervention trial evaluating cardiovascular outcomes. Randomization was stratified by participating center. From June 2004 until January 2010 a total of 714 patients were enrolled in CONTRAST.

CONTRAST was conducted in accordance with the Declaration of Helsinki and approved by the medical ethics review boards of all participating dialysis centres. Written informed consent was obtained from all patients prior to enrolment.

#### **Hemodiafiltration procedure**

Hemodiafiltration was performed in the online post-dilution mode. Patients whom were suspected to have undergone pre-dilution HDF (convection volume  $> 35$ L/treatment) were excluded from the analysis. A target convection volume of 6 liters per hour was based on a filtration fraction (FF) between 25% and 33% of an extra-corporeal blood flow rate between 300 and 400 mL/min. Because evidence relating convection volume and outcome was absent when CONTRAST was started, these targets were derived from manufacturers' guidelines.

The following dialysis machines were used: 4008S and 5008 with ONLINEplus™ (Fresenius Medical Care, Bad Homburg, Germany), AK 100/200™ ULTRA S (Gambro AB, Lund, Sweden), DBB-05™ (Nikkiso Co. Ltd, Tokyo, Japan) and Integra™ (Hospal-Gambro AB, Lund, Sweden). The following synthetic high-flux dialyzers (see appendix) were used: FX80: 25%, FX100: 12% and Optiflux F200NR: 11% [Fresenius]; Polyflux 170H: 21% and Polyflux 210H: 29% [Gambro] and others: 2%. Ultrapure dialysis fluid, defined as  $< 0.1$  colony forming units and  $< 0.025$  endotoxin units per mL, was used for all treatments.

Treatment times were fixed at baseline and could only be increased if  $spKt/V_{urea}$  was  $<1.2$ . Dialysis frequency was thrice weekly in 93% of patients at baseline and in 100% at 6 months. Routine patient care was performed according to the guidelines of the Quality of Care Committee of the Dutch Federation of Nephrology.

### Data collection

Demographics, past medical history and medication were recorded at baseline, while various clinical, treatment and laboratory parameters were collected both at baseline and after 6 months. Body mass index (BMI) was calculated as weight (kilograms) divided by the square of height ( $m^2$ ). Body surface area (BSA) was calculated using the formula by Gehan and George. (15) Systolic and diastolic blood pressures were registered as the average of pre-dialysis values on three consecutive dialysis days. Blood samples for routine laboratory measurements were taken before the start of a dialysis session and analyzed in the local hospitals by standard techniques. Serum albumin measured with bromcresol purple method was converted to bromcresol green with the formula: bromcresol green=bromcresol purple+5.5 (g/L).<sup>23</sup>

Convection volume was defined as the sum of intradialytic weight loss (IDWL) and amount of substitution fluid and reported as the mean value of 3 consecutive dialysis sessions. Convective flow rate represented the convection volume in mL/minute. Filtration fraction (FF) was calculated by dividing convective flow rate by blood flow rate and reported as a percentage of blood flow.

Patients with a urinary production of less than 100mL per day were considered anuric. In patients with residual diuresis of more than 100mL per day, interdialytic 24 hour urinary samples were collected.

At each three-monthly visit, data on clinical events, clinical characteristics, dialysis treatment (including convection volume, substitution volume and IDWL), medication, and standard laboratory values were recorded. Convection volume, substitution volume and IDWL were registered as the average of values on three consecutive dialysis days.

**Outcome**

The primary study aim in the present analysis was the rate of change per year in convection volume, substitution volume and intradialytic weight loss.

The secondary study outcome was the effect of patient characteristics (age, gender, medical history and dialysis-treatment related characteristics) on the rate of change over time of convection volume, substitution volume and IDWL.

**Data analysis**

Data were reported as means with standard deviations, medians with ranges, or proportions when appropriate. Differences between groups were examined by one-way ANOVA, Mann-Whitney test or Pearson Chi-square test.

Linear mixed effect models were performed with a random intercept and random slope or a random intercept alone (depending on the lowest Aikake's information criterion value) to model changes over time in convection volume, substitution volume and intradialytic weight loss. To explore if rates of change differed depending on follow-up time, we calculated rates of change from baseline to 1 year, baseline to 2 years and baseline to end of follow-up of measurements. Subsequently, the changes over time were modelled with a linear mixed effect model in strata of the conventional risk factors. Each model was adjusted for baseline determinants of convection volume (dialysis vintage, treatment time, blood flow, serum albumin, hematocrit and BSA) by adding them as fixed effects to the model. Differences between strata of conventional risk factors were tested with the interaction term of the concerning conventional risk factor with time. For continuous variables such as age and dialysis vintage the interaction terms age\*time and vintage\*time were tested, with age and vintage as continuous variables. Continuous variables were also stratified below or above the median for the patient group under study, to show differences between young and old patients, patients with a short and long dialysis vintage and so on. Dialysis vintage was entered into the model as a time-independent covariate, while BSA, laboratory variables and treatment parameters were entered as time-varying covariates.

**Table 1:** Baseline characteristics

	<b>N=339</b>
<b><i>Demographic data</i></b>	
Male gender	192 (56%)
Caucasian race	286 (84%)
Age (year)	64.0 ± 14.9
<b><i>Clinical characteristics</i></b>	
History of cardiovascular disease	148 (44%)
Diabetes mellitus	84 (25%)
History of renal transplantation	31 (9%)
Vascular cause of renal disease <sup>‡</sup>	164 (48%)
Dialysis vintage (year)	1.8 (1.0 – 3.7)*
Patients with RKF <sup>‡</sup>	182 (54%)
Vascular access	
Fistula	264 (78%)
Graft	22 (7%)
Central venous catheter	53 (15%)
Weight (kg)	71.4 ± 15.7
BSA (m <sup>2</sup> )	1.83 ± 0.23
BMI (kg/m <sup>2</sup> )	25.3 ± 5.0
Pre-dialysis systolic blood pressure (mmHg)	147 ± 21
Pre-dialysis diastolic blood pressure (mmHg)	75 ± 12
<b><i>Laboratory parameters</i></b>	
Hemoglobin (mmol/L)	7.38 ± 0.82
Hematocrit (%)	37 ± 17
Serum albumin (g/L)	40.5 ± 3.7
Phosphate (mmol/L)	30.5 ± 14.3
β <sub>2</sub> -microglobulin (mg/L)	1.55 ± 0.48
<b><i>Treatment characteristics</i></b>	
spKt/V <sub>urea</sub>	1.42 ± 0.24
Treatment time (minute)	240 (210 – 240)*
Blood flow rate (mL/minute)	301 ± 39
Intradialytic weight loss (L/treatment)	1.9 ± 1.4
Convection volume (L/treatment) <sup>&amp;</sup>	19.8 ± 4.6
Substitution volume (L/treatment) <sup>&amp;</sup>	17.9 ± 4.4

‡ Diabetes, hypertension or vascular pathology as initial cause of kidney failure

\* Median and interquartile range (P25 – P75) is reported

% RKF: residual kidney function, defined as diuresis of  $\geq 100$  mL per day

& measured at month 6 of follow-up

BSA: body surface area; BMI: body mass index

To convert hemoglobin from mmol/L to g/dL multiply by 1.61. To convert albumin from g/L to g/dL divide by 10.

To convert phosphate from mmol/L to mg/dL, divide by 0.323.

To model changes over time in the (potentially time-varying) determinants of convection volume described earlier (BSA, serum albumin, hematocrit, treatment time and blood flow) linear mixed effect models were used with a random intercept and random slope or a random intercept alone (depending on the lowest Akaike's information criterion value). All models were adjusted for the baseline values of the variables.

We examined whether rates of change in convection volume differed between dialysis facilities, by comparing the rate of change of convection volume, IDWL and substitution volume from two dialysis centers that provided most patients for the study: one center from the Netherlands (center A, n=47) and one center from Canada (center B, n=40). The changes over time were modelled with a linear mixed effect model stratified by dialysis facility. Each model was adjusted for baseline determinants of convection volume (dialysis vintage, treatment time, blood flow, serum albumin, hematocrit and BSA) by adding them as fixed effects to the model.

Results were considered statistically significant when  $p < 0.05$  (two-sided). All calculations were made by use of a standard statistical package (SPSS for Windows Version 20.0.1; SPSS Inc. Headquarters, Chicago, Illinois, US).

## **Results**

The baseline patient characteristics of the 339 included patients are shown in Table 1. Mean age was  $64 \pm 14.9$  years, 192 were male (56%) and the median dialysis vintage was 1.8 (P25-P75: 1.0 – 3.7) years. After inclusion patients were followed for an average of 3.0 years (range, 0.2 – 6.2 years; median 2.9 years). A total of 2717 measurements of convection volume were included in this analysis.

### Convection volume changes over time

Rates of change of convection volume, substitution volume, IDWL and filtration fraction are shown in Table 2. Convection volume increased significantly over time by 0.34 L/treatment per year (95%CI 0.14 to 0.54,  $p=0.001$ ; crude analysis:  $\Delta$  0.39L/treatment per year, 95% CI 0.16 to 0.62,  $p=0.001$ ), also shown in Figure 1a. Substitution volume increased significantly over time:  $\Delta$ 0.33 L/treatment per year (95%CI 0.13 to 0.53,  $p=0.001$ ; unadjusted analysis:  $\Delta$  0.42L/treatment per year, 95% CI 0.20 to 0.66,  $p<0.001$ ). IDWL did not change significantly over time:  $\Delta$ 0.01 L/treatment per year (95%CI -0.04 to 0.05,  $p=0.83$ ; unadjusted analysis:  $\Delta$  0.00L/treatment per year, 95% CI -0.04 to 0.05,  $p=0.91$ ). Filtration fraction did not change significantly over time:  $\Delta$ 0.51% per year (95%CI -0.09 to 1.10,  $p=0.097$ ; unadjusted analysis:  $\Delta$  0.35% per year, 95% CI -0.24 to 0.94,  $p=0.24$ ), although a borderline significant trend for an increase was observed. Figure 1b shows rates of change of substitution volume and IDWL over time. Rates of change were similar (although confidence intervals were wider) when these treatment parameters were modelled for shorter periods of follow-up time (Table 2).

### Convection volume changes in subgroups

Rates of change of convection volume stratified by subgroups are shown in Table 3. No significant differences were found between rates of change of convection volume in subgroups of age, sex, BMI, history of cardiovascular disease, diabetes, residual kidney function, dialysis vintage or cause of ESKD (vascular cause versus non-vascular cause).

### Changes in determinants of convection volume over time

The rates of changes of determinants of convection volume are shown in Table 4. Regarding the patient-related determinants: both BSA ( $\Delta$ -0.005m<sup>2</sup> per year, 95% CI -0.010 to -0.001,  $p=0.024$ ) and albumin ( $\Delta$ -0.55g/L per year, 95% CI -0.76 to -0.33,  $p<0.001$ ) decreased over time, while hematocrit remained stable. Such a decrease of BSA would account for a decrease in convection volume of approximately 5mL/treatment per year (95%CI -5 to 15). (13) Such a decrease in albumin would account for a decrease of convection volume of 72mL/treatment per year (95% CI 17 to 121). (13)

**Table 2:** Changes in convection volume, substitution volume, intradialytic weight loss and filtration fraction over time.

	$\Delta$ per year	95% CI of $\Delta$	p-value
<b>Convection volume (L/treatment)</b>			
0 – 1 years	0.34	-0.11 to 0.80	0.13
0 – 3 years	0.30	0.09 to 0.51	0.006
0 – 6.5 years (maximum follow-up)	0.34	0.14 to 0.54	0.001
<b>Substitution volume (L/treatment)</b>			
0 – 1 years	0.24	-0.20 to 0.68	0.29
0 – 3 years	0.27	0.07 to 0.49	0.010
0 – 6.5 years (maximum follow-up)	0.33	0.13 to 0.53	<0.001
<b>Intradialytic weight loss (L/treatment)</b>			
0 – 1 years	0.11	-0.01 to 0.22	0.086
0 – 3 years	0.02	-0.03 to 0.07	0.42
0 – 6.5 years (maximum follow-up)	0.01	-0.04 to 0.05	0.83
<b>Filtration fraction (%)</b>			
0 – 1 years	0.46	-0.14 to 1.06	0.13
0 – 3 years	0.37	0.07 to 0.66	0.016
0 – 6.5 years (maximum follow-up)	0.51	-0.09 to 1.10	0.097

All rates of changes are adjusted for age, gender, dialysis vintage, cardiovascular disease, diabetes mellitus, AV-fistula, treatment time, blood flow, albumin, hematocrit and body surface area (the latter 5 as time-dependent covariates).

Regarding the treatment-related determinants: blood flow increased significantly over time ( $\Delta$ 3.33mL/minute per year, 95% CI 1.02 to 5.63,  $p=0.005$ ), while treatment time did not change significantly. Such an increase in blood flow would account for an increase of convection volume of 165mL/treatment per year (95% CI 147 to 198). (13)

#### Differences in rate of change between dialysis facilities

The baseline patient characteristics of the patients in two largest dialysis facilities participating in CONTRAST, Center A ( $n=47$ ) and Center B ( $n=40$ ) are shown in Table 4. Age, gender and medical history were similar in both centers, although dialysis vintage was higher in center B. Furthermore, prevalence of vascular access type at baseline differed between centers: there were more arterio-venous fistulas and less central venous catheters in center A. Serum albumin was significantly higher in center B. Regarding treatment characteristics, when the first achieved convection volumes were measured

**Table 3:** Convection volume changes over time in various strata of risk factors.

	Estimate slope (L/treatment per year)	95% CI	p-value slope	p-value interaction term
Age < 66.8 years	0.31	-0.03 to 0.52	0.073	0.45
Age > 66.8 years	0.48	0.16 to 0.80	0.004	0.41*
Men	0.43	0.02 to 0.84	0.039	0.83
Women	0.37	0.09 to 0.65	0.010	
Body mass index < 24.8 (kg/m <sup>2</sup> )	0.34	0.05 to 0.64	0.024	0.58
Body mass index > 24.8 (kg/m <sup>2</sup> )	0.47	0.10 to 0.84	0.013	0.50*
Residual kidney function	0.42	0.13 to 0.72	0.005	0.79
No residual kidney function	0.36	-0.02 to 0.74	0.062	
Cardiovascular disease	0.27	-0.10 to 0.63	0.15	0.36
No cardiovascular disease	0.48	0.18 to 0.78	0.002	
Diabetes mellitus	0.50	-0.19 to 1.18	0.15	0.35
No diabetes mellitus	0.31	0.07 to 0.55	0.012	
Dialysis vintage < 1.8 years	0.36	0.01 to 0.72	0.048	0.82
Dialysis vintage > 1.8 years	0.43	0.12 to 0.73	0.007	0.70*
Vascular cause renal disease <sup>‡</sup>	0.38	0.02 to 0.73	0.011	0.90
No vascular cause renal disease	0.42	0.10 to 0.74	0.036	

\*p-value of interaction term when age / body mass index / dialysis vintage are modelled as a continuous variable

<sup>‡</sup> Diabetes, hypertension or vascular pathology as initial cause of kidney failure

(complete set of measurements at month 6), the convection volume, substitution volume, filtration fraction, and blood flow were significantly higher in center B.

Rates of changes in treatment parameters in Center A and Center B are shown in Table 5.

Rate of change in convection volume (Center A:  $\Delta 0.26\text{L}/\text{treatment per year}$ , 95%CI -0.29 to 0.82,  $p=0.34$ ; Center B:  $\Delta 1.45\text{L}/\text{treatment per year}$ , 95% CI 0.84 to 2.06,  $p<0.001$ ) and

**Table 4:** Rates of change of determinants of convection volume.

	$\Delta$ per year	95% CI of $\Delta$	p-value
<b>Patient related characteristics</b>			
Body surface area (m <sup>2</sup> )	-0.005	-0.010 to -0.001	0.024
Albumin (g/L)	-0.55	-0.76 to -0.33	<0.001
Hematocrit (%)	-1.0	-3.1 to 1.1	0.35
<b>Treatment related characteristics</b>			
Treatment time (minutes)	-0.22	-1.46 to 1.02	0.73
Blood flow (mL/minute)	3.33	1.02 to 5.63	0.005

All linear mixed models were adjusted for baseline values of the variables.

substitution volume (Center A:  $\Delta$ 0.21L/treatment per year, 95%CI -0.30 to 0.74,  $p=0.40$ ; Center B:  $\Delta$ 1.31L/treatment per year, 95% CI 0.69 to 1.92,  $p<0.001$ ) was significantly higher in Center B ( $p$  for difference between centers: 0.004 and 0.006 respectively) as shown in Figure 2. The higher increase in convection volume in Center B was accompanied by a higher increase in both treatment time (Center A:  $\Delta$ 05.05mL/minute per year, 95%CI 2.07 to 8.04,  $p=0.001$ ; Center B:  $\Delta$ 22.27mL/minute per year, 95% CI 13.29 to 31.55,  $p<0.001$ ) and blood flow (Center A:  $\Delta$ -6.0 minutes per year, 95%CI 10.8 to 0.10,  $p=0.001$ ; Center B:  $\Delta$ 3.0 minutes per year, 95% CI -0.60 to 6.0,  $p=0.079$ ;  $p$  for difference between centers: 0.013 and  $<0.001$  respectively). Of note, since the rate of change was so high in center B, we modelled rate of change of convection volume also excluding center B from the population, and still found a significant increase in convection volume over time:  $\Delta$ 0.26L/treatment per year (95% CI 0.03 to 0.46,  $p=0.026$ ).

### **Discussion**

We are among the first to study how convection volume in online post-dilution HDF patients changes over time and what factors affect these changes. Achieved convection volume increases slowly over time by approximately 0.3L/treatment per year. The increase in convection volume can mainly be attributed to an increase in substitution volume, but not intradialytic weight loss. Age, gender, body size and medical history do not seem to influence the rate of change of convection volume. However, relevant

**Figure 1:** Change in convection volume (1a) and substitution volume and intradialytic weight loss in L/treatment (1b) over time.

Figure 1a.

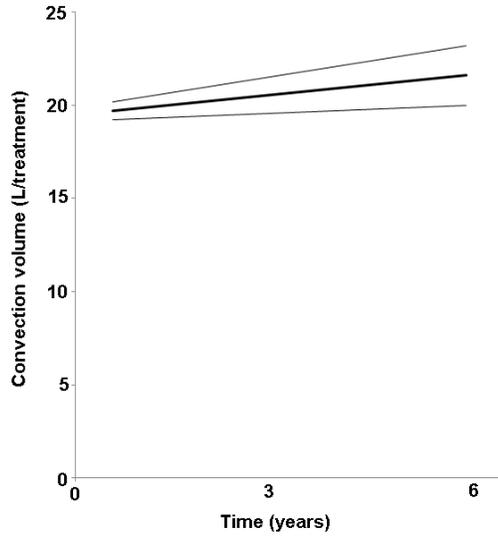
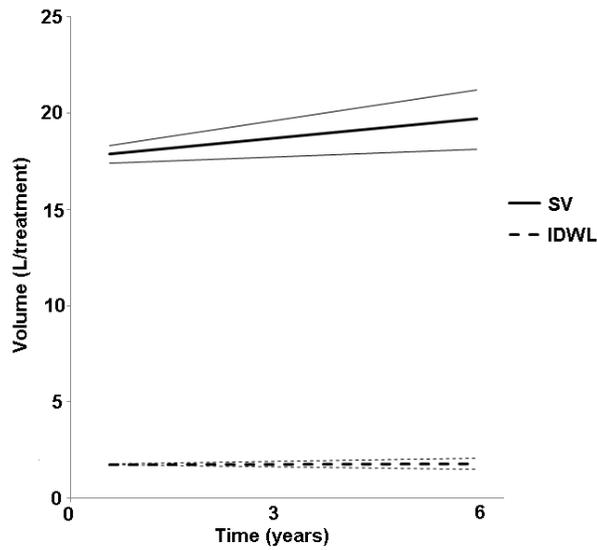
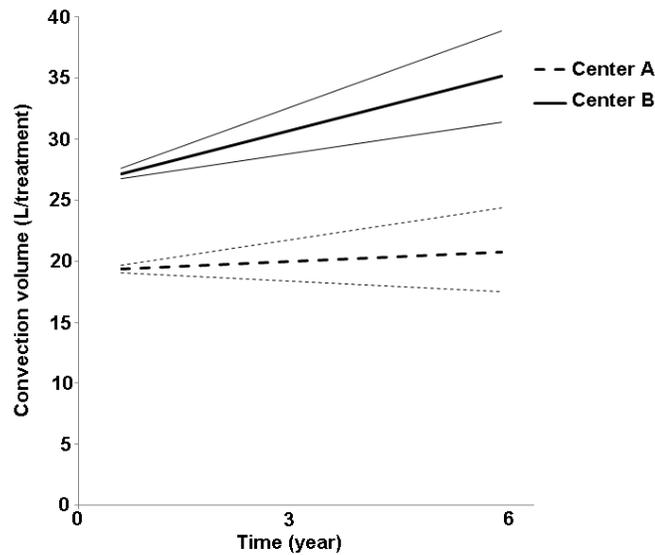


Figure 1b.



IDWL: intradialytic weight loss, SV: substitution volume

**Figure 2:** Change in convection volume over time stratified by dialysis center: Center A versus Center B.



differences are observed in rate of change in convection volume and other treatment characteristics between participating dialysis facilities.

#### **Clinical relevance of changes in convection volume**

In the last year, three large RCTs demonstrated in their HDF cohorts that a high convection volume was associated with a lower mortality risk, despite extensive adjustments for potential confounders. (7-9) Moreover, ESHOL, the study with the highest mean convection volume achieved, also showed a significant reduction of the overall mortality risk in the total group of HDF patients. (8) The studies that mentioned the magnitude of the achieved convection volume using post-dilution HDF in relation to mortality risk, the cut off points above which a reduction in risk was found varied considerably across studies.

**Table 5:** Baseline characteristics in two largest participating dialysis facilities.

	<b>Center A (n=47)</b>	<b>Center B (n=40)</b>	<b>p-value</b>
<b>Demographic data</b>			
Male gender	31 (65%)	22 (54%)	0.46
Caucasian race	34 (72%)	29 (73%)	0.93
Age (year)	62.6 ± 12.9	64.6 ± 13.2	0.49
<b>Clinical characteristics</b>			
History of cardiovascular disease	26 (54%)	15 (38%)	0.24
Diabetes mellitus	17 (37%)	16 (40%)	0.98
History of renal transplantation	2 (5%)	2 (5%)	0.99
Vascular cause of renal disease <sup>‡</sup>	33 (70%)	20 (51%)	0.15
Dialysis vintage (year)	1.9 ± 2.0	3.7 ± 4.0	0.017
Patients with RKF <sup>§</sup>	31 (65%)	22 (54%)	0.44
<b>Vascular access</b>			
Fistula	40 (86%)	24 (60%)	0.015
Graft	7 (14%)	6 (14%)	0.96
Central venous catheter	0 (0%)	11 (27%)	0.001
BSA (m <sup>2</sup> )	1.85 ± 0.24	1.84 ± 0.25	0.87
BMI (kg/m <sup>2</sup> )	25.2 ± 5.0	28.2 ± 6.9	0.034
Pre-dialysis SBP (mmHg)	145 ± 26	144 ± 14	0.94
Pre-dialysis DBP (mmHg)	74 ± 13	75 ± 10	0.73
<b>Laboratory parameters</b>			
Hemoglobin (mmol/L)	7.5 ± 1.0	7.0 ± 0.90	0.027
Hematocrit (%)	37 ± 5	42 ± 49	0.55
Serum albumin (g/L)	37.9 ± 3.7	43.0 ± 2.6	<0.001
<b>Treatment characteristics</b>			
Convection volume (L/treatment)*	19.1 ± 2.8	25.8 ± 3.4	<0.001
Substitution volume (L/treatment)*	17.7 ± 2.8	23.6 ± 3.1	<0.001
Intradialytic weight loss (L/treatment)*	1.96 ± 0.98	2.18 ± 0.39	0.33
Filtration fraction (%)*	26 ± 3	30 ± 3	<0.001
spKt/V <sub>urea</sub>	1.45 ± 0.28	1.72 ± 0.25	0.015
Treatment time (minute)	232 ± 19	222 ± 24	0.056
Blood flow rate (mL/minute)	319 ± 3.3	387 ± 48	<0.001

<sup>‡</sup> Diabetes, hypertension or vascular pathology as initial cause of kidney failure

<sup>§</sup> RKF: residual kidney function, defined as diuresis of ≥100 mL per day

\*parameters measured at month 6 instead of baseline (at randomization convection volume was 0)

BSA: body surface area; BMI: body mass index

**Table 6:** Rates of change (per year) of dialysis treatment characteristics in two largest participating dialysis facilities.

	Center A			Center B			p for difference between centers
	$\Delta$ per year	95% CI of $\Delta$	p-value	$\Delta$ per year	95% CI of $\Delta$	p-value	
Convection volume (L per treatment)	0.26	-0.29 to 0.82	0.34	1.45	0.84 to 2.06	<0.001	0.004
Substitution volume (L/treatment)	0.21	-0.30 to 0.74	0.40	1.31	0.69 to 1.92	<0.001	0.006
Intradialytic weight loss (L/treatment)	0.03	-0.22 to 0.29	0.79	0.11	-0.03 to 0.25	0.13	0.59
Filtration fraction (%)	0.29	-0.26 to 0.84	0.28	-0.52	-1.20 to 0.16	0.13	0.046
Treatment time (minute)	-6.0	-10.8 to 0.6	0.059	3.0	0.60 to 6.0	0.079	0.013
Blood flow (mL/minute)	5.05	2.07 to 8.04	0.001	22.27	13.29 to 31.25	<0.001	<0.001
spKt/V <sub>urea</sub>	0.09	0.05 to 0.13	0.001	0.06	-0.01 to 0.12	0.081	0.35

convection volume changes over time

For example, tertiles of convection volume had cut-off points at 18 and 22L/treatment in CONTRAST (7), but the cut-off points for tertiles in ESHOL were 23 and 25L/treatment. Current literature does not provide a clear cut-off point what convection volume is needed to reduce mortality risk. In expert-opinion reviews and editorials a convection volume of >20-22 L per treatment is mentioned as the presumed volume associated with likely improvement in clinical outcome variables in post-dilution HDF. (16;17)

In our analyses we show that convection volume tends to increase by approximately 0.3L/treatment per year, when adjusted for patient- and treatment-related confounders. This means that the convection volume would increase “naturally” by 1L/treatment in about 3 years. Thus, a hypothetical CONTRAST patient in the lowest tertile of convection volume (<18L) (7) would need at least 7 years to reach a convection volume regarded as relevant enough to decrease mortality risk, if patient and treatment parameters remained constant. Therefore it is questionable whether the observed increase of convection volume over time is, albeit statistically significant, also clinically relevant.

#### **Determinants of convection volume**

Recently we studied the determinants of the magnitude of convection volume in a subpopulation of CONTRAST: 314 online post-dilution HDF patients who had completed 6 months of follow-up. In a cross-sectional analysis we demonstrated that the magnitude of convection volume in online post-dilution HDF is determined by both patient characteristics and dialysis treatment characteristics. The patient characteristics serum albumin, dialysis vintage and body surface area were positively related to convection volume, while hematocrit was inversely related. The treatment characteristics blood flow and treatment time (per dialysis session) were both positively related to convection volume. Furthermore, the relation between treatment characteristics and convection volume was 3-4 times stronger than the relation between convection volume and the patient characteristics. (13)

In this manuscript we showed that during follow-up the treatment time remains stable. Blood flow increases very slightly but significantly over time by 3.3mL/minute per year. Such an increase in blood flow would be in accordance with an increase of

0.15L/treatment (95% CI 0.12 – 0.21L/treatment) in convection volume, as deduced from our previous analyses. (13) The increase in blood flow is probably one of the factors contributing to increase of convection volume over time.

Regarding the patient characteristics: hematocrit remains stable while BSA and albumin decrease over time. This is not in accordance with the increase in convection volume. However, BSA and albumin, although significant determinants, contribute relatively little to convection volume, as we have shown earlier. (13)

Studies in the CONTRAST population have repeatedly shown that the overall health of ESKD patients does not improve over time: nutritional status (BMI and serum albumin) worsens, while inflammatory parameters (C-reactive protein and interleukin-6) increase (18), cardiac function (left ventricular ejection fraction) decreases [ref: Mostovaya et al] and quality of life also declines. (19) Furthermore, the incidence of cardiovascular events is high. (7) However, no decline is observed in convection volume over time. The fact that convection volume tends to increase while overall health of patients declines is not concurrent with the hypothesis that only healthy patients can reach high convection volumes (dose-targeting bias).

#### **Differences between dialysis facilities**

The two largest participating dialysis facilities were compared in terms of rate of change of convection volume and other treatment characteristics. Center A is a Dutch dialysis facility, while center B is located in Canada. At baseline patients from center B had a higher dialysis vintage and a better nutritional status (higher albumin and BMI), than those from center A.

Both the initial convection volume, as well as the rate of change of convection volume were significantly higher in center B. This was accompanied by a higher starting value as well as a rigorous increase in blood flow and a relative increase in treatment time when compared to center B.

In the ESHOL study it was mentioned that the dialysis staff was specifically trained to achieve high convection volumes. (8) It is tempting to speculate that this increases the likelihood that high convection volumes are not only prescribed but also achieved in

clinical practice. By demonstrating large differences in treatment characteristics between dialysis centres our data concurs with the Maduell et al observation that training and dedication of dialysis staff likely plays an important role in determining the achieved convection volume. (8)

### **Strengths and limitations**

Strengths of the present study are a concise prospective data collection and a long period of follow-up. In addition, all measurements were taken into account with the linear mixed models, where time-dependent co-variables were modelled adequately.

This study also has several limitations. Firstly, a relevant proportion of patients died or received a kidney transplantation during the follow-up period. Although mixed effect models are the models for this type of data to validly estimate the relationships, loss of individuals results in a decrease of precision of the relations. Secondly, the vascular access was only recorded at baseline. However, it cannot be excluded that a change in the access occurred. Theoretically, vascular access type and quality could influence the magnitude and changes of convection volume. Unfortunately we did not collect the data.

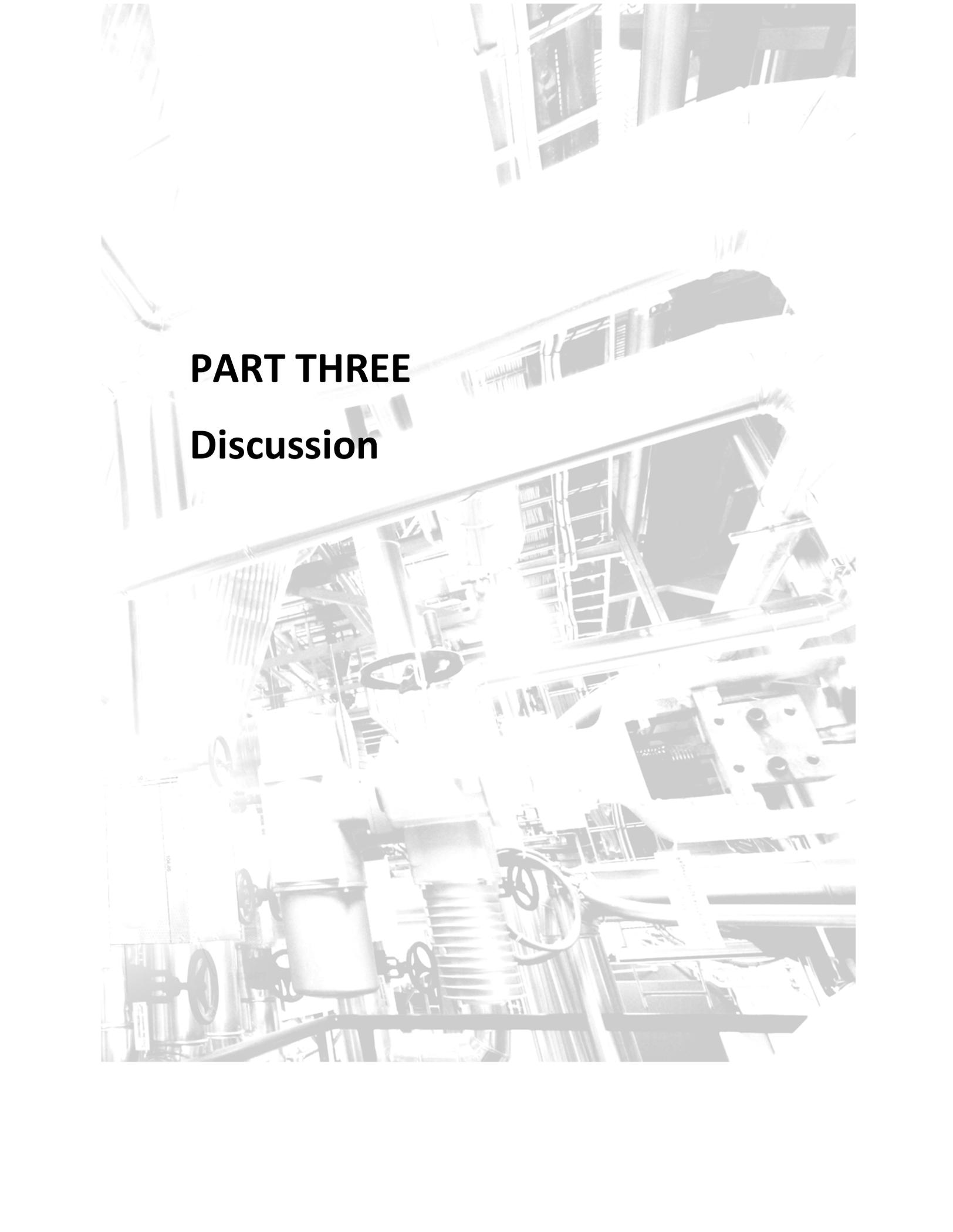
### **Conclusion**

Achieved convection volume increases slowly over time by approximately 0.3L/treatment per year, although it is questionable whether this change is clinically significant. Age, gender, BMI and medical history do not influence the rate of change of convection volume. The fact that convection volume increases parallel to blood flow, while it is not in concordance with rate of change in patient characteristics, underlines the importance of treatment characteristics in determining convection volume. Large differences in rate of change in convection volume between centres also support the hypothesis that treatment characteristics and dedication of dialysis staff is of great importance in achieving high convection volumes.

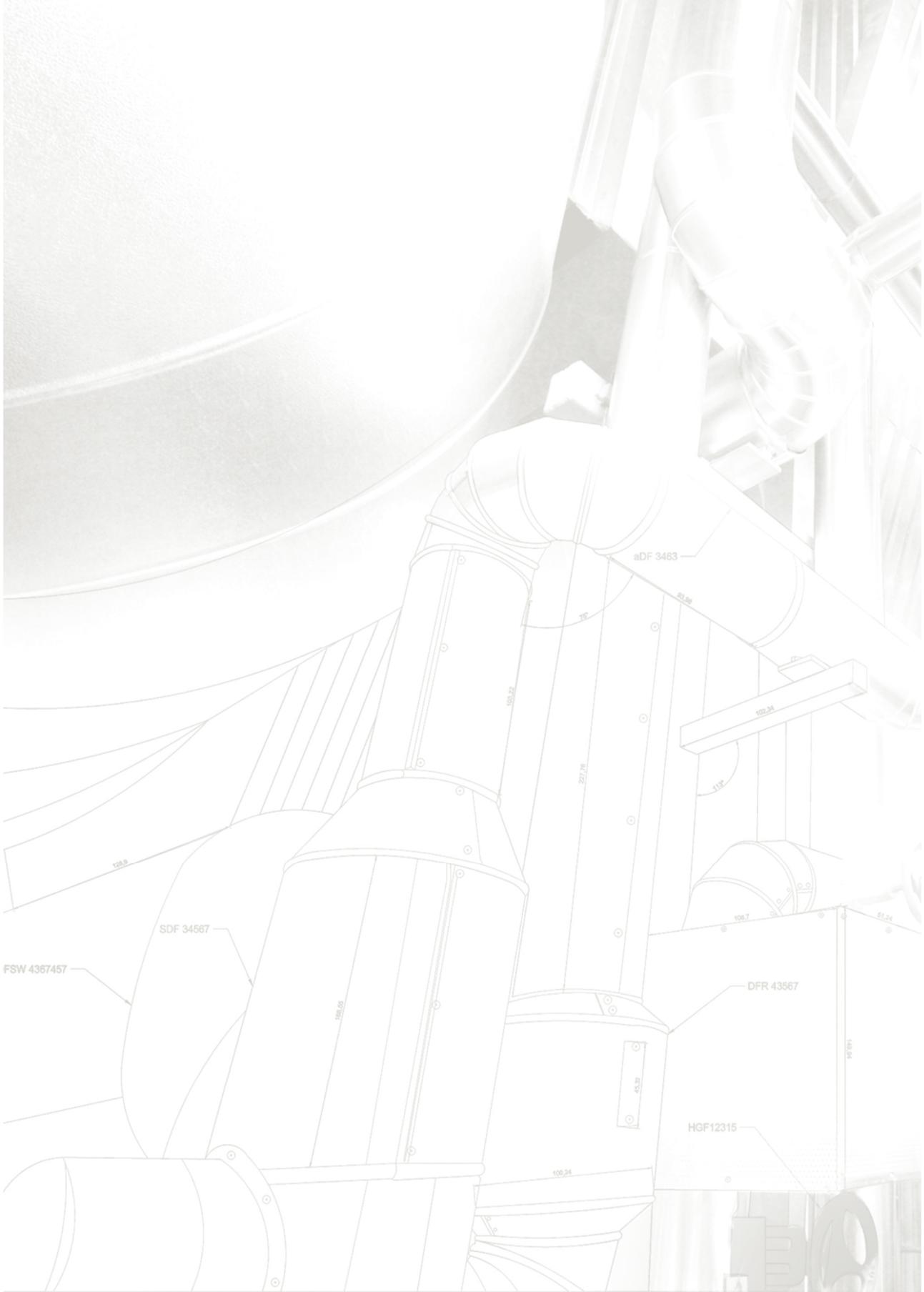
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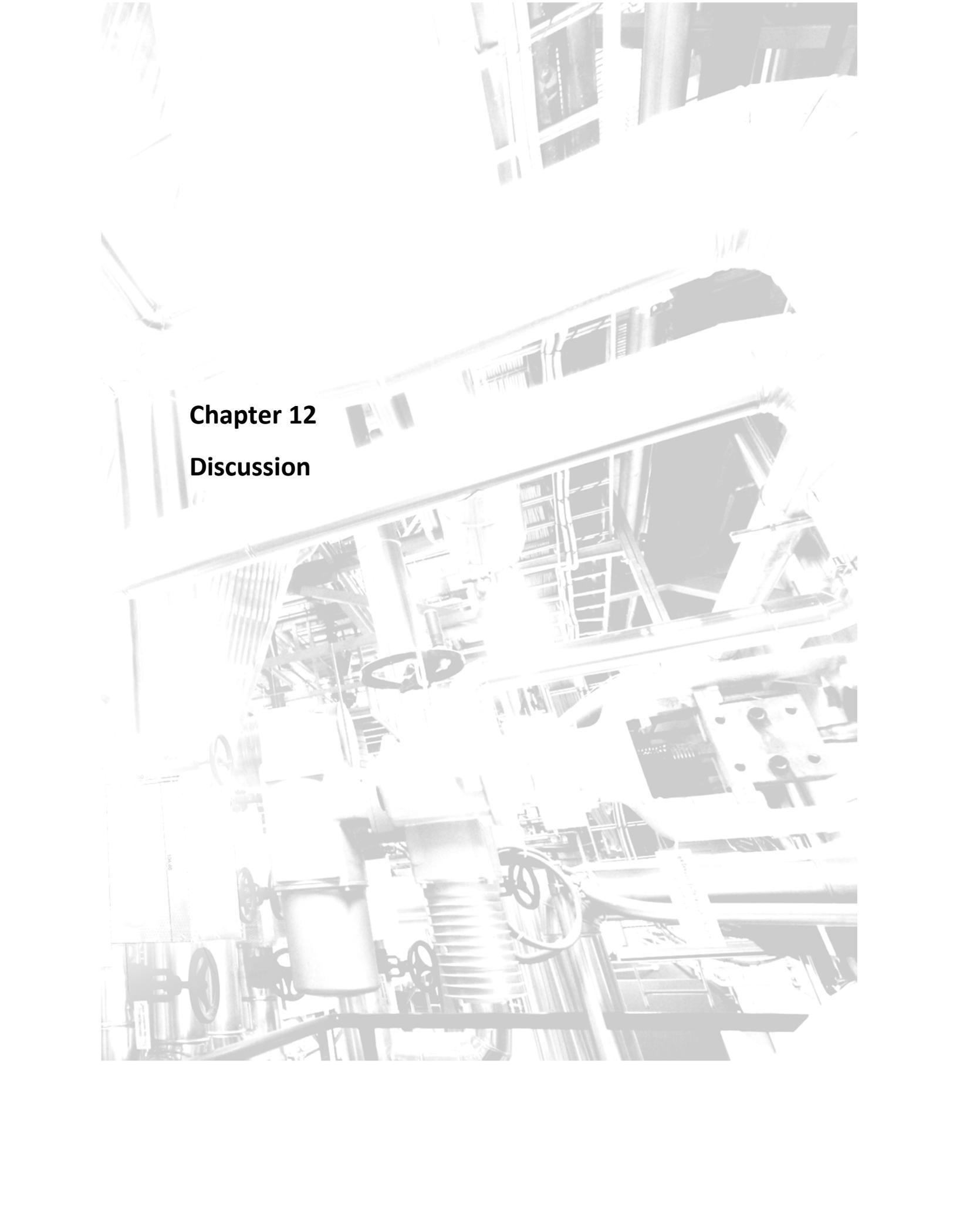
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**PART THREE**  
**Discussion**





**Chapter 12**  
**Discussion**

In this thesis we first studied the relation between structural and functional cardiovascular parameters and prognosis in end stage kidney disease (ESKD) patients. Secondly, we assessed the determinants of rate of change (including dialysis modality) of these cardiovascular parameters. Thirdly, we studied convection volume in hemodiafiltration (HDF), namely what determines convection volume and how convection volume changes over time.

All analyses of the original articles in this thesis were written based on data from participants of the CONvective TRANsport Study (CONTRAST): a randomized controlled trial comparing mortality and cardiovascular events in online post-dilution HDF versus the standard low-flux hemodialysis (HD) in 714 chronic intermittent dialysis patients (HDF: n=358, HD: n=356) from 29 dialysis centers in the Netherlands (n=26), Canada (n=2) and Norway (n=1). **Chapter 1** briefly describes the study design of CONTRAST as well as the results of earlier publications on the main outcome and secondary outcome parameters.

### **Structural and functional cardiovascular parameters markers and prognosis**

Cardiovascular disease is an important cause for morbidity and mortality in ESKD patients. The origin of cardiovascular disease is multifactorial and cannot be explained by traditional cardiovascular risk factors alone. (1) Non-traditional factors such as retention of uremic toxins, micro-inflammation, atherosclerosis, a fluctuating extracellular fluid volume and hypertension have been implicated as additional causes of cardiovascular damage. (1-3)

Increased left ventricular mass (LVM) has been well described as a frequent component of ESKD. In fact, more than seventy percent of patients starting dialysis show left ventricular hypertrophy (LVH) on echocardiography. (4) A high LVM is associated with an increased risk of cardiovascular morbidity and mortality. (5;6) In **Chapter 2** we confirmed the relation between LVM and overall mortality as well as cardiovascular mortality. We also expanded the evidence by finding a strong relation between LVM and risk of sudden death in particular. Since LVM was indeed an important a predictor of mortality, we also studied which patient- and treatment-characteristics are related to LVM in **Chapter 2**. Although

we found several plausible determinants, we did not identify any characteristics that could easily be modified in routine clinical practice.

Blood pressure (BP) in ESKD patients is highly variable and strongly related to volume overload. (7) Overall, BP is elevated and represents a large burden of morbidity and mortality in this population. (8;9) What type of measurement represents BP burden the best and predicts clinical events best is not clear. Furthermore, the type of BP measurement (systolic or diastolic, pre- or post-dialysis) that predicts clinical events best is still unclear. In **Chapter 5** we studied whether the easily feasible pre- and post-dialysis measurements could be used as good predictors of clinical events. We found that the mean of the pre-and post-dialysis BP measurements showed the strongest relation with future clinical events, when compared to only the pre- or only the post-dialysis BP measurements. Furthermore, diastolic BP showed the strongest relations with overall and cardiovascular mortality in our population.

#### **Changes in cardiovascular markers over time**

Little information is available on how structural and functional cardiovascular parameters change over time in ESKD patients.

Several observational studies showed that LVM tends to either increase or remain stable in prevalent HD patients. (5;10) We examined the rate of change of LVM over time, and whether the rate of change was different in certain subgroups of our population in **Chapter 4**. LVM was high in our population, and did not change significantly over time within a four year time frame. We did not find that rate of change of LVM differed across subgroups of age, gender, residual kidney function, dialysis vintage, history of cardiovascular disease, diabetes and convection volume (in HDF patients).

Left ventricular ejection fraction (EF) describes the percentage of blood flow that is ejected from the left ventricle during systole, and is a surrogate marker of cardiac function. A low EF is related to increased mortality risk in ESKD patients. (11;12) As described in the literature the natural course of EF in ESKD patients is to decrease slowly over time. (11;13) We studied the rate of change of EF in **Chapter 4** and found that in our population EF also tends to decrease within a four year time frame, and that this rate of

change is not different across the subgroups of age, gender, residual kidney function, dialysis vintage, history of cardiovascular disease, diabetes and convection volume (in HDF patients).

Pulse wave velocity (PWV) is a measure of arterial stiffness and is also related to cardiovascular and overall mortality in ESKD patients. (14;15) We studied rate of change of PWV in our population in **Chapter 4** and found that while PWV was high at baseline, these values remained stable over time within a three year time frame, and rate of change was not different across the subgroups described above.

How BP parameters change over time in our population is described in **Chapter 6**. Systolic BP, diastolic BP and pulse pressure all decline significantly over time. Older patients, males, patients with a higher dialysis vintage and with a history of cardiovascular disease and those with a lower left ventricular EF experience a greater decline in BP over time. Thus, it seems that BP decline is related to cardiac failure in our population and no determinants of rate of change of BP are identified that could be easily modified in daily clinical practice.

We further study the reasons for BP decline in **Chapter 7**, where we examine how cardiac output (CO) and peripheral resistance (PR) change over time, in a subpopulation of CONTRAST (n=84). In this subgroup we see a similar BP decline, parallel to a decline in PR, while CO remains stable over time. Thus, it seems that a decline in renin-angiotensin-aldosterone system activation and renal sympathetic nerve activity due to deterioration of kidney function over time seems another explanation for the BP decline in dialysis patients.

Thus, LVM, EF, PWV and BP are related to all cause and cardiovascular mortality, but are not easily modified in our population treated with chronic intermittent dialysis. Future studies should focus on prevention of development of abnormalities of structural and functional cardiovascular parameters in earlier stages of chronic kidney disease (CKD). Potentially, a change in dialysis frequency, e.g., nocturnal dialysis, as this is a regime that more resembles the natural daily dialysis function of the kidney, may be of help in reversing structural and functional cardiovascular parameters and with that the risk of morbidity and mortality. Indeed, several small (n = 5, 25-125 participants) randomized

controlled trials (RCTs) and observational studies have shown improvements in cardiac morphology and function after such treatment. (16) Yet, the effect of nocturnal dialysis on morbidity and mortality should be addressed in a large RCT.

#### **The effect of hemodiafiltration on structural and functional cardiovascular parameters**

HDF is a dialysis modality which uses a combination of convective transport and diffusion to clear more and larger solutes than conventional hemodialysis HD. (17) HDF reduces inflammatory parameters related to atherosclerosis and improves intradialytic haemodynamic stability (18), possibly advantageous factors in decreasing the risk of cardiovascular disease. Thus we evaluated whether HDF would have a beneficial effect on structural and functional cardiovascular parameters in **Chapter 3**. We studied whether rates of change of LVM, EF and PWV differed for patients randomized for HDF or HD. We found no significant difference in rate of change of LVM, EF or PWV between treatment modalities, although trends were observed for 1) an increase of LVM in HD, while LVM in HDF remained stable and 2) a decrease of EF in HD, while EF in HDF remained stable. If more patients had undergone echocardiography and PWV measurements the precision of our estimates would have been increased, and with that our ability to detect significant differences between treatment modalities would be enhanced. In the future, echocardiography and PWV studies in a larger population would provide more definite answers to this question. Such an initiative is started by pooling individual participant data on this issue from the three RCTs, ESHOL, CONTRAST and the Turkish HDF trial .

#### **Convection volume in hemodiafiltration: what do we know from previous studies**

Recently three RCTs (including CONTRAST) were published comparing post-dilution HDF to standard HD. Two trials did not find difference in overall mortality and cardiovascular events between the treatment modalities. However, one trial did demonstrate that patients with HDF had a better survival. All the RCTs have shown in sub-analyses that a high convection volume was related to a lower risk of overall mortality. (19-21) Convection volume was defined as the sum of the substitution volume and the net

ultrafiltration volume. Interestingly, the RCT with the highest convection volume was also the one that showed a superior survival in HDF patients.

Although it is tempting to speculate about a dose-response relation between convection volume and mortality, subgroup-analyses in individual studies cannot provide a definite conclusion on this issue. Residual confounding, as could be caused by the quality of vascular access, cannot be entirely excluded. Theoretically, a high blood flow may permit a large convection volume at the one hand, and represent a good clinical condition at the other (the so-called dose targeting bias). Yet in all trials reports maximally adjustment was attempted to remove the potential of residual confounding, so it seems to be unlikely that residual confounding is responsible. In **Chapter 8** we review the existing clinical evidence on HDF and perform a meta-analysis regarding survival and cardiovascular mortality. Although two large trials find no difference, in the pooled meta-analysis HDF seems superior in terms of overall mortality and cardiovascular mortality when compared to HD. However, since the RCTs all suffered from several potential risks of bias, the results of the meta-analysis should be interpreted with some caution. An individual patient data meta-analysis would provide a more sufficient answer to this question, as several of the biases apparent when using published aggregated data, can be dealt with in an IPD meta-analysis.

#### **Convection volume in hemodiafiltration: new insights**

Results from recent RCTs have shown that convection volume is a relevant parameter of HDF treatment. (19-21) However, little is known about the determinants of the magnitude of convection volume. Penne et al showed in a previous subanalysis of CONTRAST performed in 235 HDF patients that treatment time and blood flow (both positively related) are important treatment-related determinants of convection volume, while hematocrit (negative relation) and serum albumin (positive relation) are relevant patient-related determinants of convection volume. (22) As shown in **Chapter 9**, we have repeated this analysis in the entire CONTRAST HDF population (n=314 at 6 months of follow-up), and found similar results. Treatment time and blood flow were identified as the most powerful determinants of convection volume. Furthermore, we saw that convection

volume differed greatly between dialysis facilities, as did the filtration fraction, blood flow and treatment time. In over 7 centers blood flow and treatment time were similar for all patients, implying that dialysis prescription was uniform in those centers. Convection volume was not related to type of vascular access and dialyzer characteristics.

Another relevant finding in **Chapter 9** was that except for some variation in body size, patient characteristics at baseline did not differ across tertiles of convection volume. Thus our data does not support the hypothesis that the beneficial effect of high convection volumes is determined by a more favorable clinical profile beforehand (dose-targeting bias).

It seems that predominantly treatment characteristics determine the magnitude of convection volume as opposed to intrinsic patient characteristics. In **Chapter 10** we summarize available literature in this subject and hypothesize how higher convection volumes could indeed be achieved in clinical practice.

We studied how convection volume tended to change over time in **Chapter 11**. In prevalent dialysis patients convection volume seems to increase over time. This increase is mainly related to increase in substitution fluid over time, but not intradialytic weight change. While age, gender and medical history did not determine rate of change in convection volume, the dialysis prescription related variables treatment time and blood flow did influence the rate of change. Relevant differences in rate of change were observed between treatment facilities.

A dose-response relation between the magnitude of convection volume and survival seems plausible. Both cross-sectional and longitudinal analyses on the magnitude of convection volume indicate that predominantly dialysis prescription related characteristics are important in determining the magnitude of convection volume. This poses the question whether a high convection volume can be achieved in the majority of HDF patients in daily clinical practice. A feasibility study has started in a limited number of hospitals in the Netherlands to address that issue.

**Where do we go from here in hemodiafiltration?**

From a meta-analysis it seems that treatment with HDF may have a beneficial effect on survival, although several issues are still unclear. (23;24) For instance the question as to whether certain subgroups behave differently during treatment with HDF. As shown in ESHOL, a high Charlson co-morbidity index score at baseline seems an independent predictor for the beneficial effect of HDF on all-cause mortality. (20) Whether other subgroups may especially benefit from high volume HDF may be resolved in a meta-analysis with individual patient data rather than from a meta analyses using published aggregated subgroup data.

Presently, it is unknown what the most efficient way is to achieve high volumes when considering the modifiable factors such as treatment time, blood flow rate and filtration fraction (ratio ultrafiltration volume and blood flow rate). In addition, it is unclear whether specific characteristics of the dialyzer, such as membrane surface area and the capillary inner diameter, or type of vascular access affect the magnitude of convection volume. (22) Several studies are on-going, including the earlier mentioned Dutch feasibility study to address these issues.

In the ESHOL study it was mentioned that the dialysis staff was specifically trained to achieve high convection volumes.(25) It is tempting to speculate that this increases the likelihood that high convection volumes are not only prescribed but also achieved in clinical practice. Currently, a feasibility study on this very subject is being conducted in the Netherlands. If high convection volumes indeed are achievable in the majority of patients, a new RCT comparing high-volume HDF to standard treatment will provide answers to whether HDF is indeed superior to HD in terms of (cardiovascular) morbidity and mortality.

Since all of the RCTs studying mortality in HDF versus HD were performed in prevalent dialysis patients with varying vintage, we cannot predict the effect of HDF in incident patients. An overlapping and leading effect of a previous dialysis modality could influence the clinical outcome.

It seems logical that HDF treatment would have to be administered for a certain period of time, before a beneficial effect on clinical outcome occurs. In ESHOL a 5% difference in

mortality risk between HDF and HD was seen after approximately 18 months of treatment. (20) However it is not known how long a patient should be treated with HDF before mortality risk decreases substantially.

The RCTs comparing HDF to HD in terms of mortality and cardiovascular events were generally based on dialysis regimes that applied treatment three times per week. The role of HDF in more intensified dialysis programs, such as daily and nocturnal dialysis, is as of yet unclear. Future studies or analyses on existing data are needed to clarify this issue.

Lastly, at present it is unknown why the outcome of dialysis patients is improved by high volume HDF. Concerning the mechanisms behind this treatment modality, both superior removal of uremic toxins and better hemodynamic stability, with fewer episodes of hypotension and consequently less cardiac stunning and gut ischemia, may play an important role.(26-28) Notably, none of the large randomized trials reported a relation between change in beta2-microglobulin levels (a well-established marker of middle molecular weight substance clearance) and outcome. (19-21)

As the present analyses include only studies that enrolled adults who require long term dialysis, our study does not provide evidence for children. In this category of patients HDF may reverse the delay in growth, which is commonly observed during treatment with HD. (29) Yet, this calls for an international registry to be set up with uniform data collection and follow-up, joined with aggregated statistical analysis on various important clinical outcomes in this patient group.

### **Summary**

Cardiovascular damage is an important contributor to morbidity and mortality in dialysis patients. Structural and functional cardiovascular parameters in dialysis patients are abnormal and related to the high morbidity and mortality. In this thesis we did not find determinants of these cardiovascular markers that could easily be modified in daily clinical practice (nor in terms of treatment guidelines nor in terms of dialysis modality). Thus future research should focus on prevention of reaching these abnormal values of

cardiovascular surrogate markers in earlier stages of CKD. Another option would be to explore the effect of more intensified dialysis programs on these markers. (16)

A meta-analysis of three large RCTs shows that HDF patients seem to have a lower overall and cardiovascular mortality as compared to HD. A high convection volume is related to a lower mortality risk. In this thesis we show that treatment related dialysis characteristics and hospital specific aspects are more important in determining the magnitude of convection volume than intrinsic patient characteristics. Future studies should focus on whether it is feasible to achieve higher volumes in the majority of patients, and, if this is indeed the case, whether high prescribed convection volumes indeed lead to a better survival.

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## Summary



**Chapter 1.1: General introduction and thesis outline.**

End stage kidney disease (ESKD) is pathophysiologically characterized by severe irreversible kidney damage and clinically by an almost completely absent glomerular filtration rate. In the Netherlands, approximately 0.1% of the population suffers from ESKD. The morbidity and mortality in this patient group is extremely high, cardiovascular disease accounting for a substantial part of fatal and non-fatal events. The presence of cardiovascular disease risk can be estimated indirectly by markers of cardiovascular damage, including systolic blood pressure, left ventricular cardiac mass, left ventricular ejection fraction and pulse wave velocity. Currently, it is largely unknown how these cardiovascular structural and functional parameters change over time in the ESKD population, and how this rate of change could be modified. Therefore, the first aim of this thesis is to study the relation between structural and functional cardiovascular markers and mortality / cardiovascular events in ESKD patients.

The best treatment option for ESKD patients is a kidney transplantation. However, due to shortage of organ donors and the fact that not all ESKD patients are eligible for transplantation, a considerable proportion of the ESKD population (40%) is treated by dialysis. During standard chronic intermittent hemodialysis (HD), small uremic toxins are removed by diffusion, while larger solutes are retained within the body. In hemodiafiltration (HDF) diffusion is combined with convection, enabling the removal of middle- and large molecules up to 40kDa. As retention of middle and large uremic toxins has been related to the adverse clinical outcome in patients with ESKD, it has been suggested that removal of these substances by HDF may improve its prognosis, and in particular have a beneficial effect on structural and functional markers of cardiovascular risk. Thus, the second aim of this thesis is to study determinants of change (including dialysis modality) in structural and functional cardiovascular markers of risk in ESKD patients.

Recently, the results of three large randomized controlled trials, assessing the effect of HDF as compared to HD on fatal and non-fatal cardiovascular disease and all-cause mortality, were published. Two trials showed no significant difference in all-cause mortality or cardiovascular events between HDF and HD, while the third trial with the

highest achieved convection volumes reported superiority of HDF over HD with respect to all-cause mortality, as well as cardiovascular mortality. Sub-group analyses in all three studies consistently showed a relation between a high achieved convection volume and a lower mortality risk. Hence it appears that delivered convection volume in HDF is of much importance. The final part of the present thesis aims at assessing what determines convection volume and how convection volume changes over time.

### **Chapter 1.2: What have we learned from CONTRAST?**

Data from the CONvective TRANsport STudy (CONTRAST) was used to address the research aims stated in chapter 1.1. CONTRAST is a randomized controlled trial comparing mortality and cardiovascular events between HDF and HD in 714 dialysis patients from 29 dialysis centers in the Netherlands, Canada and Norway. This chapter summarizes and discusses currently available knowledge acquired by CONTRAST; including the main outcome, comparisons of HDF to HD as well as studies performed in subgroups of CONTRAST.

### **Chapter 2: Left ventricular mass in dialysis patients, determinants and relation with outcome.**

Left ventricular mass (LVM) is known to be related to overall and cardiovascular mortality in ESKD patients. The aims of this chapter were 1) to determine whether LVM is associated with mortality and various cardiovascular events and 2) to identify determinants of LVM including biomarkers of inflammation and fibrosis. To assess this, data from 327 ESKD patients, a subset of CONTRAST, was analysed. Echocardiography was performed at baseline. The risk of all-cause mortality, cardiovascular death and sudden death was increased in patients in the highest tertile (>260grams) of LVM. Regarding determinants of LVM, positive relations were found for male gender, residual renal function, phosphate binder therapy, and an inverse relation for a previous kidney transplantation and albumin. The biomarkers interleukin-6, high-sensitivity C-reactive protein, hepcidin-25 and connective tissue growth factor were not related to LVM.

**Chapter 3: Effects of hemodiafiltration on change in cardiovascular parameters over time, results from a randomized trial.**

Increased LVM, low ventricular ejection fraction (EF) and high pulse wave velocity (PWV) relate to overall and cardiovascular mortality in end stage kidney disease (ESKD) patients. The aim of this chapter was to determine the effect of HDF versus HD on LVM, EF and PWV. For this purpose echocardiography was performed to assess LVM and EF in 342 patients of CONTRAST followed up to 4 years, while PWV was measured in 189 patients up to 3 years. Treatment with HDF did not affect changes in LVM, EF or PWV over time, as compared to HD. However, non-significant trends were observed for 1) an increase of LVM in HD, while LVM in HDF remained stable and 2) a decrease of EF in HD, while EF in HDF remained stable. No differences in rate of change of cardiovascular parameters were observed between treatment groups for subgroups of age, gender, residual kidney function, dialysis vintage, history of cardiovascular disease, diabetes or convection volume.

**Chapter 4: Left ventricular mass, ejection fraction and pulse wave velocity over time in end stage kidney disease patients.**

In this chapter we further explored LVM, EF and PWV in the ESKD population. Our aim was to identify determinants of rate of change of LVM, EF and PWV over time in this population. For this analysis data of two subgroups of CONTRAST was used: 342 patients who underwent echocardiography and 189 who had PWV measurements. LVM and PWV remained stable within a three year interval, while EF decreased (borderline significantly) over time. None of the baseline factors: age, gender, residual renal function, dialysis vintage, history of cardiovascular disease, diabetes, blood pressure, ultrafiltration volume, phosphate levels or phosphate binder use were related to rate of change of LVM, EF or PWV. Apparently, traditional risk factors do not explain differences in rate of change of these parameters.

**Chapter 5: Blood pressure in dialysis patients, relation with mortality and cardiovascular events.**

Reports on the relation between blood pressure (BP) and clinical events in patients with ESKD are contradictory. The aim of this chapter was to determine what relation exists between different measures of BP and all-cause mortality, cardiovascular mortality and (both fatal and non-fatal) cardiovascular events in this population. Data from all 714 patients of CONTRAST was used for this analysis. At baseline, BP was measured three times pre-, and three times post-dialysis. The means of these pre- and post-dialysis measurements were computed, as well as the mean of all six blood pressure measurements. Diastolic BP (DBP) was more strongly related to mortality risk than systolic BP (SBP) and pulse pressure (PP) in ESKD patients. Averaged BP measurements provided the strongest relations as compared to pre- or post-dialysis measurements only.

**Chapter 6: Blood pressure and antihypertensive use over time in end stage kidney disease patients.**

An elevated BP represents an important burden of morbidity and mortality in ESKD patients. The aim of this chapter was to assess changes over time in BP in ESKD patients and evaluate the impact of age, sex, medical history, antihypertensive use and dialysis-treatment related characteristics on these changes. Data from all 714 patients of CONTRAST was used for this analysis. Blood pressure was measured as described previously in chapter 5. SBP, DBP, mean arterial pressure (MAP) and PP all declined over time. Age, gender, body mass index (BMI), a history of CVD and dialysis vintage were found important determinants of rate of decline of BP. Males and older patients (>67 years) experienced a greater decline in SBP and PP, when compared to females and patients <67 respectively. A dialysis vintage >2 years was related to a higher rate of decline in SBP and DBP, when compared to patients with a vintage < 2 years. Patients with a history of cardiovascular disease experienced a greater decline in DBP. Patients with a BMI >25kg/m<sup>2</sup> had a smaller decline in SBP and PP over time than those with a lower BMI.

**Chapter 7: Peripheral resistance, cardiac output and blood pressure over time in end stage kidney disease.**

Peripheral resistance (PR) is a marker of sympathetic activity. In ESKD patients, data on PR changes over time are scarce. The aim of this chapter was to examine changes over time in PR, cardiac output (CO), MAP, SBP and DBP. Analysis was performed with data from 84 patients of CONTRAST who received echocardiography and simultaneous BP measurements on a non-dialysis day at baseline, and annually thereafter. PR was computed as MAP/CO. MAP decreased over time, mainly due to a decrease in DBP. This decline of MAP could be explained by a decrease in PR over time, but not a change in CO.

**Chapter 8: Clinical evidence on hemodiafiltration: a systematic review and meta-analysis.**

In this chapter, a systematic literature search and meta-analysis were performed to assess the effects of HDF on clinical outcome, if compared to HD. Furthermore, the relation between the convection volume in HDF and clinical outcome was studied. The literature search identified six randomized controlled trials (RCTs). In a meta-analysis of these RCTs, HDF treatment was related to a decreased risk of mortality and cardiovascular death. *Post hoc* analyses of the three largest RCTs suggested an inverse relation between the magnitude of convection volume and mortality risk. The evidence presented in this analysis supported a wider acceptance of HDF.

**Chapter 9: Treatment policy rather than patient characteristics determines convection volume in online post-dilution hemodiafiltration.**

Sub-analyses of three RCTs showed that HDF patients who achieved the highest convection volumes had the lowest mortality risk. The aims of this chapter were (1) to identify determinants of convection volume and (2) to assess whether differences exist between patients achieving high and low volumes. Analysis was performed with data from 314 HDF patients from CONTRAST who completed 6 months of follow-up were included for analysis. Treatment time, blood flow rate (both major determinants) as well as dialysis vintage, serum albumin and hematocrit were independently related to convection

volume. Neither vascular access nor dialyzer characteristics showed any relation with convection volume. Except for some variation in body size, patient characteristics did not differ across tertiles of convection volume. These findings indicate that the magnitude of convection volume depends on center policy rather than individualized patient prescription.

**Chapter 10: How to arrive at higher convection volumes? Clinical evidence in online post-dilution hemodiafiltration.**

HDF is advocated as a superior renal replacement therapy for patients with ESKD. Convection volume is currently considered the best and easiest quantifier of HDF efficiency. *Post hoc* analyses of observational studies and RCTs suggest that the risk on mortality and clinical events is significantly lower in HDF patients who are treated with high convection volumes. In this chapter we reviewed the available clinical evidence and overall expert opinion on how convection volumes can be increased in patients undergoing online post-dilution HDF.

**Chapter 11: Change in convection volume over time in online post-dilution hemodiafiltration patients.**

Recent RCTs showed a relation between a high convection volume and a low mortality risk in *post hoc* subgroup analyses. It unclear whether an individual patient convection volume remains stable over time. The aim of this chapter was to examine the rate of change of convection volume in patients undergoing online post-dilution HDF. For this purpose data from 339 HDF patients from CONTRAST was analyzed. Convection volume was measured every 3 months up to 6 years. Achieved convection volume tended to increase over time. Patient characteristics were not related to rate of change. However, large differences in rate of change existed between dialysis centers. This supported the hypothesis that mainly treatment characteristics determine the volume of convection.

**Chapter 12: Discussion**

Cardiovascular damage is an important contributor to morbidity and mortality in ESKD patients. Structural and functional cardiovascular parameters in ESKD patients are abnormal and related to the high morbidity and mortality. In this thesis we did not find determinants of these cardiovascular markers that could easily be modified in daily clinical practice (nor in terms of treatment guidelines nor in terms of dialysis modality). Thus future research should focus on prevention of reaching these abnormal values of cardiovascular surrogate markers in earlier stages of chronic kidney disease. Another option would be to explore the effect of more intensified dialysis programs on these markers.

A meta-analysis of three large RCTs shows that HDF patients seem to have a lower overall and cardiovascular mortality as compared to HD. A high convection volume is related to a lower mortality risk. In this thesis we show that treatment related dialysis characteristics and hospital specific aspects are more important in determining the magnitude of convection volume than intrinsic patient characteristics. Future studies should focus on whether it is feasible to achieve higher volumes in the majority of patients, and, if this is indeed the case, whether high prescribed convection volumes indeed lead to a better survival.





## Samenvatting



**Hoofdstuk 1.1: Algemene samenvatting en overzicht van het proefschrift.**

Eindstadium nierfalen (ESNF) wordt gekenmerkt door ernstige en onomkeerbare nierschade en klinisch door een bijna volledig afwezige glomerulaire filtratie snelheid. In Nederland lijdt ongeveer 0.1% van de bevolking aan ESNF. De mortaliteit en morbiditeit zijn erg hoog in deze patiëntgroep, waarbij cardiovasculaire aandoeningen hier aanzienlijk aan bijdragen. De aanwezigheid van risico op cardiovasculaire ziekten kan geschat worden door te kijken naar zogenaamde markers van cardiovasculaire schade, zoals systolisch bloeddruk, massa van de linker kamer van het hart, ejectie fractie van de linker kamer en polsgolfsnelheid. Momenteel is het grotendeels onbekend hoe deze structurele en functionele cardiovasculaire parameters veranderen over tijd bij ESNF patiënten, en of deze snelheid van verandering zou kunnen worden gewijzigd. Daarom is het eerste doel van dit proefschrift om de relatie te bestuderen tussen structurele en functionele cardiovasculaire markers en het risico op sterfte / cardiovasculaire ziekten bij ESNF patiënten.

De beste behandeling voor ESNF is een niertransplantatie. Echter, omdat er een tekort is aan donor nieren en niet alle ESNF patiënten in aanmerking komen voor een transplantatie, wordt een aanzienlijk deel van de ESNF populatie behandeld met dialyse. Tijdens de standaard vorm van chronische intermitterende hemodialyse (HD) worden kleine uremische toxines middels diffusie uit het bloed verwijderd, terwijl de afvalstoffen met de grotere moleculen achterblijven in het lichaam. Bij hemodiafiltratie (HDF) wordt de diffusie gecombineerd met convectie, zodat ook de middelgrote en grote moleculen met een gewicht tot 40 kiloDalton worden verwijderd. Gezien de retentie van middelgrote en grote uremische toxines gerelateerd is aan een ongunstige klinische uitkomst in ESNF patiënten, heeft men in het verleden gesuggereerd dat het verwijderen van deze stoffen middels HDF zou kunnen leiden tot een betere prognose en, in het bijzonder, een gunstig effect zou hebben op structurele en functionele markers van het cardiovasculaire risico. Derhalve is het tweede doel van dit proefschrift om determinanten van verandering (inclusief dialyse modaliteit) van structurele en functionele cardiovasculaire parameters te bestuderen bij ESNF patiënten.

Recentelijk zijn de resultaten gepubliceerd van drie grote gerandomiseerde gecontroleerde studies, die allen het effect van HDF in vergelijking met HD hebben bestudeerd op het voorkomen van fatale en niet fatale cardiovasculaire ziekten en totale sterfte. Twee van deze studies hebben geen significant verschil gevonden in sterfte en voorkomen van cardiovasculaire ziekten tussen HDF en HD, terwijl de derde studie, tevens de studie waarbij de hoogste convectie volume is bereikt, een betere overleving en minder cardiovasculaire ziekten heeft gerapporteerd in de HDF groep. Subgroep analyses in alle drie de studies toonden een relatie tussen een hoge bereikte convectie volume en een verlaagde kans op sterfte. Het lijkt daarom dat de hoeveelheid convectie volume tijdens HDF een belangrijke eigenschap van de behandeling is. Het laatste deel van dit proefschrift is gericht op het beoordelen wat de convectie volume bepaalt en hoe convectie volume verandert over tijd.

### **Hoofdstuk 1.2: Wat hebben wij geleerd van CONTRAST?**

Om de onderzoeksvragen die beschreven zijn in hoofdstuk 1.1 te kunnen beantwoorden werden gegevens gebruikt van de CONvective TRANsport STudy (CONTRAST). CONTRAST is een gerandomiseerde gecontroleerde trial die algemene sterfte en het voorkomen van cardiovasculaire ziekten heeft vergeleken bij HDF versus HD. Aan de studie deden 714 dialysepatiënten in 29 dialyse centra uit Nederland, Canada en Noorwegen. In dit hoofdstuk wordt de op dit moment beschikbare kennis die dankzij CONTRAST is verworven samengevat en besproken, inclusief de primaire uitkomsten, vergelijkingen tussen HDF en HD en tevens onderzoeken in subpopulaties van CONTRAST.

### **Hoofdstuk 2: Linker ventrikel massa bij dialyse patiënten, determinanten en relatie met de prognose.**

Linker ventrikel massa (LVM) is gerelateerd aan algemene en cardiovasculaire sterfte in ESNF patiënten. De doelen van dit hoofdstuk waren om 1) vast te stellen of LVM geassocieerd is met sterfte en verschillende vormen van cardiovasculaire ziekten en 2) om determinanten van LVM te identificeren, inclusief biomarkers van ontsteking en fibrose.

Om dit vast te stellen werden gegevens van 327 ESNF patiënten, een subgroep van CONTRAST, geanalyseerd. Bij aanvang van de studie werd er een echo van het hart verricht. Het risico op sterfte door alle oorzaken, cardiovasculaire sterfte en plotselinge hartdood was verhoogd bij patiënten in het hoogste tertiel van LVM (>260 gram). Wat betreft de determinanten van LVM, er is een positieve relatie gevonden tussen LVM en mannelijk geslacht, restnierfunctie, behandeling met fosfaatbinders, en een inverse relatie met een eerdere niertransplantatie en albumine. De biomarkers interleukine-6, high-sensitivity C-reactive protein, hepcidine-25 en connective tissue growth factor waren niet gerelateerd aan LVM.

### **Hoofdstuk 3: Effecten van hemodiafiltratie op verandering in cardiovasculaire parameters over tijd, de resultaten van een gerandomiseerde studie.**

Een toegenomen LVM, een lage linker kamer ejectie fractie (EF) en een hoge polsgolfsnelheid (PWV) zijn gerelateerd aan totale en cardiovasculaire sterfte bij ESNF patiënten. Het doel van dit hoofdstuk was om het effect van HDF versus HD te bepalen op LVM, EF en PWV. Hiervoor werd een echo van het hart verricht bij 342 patiënten om LVM en EF te bepalen, deze mensen werden gedurende 4 jaar gevolgd. PWV werd gemeten in 189 patiënten gedurende 3 jaar. Behandeling met HDF heeft geen significant effect op verandering in LVM, EF en PWV over tijd gehad ten opzichte van HD. Er werden wel niet-significante trends gezien voor 1) een toename van LVM in HD, terwijl LVM in HDF stabiel bleef en 2) een afname van EF in HD, terwijl EF in HDF stabiel bleef. Er werd geen verschil in verandering van de cardiovasculaire parameters geobserveerd tussen de behandelgroepen voor subgroepen van leeftijd, geslacht, restnierfunctie, duur dialysebehandeling, voorgeschiedenis van hart- en vaatziekten, diabetes of convectie volume.

### **Hoofdstuk 4: Linker ventrikel massa, ejectie fractie en polsdruksnelheid over tijd in patiënten met eindstadium nierfalen.**

In dit hoofdstuk werden LVM, EF en PWV bij ESNF patiënten verder bestudeerd. Het onderzoeksdoel was om determinanten van verandering van LVM, EF en PWV over tijd in

deze populatie te identificeren. Voor deze analyse werden gegevens gebruikt van twee subgroepen van CONTRAST: 342 patiënten die een echo van het hart hadden ondergaan en 189 patiënten die een PWV meting hadden gehad. LVM en PWV bleven gedurende drie jaar stabiel, terwijl EF afnam (doch net niet significant) over tijd. Er werd geen relatie gevonden tussen de mate van verandering van LVM, EF en PWV en de patiënt eigenschappen: leeftijd, geslacht, restnierfunctie, duur dialyse behandeling, voorgeschiedenis van hart- en vaatziekten, diabetes, bloeddruk, ultrafiltratie volume, serum fosfaat en gebruik van fosfaat binders. Blijkbaar verklaren de traditionele risicofactoren niet hoe deze cardiovasculaire parameters veranderen over tijd.

#### **Hoofdstuk 5: Bloeddruk in dialyse patiënten, relatie met sterfte en cardiovasculaire ziekten.**

De op dit moment beschikbare gegevens over de relatie tussen bloeddruk (BD) en klinische events bij ESNF patiënten zijn tegenstrijdig. Het doel van dit hoofdstuk is om te bepalen wat voor een relatie er bestaat tussen verschillende soorten en metingen van BD en totale sterfte, cardiovasculaire sterfte en (zowel fatale als niet-fatale) cardiovasculaire events in deze populatie. Voor deze analyse werden gegevens van alle 714 patiënten van CONTRAST gebruikt. Bij aanvang van de studie werd de BD driemaal voor en driemaal na dialyse gemeten. Het gemiddelde van de drie voor en de drie na metingen werd berekend, en tevens het gemiddelde van alle zes de metingen. Diastolische BD (DBD) was sterker gerelateerd aan sterfte dan systolische BD (SBD) en polsdruk (PD) in ESNF patiënten. Gemiddelde BD metingen hadden de sterkste relatie met events, vergeleken met enkel de pre- of enkel de post-dialyse metingen.

#### **Hoofdstuk 6: Bloeddruk en gebruik van antihypertensiva over tijd in patiënten met eindstadium nierfalen**

Een verhoogde BD levert een belangrijke bijdrage aan morbiditeit en mortaliteit bij ESNF patiënten. Het doel van dit hoofdstuk was om veranderingen in BD over tijd te bestuderen in ESNF patiënten en de invloed van leeftijd, geslacht, voorgeschiedenis, gebruik van antihypertensiva en dialyse-behandeling gerelateerde kenmerken op deze verandering te

onderzoeken. Hiervoor werden de gegevens van alle 714 CONTRAST deelnemer gebruikt. De BD werd gemeten zoals eerder omschreven in hoofdstuk 5. SBD, DBD en PD namen allen af over tijd. Leeftijd, geslacht, body mass index (BMI), een voorgeschiedenis van hart- en vaatziekten en duur van dialyse behandeling waren belangrijke determinanten van de snelheid waarmee de BD afnam. Mannen en oudere (>67 jaar) patiënten hadden een grotere afname in SBD en PD, in vergelijking met vrouwen en jongere (<67 jaar) patiënten. Wanneer men >2 jaar werd behandeld met dialyse, was de afname van SBD en DBD hoger dan bij patiënten die korter werden behandeld. Patiënten met een voorgeschiedenis van hart- en vaatziekten hadden een grotere afname in DBD. Patiënten met een BMI >25kg/m<sup>2</sup> hadden een kleinere afname in SBD en PD over tijd dan degenen met een lagere BMI.

#### **Hoofdstuk 7: Perifere weerstand, hartminuutvolume en bloeddruk veranderingen over tijd in eindstadium nierfalen.**

Perifere weerstand (PW) is een marker van sympathische activiteit. Bij ESNF patiënten zijn gegevens over veranderingen van PW over tijd schaars. Het doel van dit hoofdstuk is om veranderingen over tijd in PW, hartminuutvolume (HMV), gemiddelde arteriële BD (GABD), SBD en DBD te bestuderen in ESNF patiënten. Hiervoor werden gegevens van 84 CONTRAST patiënten geanalyseerd, bij wie er een echo van het hart en een gelijktijdige BD meting werd verricht bij aanvang van de studie en daarna jaarlijks. PW werd berekend als GABD / HMV. GABD nam af over tijd, voornamelijk door een afname in DBD. De afname in GABD kon worden verklaard voor een afname in PW over tijd, er was echter geen verandering in HMV.

#### **Hoofdstuk 8: Klinische gegevens over hemodiafiltratie: een systematische review en meta-analyse.**

In dit hoofdstuk werden een systematisch literatuuronderzoek en een meta-analyse uitgevoerd om vast te stellen wat de effecten van HDF waren op de klinische uitkomst, in vergelijking met HD. Tevens werd de relatie tussen convectie volume in HDF en klinische uitkomst bestudeerd. Bij het literatuuronderzoek werden zes gerandomiseerde klinische trials geïdentificeerd. Een meta-analyse van deze trials liet zien dat HDF behandeling

gerelateerd was aan een verlaagde risico op totale en cardiovasculaire sterfte. *Post hoc* analyses van de drie grootste trials suggereren een inverse relatie tussen de mate van convectie volume en risico op sterfte. Het bewijs geleverd door deze analyse ondersteunt een wijdere acceptatie van HDF.

### **Hoofdstuk 9: Het behandelbeleid, en niet de patiënteigenschappen bepalen de convectie volume in online post-dilutie hemodiafiltratie.**

Sub-analyses van drie gerandomiseerde gecontroleerde trials lieten zien dat HDF patiënten die de hoogste convectie volumes bereikten de laagste risico's op sterfte hadden. De doelen van dit hoofdstuk waren 1) om determinanten van convectie volume te identificeren en 2) om vast te stellen of er verschillen bestaan tussen patiënten die lage en hoge volumes behalen. Hiervoor werden gegevens geanalyseerd van 314 HDF patiënten van CONTRAST, die minstens 6 maanden werden gevolgd tijdens de studie. Duur van een dialysebehandeling, stroomsnelheid van het bloed door de vaattoegang (allebei belangrijke determinanten) en albumine, hematocriet en hoe lang iemand al met dialyse werd behandeld waren onafhankelijk gerelateerd aan convectie volume. Noch type vaattoegang noch eigenschappen van de kunstnier waren gerelateerd aan convectie volume. Met uitzondering van variatie in lichaamsgrootte, waren er geen verschillen in patiënt eigenschappen tussen de tertielen van convectie volume. Deze bevindingen indiceren dat de grootte van de convectie volume voornamelijk afhankelijk is van een behandelbeleid in een dialysecentrum en niet zozeer individuele patiënt voorschriften.

### **Hoofdstuk 10: Hoe kunnen hogere convectie volumes worden bereikt? Klinische gegevens over online post-dilutie hemodiafiltratie.**

HDF wordt bepleit als een superieure behandeling voor ESNF patiënten. Convectie volume wordt beschouwd als de beste en makkelijkste manier om HDF efficiëntie te kwantificeren. *Post hoc* analyses van observationele studies en gerandomiseerde gecontroleerde trials suggereren dat het risico op sterfte en klinische events significant lager is in HDF patiënten die met hogere convectie volumes worden behandeld. In dit hoofdstuk werden het beschikbare klinische bewijsmateriaal en de algemene opvattingen

van experts besproken over hoe convectie volume zou kunnen worden verhoogd in patiënten die online post-dilutie HDF ondergaan.

### **Hoofdstuk 11: Veranderingen in convectie volume over tijd bij online post-dilutie hemodiafiltratie patiënten.**

Recent gepubliceerde gerandomiseerde gecontroleerde trials hebben een relatie tussen een hoge convectie volume en een lage risico op sterfte aangetoond in subgroep analyses. Het is niet duidelijk of de convectie volume van individuele patiënten stabiel blijft over tijd. Het doel van dit hoofdstuk was om de mate van verandering van convectie volume over tijd te bestuderen in patiënten die online post-dilutie HDF ondergaan. Hiervoor werden gegevens van 339 HDF patiënten van CONTRAST geanalyseerd. De convectie volume werd gedurende 6 jaar elke 3 maanden gemeten. De bereikte convectie volume nam toe gedurende de tijd. Patiënteigenschappen waren niet gerelateerd aan de mate van verandering. Er waren echter grote verschillen tussen de dialyse centra. Dit ondersteunt de hypothese dat voornamelijk behandel eigenschappen de convectie volume bepalen.

### **Hoofdstuk 12: Discussie.**

Cardiovasculaire schade levert een belangrijke bijdrage aan de morbiditeit en mortaliteit van ESNF patiënten. De structurele en functionele cardiovasculaire parameters van ESNF patiënten zijn afwijkend en gerelateerd aan de hoge morbiditeit en mortaliteit. In dit proefschrift werden er geen determinanten van deze cardiovasculaire markers geïdentificeerd, die makkelijk in de klinische praktijk veranderd zouden kunnen worden (noch wat betreft de behandel richtlijnen, noch de dialyse modaliteit). Derhalve zou toekomstig onderzoek zich moeten richten op het voorkomen van het bereiken van deze abnormale waarden van cardiovasculaire markers in eerdere stadia van het chronisch nierfalen. Een andere mogelijkheid zou zijn om het effect van meer intensieve dialyse behandel soorten op deze markers te onderzoeken.

Een meta-analyse van drie gerandomiseerde gecontroleerde trials heeft aangetoond dat HDF patiënten een lagere totale en cardiovasculaire sterfte hebben dan HD patiënten. Een

hoge convectie volume hangt samen met een lagere risico op sterfte. In dit proefschrift hebben wij laten zien dat de karakteristieken van de dialyse behandeling en ziekenhuis-specifieke eigenschappen belangrijker zijn voor het bepalen van convectie volume dan intrinsieke patiënteigenschappen. Toekomstige studies zouden dienen te onderzoeken of het haalbaar is om hogere convectie volumes te behalen bij het merendeel van de patiënten. En, indien dit inderdaad het geval is, of hoge voorgeschreven convectie volumes inderdaad leiden tot een betere overleving.



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SDF 34567

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159.77

227.76

100.34

45.32

106.7

61.34

114.691

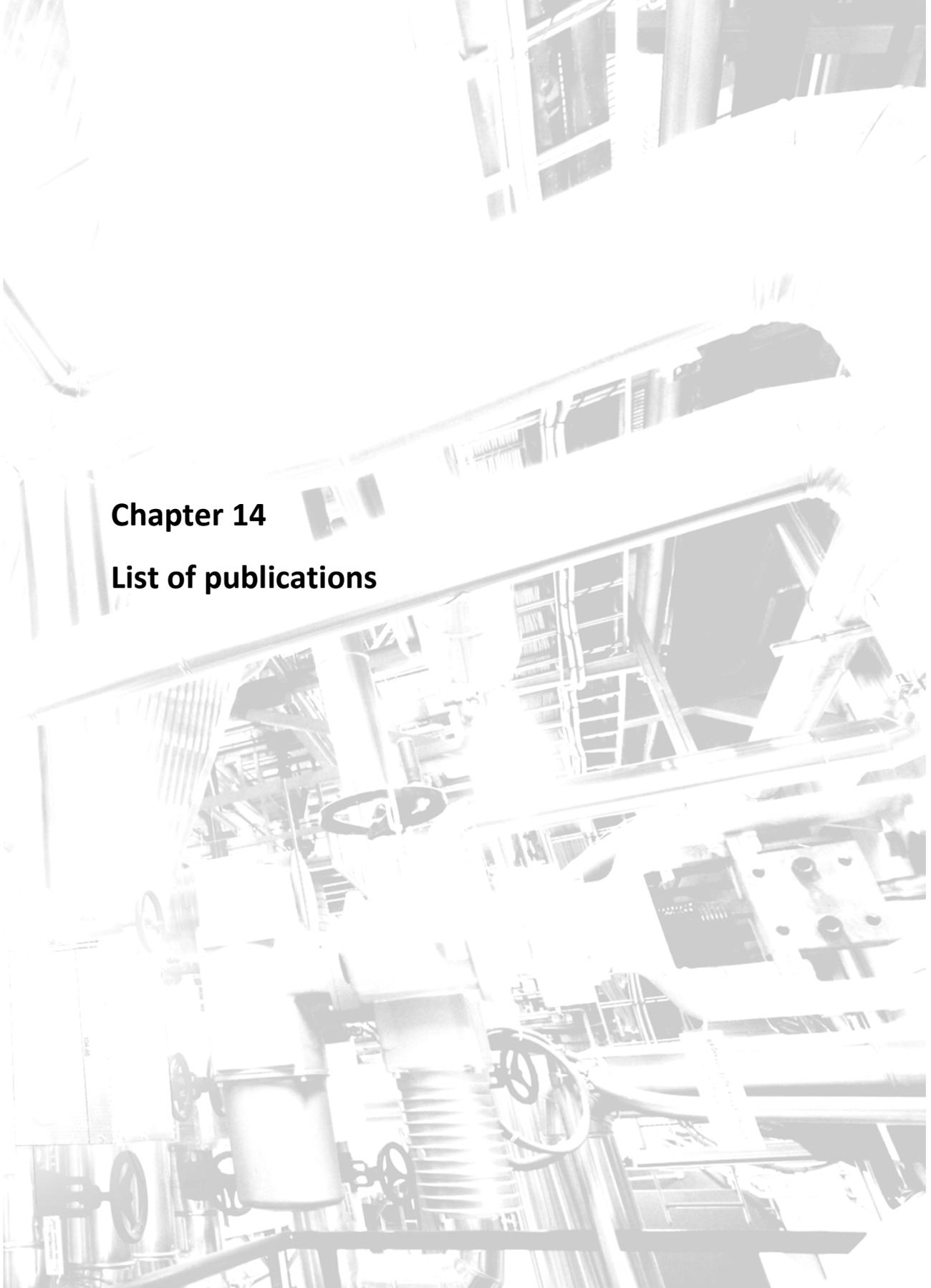
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114

75

## **Chapter 14**

### **List of publications**





**List of publications related to this thesis**

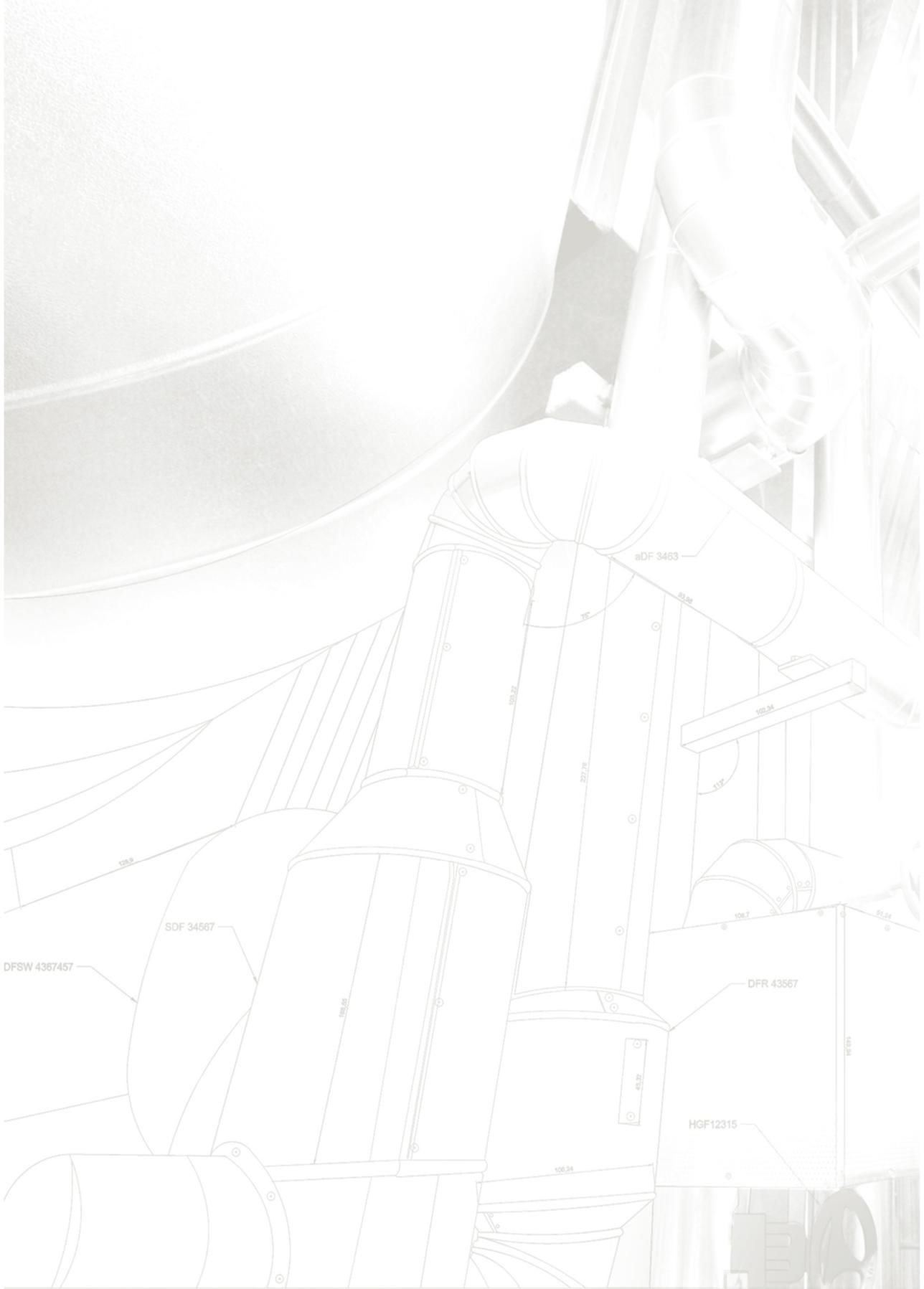
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Mostovaya, I. M., Blankestijn, P. J., Bots, M. L., Covic, A., Davenport, A., Grooteman, M. P.C., Hegbrant, J., Locatelli, F., Vanholder, R., Nubé, M. J. (2014), Clinical Evidence on Hemodiafiltration: A Systematic Review and a Meta-analysis. *Seminars in Dialysis*, 27: 119–127

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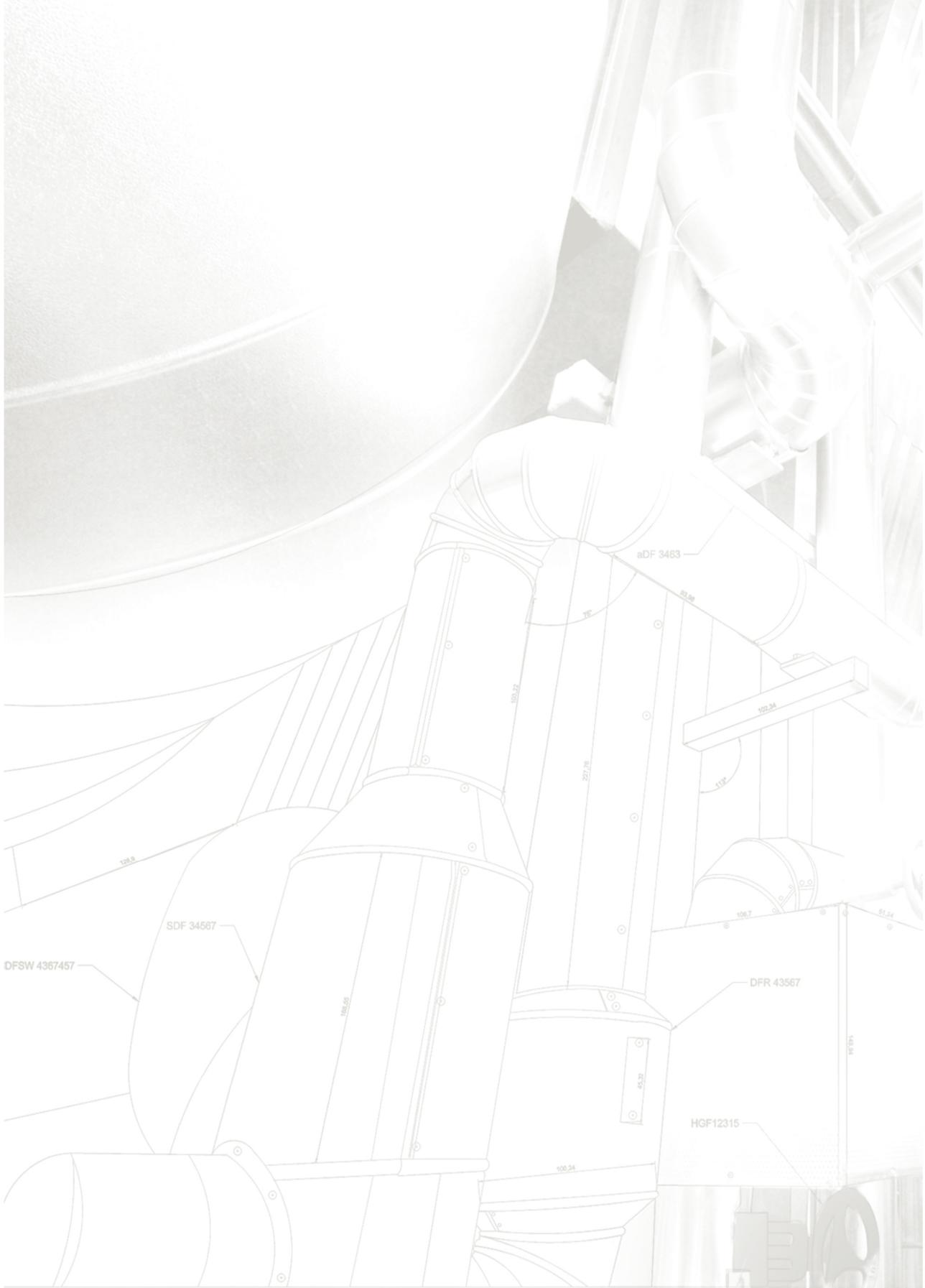
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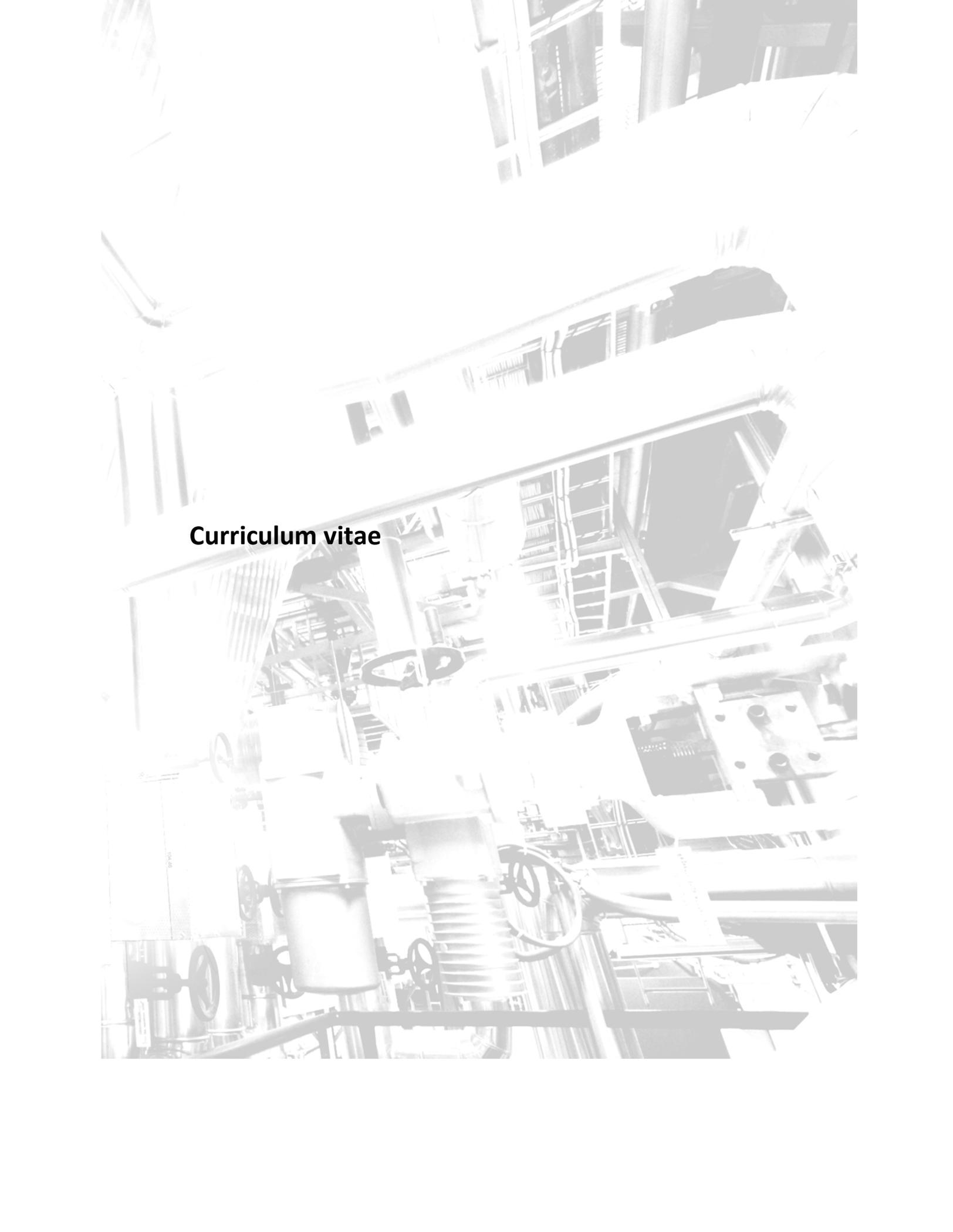
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**Curriculum vitae**



Irina Maximovan Mostovaya was born on August 5<sup>th</sup> 1985 in Kemerovo, Russia. At the age of 7 she emigrated to Groningen, the Netherlands together with her parents and brother. After graduating secondary school at the Willem Lodewijk Gymnasium in Groningen, she started her medical studies at the University of Groningen in 2003. She obtained her medical degree in 2009 and worked as a Urology resident at the Deventer Ziekenhuis in Deventer. In 2011 she started her PhD research at the department of Nephrology in the University Medical Center Utrecht under supervision of Professor dr. M.L. Bots and dr. P.J. Blankestijn. She also received guidance from other members of the Executive Committee of the CONvective TRANsport Study (CONTRAST). During this research, she followed a Postgraduate Master of Science in Epidemiology at Utrecht University, which she graduated in 2013.