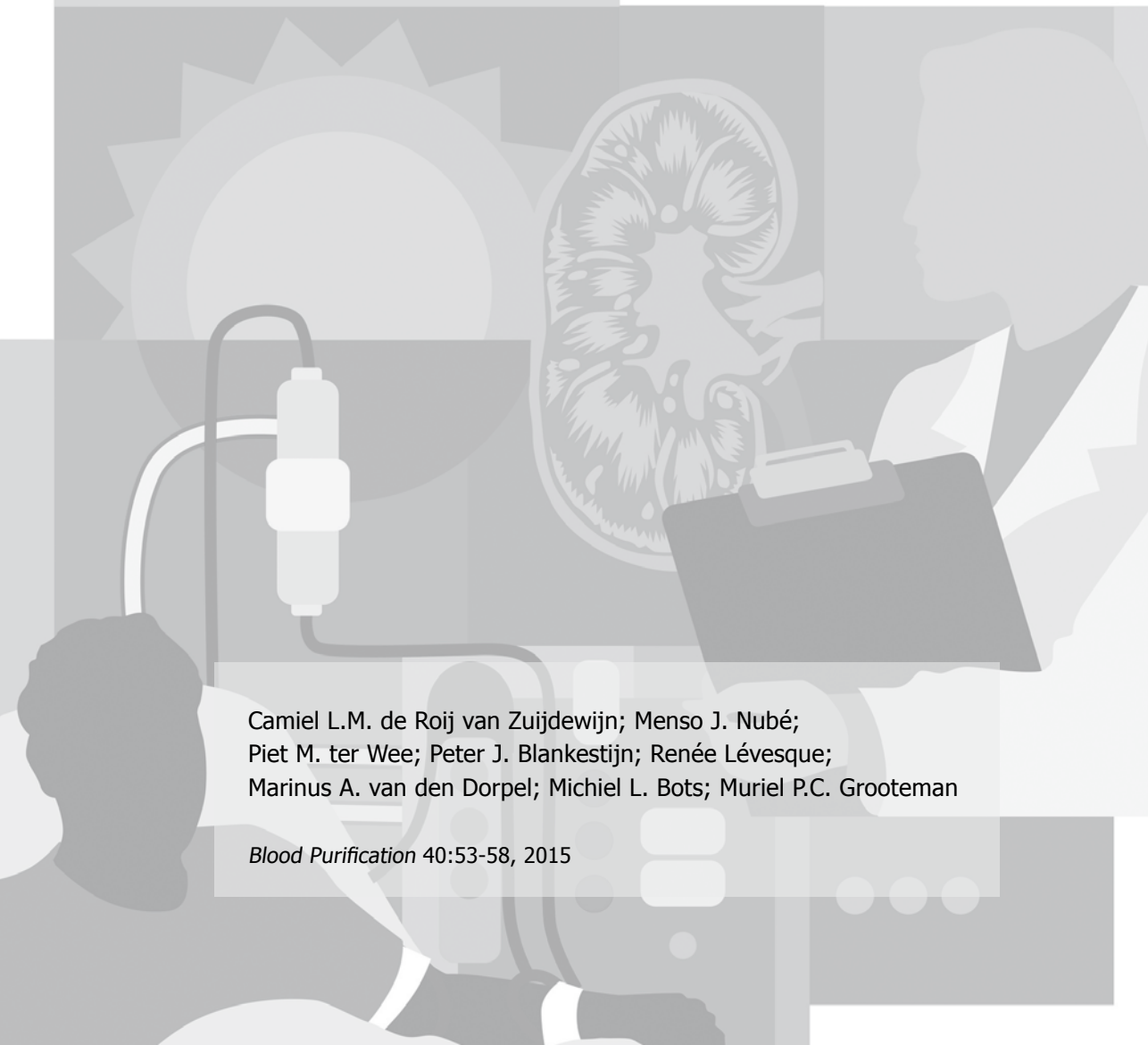
Chapter 4.2

# Treatment time or convection volume in HDF: what drives the reduced mortality risk?



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## ABSTRACT

### Introduction

Treatment time is positively associated with survival in hemodialysis (HD) patients and with convection volume in hemodiafiltration (HDF) patients. High-volume HDF is associated with improved survival. Therefore, we investigated whether this survival benefit is explained by treatment time.

### Methods

Participants were subdivided into four groups: HD and tertiles of convection volume in HDF. Three Cox regression models were fitted to calculate hazard ratios (HRs) for mortality of HDF subgroups versus HD: (1) crude, (2) adjusted for confounders, (3) model 2 plus mean treatment time. As the only difference between the latter models is treatment time, any change in HRs is due to this variable.

### Results

114/700 Analyzed individuals were treated with high0volume HDF. HRs of high-volume HDF are 0.61, 0.62 and 0.64 in the three models, respectively ($p$-values<0.05). Confidence intervals of models 2 and 3 overlap.

### Conclusion

The survival benefit of high-volume HDF over HD is independent of treatment time.

## INTRODUCTION

Despite increasing knowledge of the uremic syndrome and use of contemporary medication, ultrapure water and biocompatible dialyzers, both morbidity and mortality remain extremely high among hemodialysis (HD) patients.[1-3] Therefore, it seems rational that dialysis treatment should be as optimal as possible. The first attempt to define dialysis adequacy was the introduction of $Kt/V_{urea}$ three decades ago.[4] $Kt/V_{urea}$ is a dimensionless value, taking not only the dialyzer clearance of urea (K) into account, but also the treatment time (t) and the volume of urea distribution (V). Although especially older studies indeed showed a positive relationship between $Kt/V_{urea}$ and survival,[5,6] a more recent randomized controlled trial (RCT), comparing two different $Kt/V_{urea}$ values (eKt/V 1.16±0.09 and 1.53±0.09) during HD with either high-flux or low-flux membranes in a two-by-two factorial design, did not.[7] Possibly, the accumulation of substances larger than urea, such as middle-molecular weight (MMW) retention products, play a more fundamental role in the toxicity of the uremic syndrome. Nevertheless, defining dialysis adequacy in terms of toxin removal, treatment time and body size remains appealing. In this respect, it should be noted that meanwhile an independent and positive association between treatment time and survival has been clearly demonstrated.[6,8-13] Currently, it is unknown whether the beneficial effect of treatment time on survival depends on a better clearance of uremic toxins from undisclosed body compartments, a better intra-dialytic hemodynamic stability, both or other reasons.



As retention of MMW substances may play an important role in the toxicity of the uremic syndrome, the treatment modality may also influence outcome. In multiple RCTs, overall clinical outcome did not differ between HD patients treated with either low- or high-flux dialysers.[7,14,15] In post-dilution online hemodiafiltration (ol-HDF) however, convective transport is considerably higher than in high-flux HD.[16] Recently, the results of three large RCTs, comparing ol-HDF with HD, were published.[17-19] The results of these studies and a recent meta-analysis of these studies strongly suggest a survival benefit of ol-HDF over HD when high convection volumes (> 21.95L/session) are achieved.[20] Considering the convection volume, it was recently shown that its magnitude is for the main part determined by treatment-related factors, such as session time and blood flow rate, and only for a minor part by patient-related factors, including hematocrit and albumin.[21,22]

The present analysis studied the question whether the beneficial survival effect of high volume HDF is due to the high convection volumes per se or to longer treatment times.

## METHODS

Data of the CONvective TRAnsport STudy (CONTRAST; NCT00205556) were used, of which the design has been described elsewhere.[17,23] In short, CONTRAST was a randomized controlled trial designed to evaluate the survival effect of post-dilution online HDF compared to low-flux HD. In total, 714 Patients were enrolled in 29 facilities in the Netherlands (n=26), Canada (n=2) and Norway (n=1). Inclusion ran from 2004 to 2010 and patients were followed until death or up to January 2011. Adults (≥18) were eligible if treated with low-flux HD two or three times per week for more than two months. Furthermore, a target spKt/$V_{urea}$ of ≥ 1.2 was required. Exclusion criteria were severe incompliance to dialysis prescription, treatment with HDF or high-flux HD in the six months preceding randomization or a life expectancy of less than three months due to non-renal disease. Written informed consent was obtained from all participants prior to randomization. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by a central medical ethics review board.

### Participants

All participants treated with HD (n=356) and all HDF participants with known mean reached convection volume (n=344) were available for analysis. HD participants functioned as reference group. HDF participants were subdivided into tertiles of mean reached convection volume per dialysis treatment, i.e. low volume HDF (<18.18L/treatment, n=115), middle volume HDF (18.18-21.95L/treatment, n=114) and high volume HDF (≥21.95L/treatment, n=115). Thus, in short, a four-point scaled ordinal variable of convection volume was created.

### Clinical characteristics

Various demographic, clinical and biochemical participant characteristics were collected at baseline. Laboratory values used were drawn prior to dialysis at baseline. For albumin, bromcresol green values were used in the analysis. Albumin values measured with the bromcresol purple method were converted to bromcresol green values using the formula: bromcresol green = bromcresol purple + 5.5 (g/L).[24]

### Treatment time

Treatment time was assessed at baseline and consequently every three months thereafter, up to 75 months after randomization. The mean effective treatment time per dialysis session was calculated for every individual and used in the present analysis.

### Censoring and follow-up

In the CONTRAST study, all participants (n=714) were followed from randomization until death due to any cause or end of the study (intention to treat). In the present analysis, 700 patients were included as data on convection volume was not available in 14 HDF participants. Out of these 700 participants, 224 died. The other participants (476 out of 700) were censored, either at the end of study follow-up (n=255) or at the occurrence of an event that resulted in the discontinuation of the HDF treatment or a loss of information on the convection volume (n=221). Examples of such events are moving to a non-participating center, renal transplantation or a switch to peritoneal dialysis.

### Statistical analysis

Baseline characteristics between HD and high volume HDF were compared using a Student t-test, a Mann-Whitney U test or a $\chi^2$ test, when appropriate. To investigate whether the effect of treatment time on mortality is equal for HD and every tertile of HDF, a crude Cox model with the four-point scaled ordinal variable of convection volume, treatment time and the interaction term between these two variables was fitted. As the interaction terms were non-significant (*p*-values >0.1), the effect of treatment time on mortality was thus equal for HD and all HDF tertiles. Thereafter, hazard ratios (HRs) for mortality were calculated using three Cox proportional hazards models. A two-sided *p*-value ≤0.05 was considered statistically significant. The first model was an unadjusted analysis and estimated the HR for mortality of the different HDF tertiles versus HD patients. In the second model, HRs of the HDF subgroups versus the HD group were adjusted for potential confounders, which were determined upfront by an expert panel. These confounders were age, sex, previous cardiovascular disease, diabetes, previous kidney transplantation, residual kidney function, serum albumin, serum creatinine, hematocrit, center differences, vascular access and the use of α- and ß-blockers, calcium antagonists and RAS inhibitors. All confounders were determined at baseline. Model three estimated HRs of HDF subgroups versus HD as in model two and adjusted for treatment time as well. As the only difference between models two and three is treatment time, any change in HRs between these models results from this variable. A HR for mortality of high volume HDF versus HD in model three below the lower bound or above the upper bound of the 95% CI of the HR for mortality of model two would indicate a difference in survival effect due to treatment time. All statistical analyses were performed using the statistical software package IBM SPSS Statistics 22.0 (SPSS Inc, Chicago, IL, USA).

## RESULTS

### Participant characteristics

In total, 700 participants were available for analysis. As high volume HDF participants (n=115) had a survival benefit over HD participants (n=356), these patients comprise the groups of interest in the present analysis.[17,18] Baseline participant characteristics are shown in table 1.The mean age was 64.0 and 63.3 years, respectively and the majority was male (64.9% and 68.7%, respectively). Of the HD participants, 53.4% had residual kidney function, which was 49.6% in the high-volume HDF group. While the proportion of diabetics was somewhat higher in high-volume HDF participants (29.6%, versus HD 21.9%), the proportion of participants with a history of cardiovascular disease was a bit lower in this group (38.3%, versus HD 45.5%). spKt/$V_{urea}$ differed between these groups ($p$ for difference<0.001). Furthermore, the blood flow rate was different between the HD group and the high-volume HDF group (300 mL/min and 320 mL/min, respectively). The variable of interest, mean treatment time, was distributed as follows: HD 3.82±0.37 hours, low volume HDF 3.54±0.46 hours, middle volume HDF 3.83±0.27 hours and high volume HDF 3.93±0.35 hours. Treatment time differed significantly between HD and high volume HDF ($p$ for difference = 0.03).

### Results Cox regression

Results are shown in table 2. As HD participants are the reference group, HR is 1.0. Crude analysis showed a HR of high-volume HDF participants versus HD of 0.61 (95% CI 0.41-0.93), a significant decrease in all-cause mortality risk ($p$=0.02). Model 2 showed that adjustment for 14 upfront determined potential confounders resulted in a HR of 0.62 (95% CI 0.40-0.96; $p$<0.05). Ultimately, the mean effective treatment time was added as a covariate in model 3, which showed a HR for all-cause mortality of the high-volume HDF group versus HD of 0.64 (95% CI 0.41-0.99; $p$<0.05). As the HR of high-volume HDF in model 3 (0.64 [including treatment time]) is within the 95% CI of the HR of high-volume HDF in model 2 (0.40-0.96), the survival benefit of high-volume HDF is not explained by treatment time in this study.

## DISCUSSION

In the present study, we showed with three Cox proportional hazards models that the survival benefit of high-volume HDF (≥21.95L/treatment) over conventional HD is independent of treatment time in the CONTRAST study. As the duration of the

**Table 1.** Baseline participant characteristics.

| Determinant | HD patients; convection volume 0L (n=356) | High volume HDF patients; convection volume ≥ 21.95L (n=115) | *p* for difference |
|---|---|---|---|
| *Demographic variables* | | | |
| Age (years) | 64.0 (13.4) | 63.3 (13.2) | 0.64 |
| Gender (male) | 231 (64.9%) | 79 (68.7%) | 0.45 |
| BMI (kg/m$^2$) | 25.6 (4.6) | 26.4 (5.3) | 0.11 |
| SGA (nourished) | 195 (54.8%) | 66 (57.4%) | 0.86 |
| *Medical history* | | | |
| Diabetes (yes) | 78 (21.9%) | 34 (29.6%) | 0.12 |
| Cardiovascular disease (yes) | 162 (45.5%) | 44 (38.3%) | 0.17 |
| Renal transplantation (yes) | 44 (12.4%) | 13 (11.3%) | 0.76 |
| Residual kidney function* (yes) | 190 (53.4%) | 57 (49.6%) | 0.48 |
| Pre-dialysis SBP (mmHg) | 148 (22) | 145 (21) | 0.10 |
| *Laboratory values* | | | |
| Hematocrit (L/L) | 0.36 (0.04) | 0.35 (0.04) | 0.22 |
| Phosphate (mmol/L) | 1.63 (0.47) | 1.58 (0.47) | 0.31 |
| Albumin[#] (g/L) | 40.6 (3.9) | 41.2 (3.6) | 0.12 |
| Cholesterol (mmol/L) | 3.69 (1.07) | 3.84 (0.92) | 0.17 |
| Creatinine (µmol/L) | 879 (250) | 880 (267) | 0.99 |
| *Medication* | | | |
| Beta blocker (yes) | 196 (55.1%) | 57 (49.6%) | 0.28 |
| Calcium antagonist (yes) | 116 (32.6%) | 36 (31.3%) | 0.77 |
| RAS inhibitor[$] (yes) | 172 (48.3%) | 55 (47.8%) | 0.89 |
| Statin (yes) | 168 (47.2%) | 59 (51.3%) | 0.47 |
| Platelet aggr inhibitor (yes) | 128 (36.0%) | 44 (38.3%) | 0.68 |
| *Dialysis properties* | | | |
| Dialysis vintage (years) | 2.17 (1.00-4.00) | 2.08 (1.08-5.33) | 0.66 |
| Mean treatment time (hours) | 3.82 (0.37) | 3.93 (0.35) | 0.03 |
| Blood flow rate (mL/min) | 300 (41) | 320 (35) | 0.02 |
| Number of treatments/week | | | 0.81 |
| 2 | 18 (5.1%) | 5 (4.3%) | |
| 3 | 337 (94.7%) | 110 (95.7%) | |
| 4 | 1 (0.3%) | 0 (0.0%) | |
| Vascular access (AVF) | 288 (80.9%) | 91 (79.1%) | 0.70 |
| Kt/V | 1.38 (0.19) | 1.46 (0.23) | 0.001 |

Data are presented as mean (sd), number (percentage) or median (interquartile range), when appropriate

* Defined as diuresis ≥ 100 mL/24h

[#] Bromcresol green values

[$] Treatment with either an ACE inhibitor or an ATII antagonist

Abbreviations: HD = hemodialysis; HDF = hemodiafiltration; BMI = Body Mass Index; SGA = Subjective Global Assessment; SBP = Systolic Blood Pressure: RAS = Renin-angiontensin system; AVF = arteriovenous fistula

dialysis session is an important determinant of the convection volume achieved, this finding is extremely relevant because it highlights the importance of the convection volume per se.[22] To the best of our knowledge, this is the first study that

**Table 2.** Results.

| | HD patients; convection volume 0L (n=356) | HDF patients; convection volume < 18.18L (n=115) | HDF patients; convection volume 18.18-21.95L (n=114) | HDF patients; convection volume ≥ 21.95L (n=115) |
|---|---|---|---|---|
| Crude | 1.0 | 0.95 (0.66-1.38) | 0.83 (0.57-1.21) | 0.61 (0.41-0.93)[&] |
| Adjusted* | 1.0 | 0.78 (0.52-1.16) | 0.83 (0.56-1.23) | 0.62 (0.41-0.95)[&] |
| Adjusted including treatment time[#] | 1.0 | 0.74 (0.49-1.12) | 0.83 (0.56-1.23 | 0.64 (0.42-0.98)[&] |

Hazard ratios (HRs) for death of participants treated with HDF divided in tertiles of achieved convection volume as compared to participants treated with HD (reference group, HR 1.0); HRs with 95% confidence intervals

* Adjusted for: center differences, age, sex, previous vascular disease, diabetes, previous transplantation, baseline residual kidney function, baseline albumin, baseline creatinine, baseline hematocrit, vascular access and use of α- and β-blockers, RAS inhibitors and calcium antagonists at baseline (208 events, 75 missing)

[#] Adjusted for all confounders mentioned above plus treatment time (208 events, 75 missing)

[&] indicates a significant difference in all-cause mortality risk at the level of $p \leq 0.05$

Abbreviations: HD = hemodialysis; HDF = hemodiafiltration

distinguishes the magnitude of the convection volume from treatment time in a survival analysis.

Treatment time in HD has been discussed for decades, because of the dissimilar perspectives for patients, companies and medical staff. For most patients, the duration of a dialysis session can hardly be short enough because of the discomfort and side effects of the treatment, such as hemodynamic instability, nausea and tiredness. For companies that exploit facilities, short dialysis sessions are profitable as more patients can be treated within the same time frame with the same equipment. For the medical staff it is difficult to find a balance between offering an adequate dialysis treatment on the one hand and taking the inconvenience for patients into account at the other. Therefore, the findings of the National Cooperative Dialysis Study (NCDS) in the 1980's appeared promising as it showed that $Kt/V_{urea}$ was the preferred parameter to determine dialysis adequacy, whereas treatment time (3.0±0.5 versus 4.5-5.0 h) had no independent association with mortality. As a result, time (t) could be reduced as long as K increased proportionally.[4,25] However, in this study, dismissal of treatment time as a predictor of clinical outcome was based on a *p*-value of 0.06, which might very well have been a type II statistical error. Moreover, numerous more recent studies actually did demonstrate an independent relation between survival and treatment time, irrespective of $Kt/V_{urea}$.[11,13,26,27] Currently, four hours per session is recommended in a thrice-weekly dialysis schedule.[13] As this advice is mainly based on non-randomized studies,

which are prone to confounding, a treatment time of four hours is rather arbitrarily, especially since patient characteristics, such as body size and residual kidney function, are not taken into consideration.[28,29]

After the present analysis, the question remains why high-volume HDF is associated with a better clinical outcome. Of the possible explanations, enhanced clearance of retained MMW uremic toxins appears obvious, although no single uremic toxin has unequivocally been related to mortality yet. In this respect, it is interesting to note that the magnitude of convection volume is considered the dose of HDF, as formulated during a previous EUDIAL concensus meeting.[30] Other effects of HDF that could be related to a superior clinical outcome include a better intradialytic hemodynamic stability,[31] a reduced inflammatory state and/or an improved nutritional status. Nevertheless, the exclusion of treatment time as an important contributor to the beneficial effect of high volume HDF is an important step forward in the understanding of this, still controversial, area.

Our study has some limitations. First, although 'intention to treat' is the preferred type of analysis, patients were analyzed 'as treated', because the aim of the study was to investigate whether or not the survival advantage of high-volume HDF depends on treatment time. Obviously, this question cannot be solved in patients who were not treated with HDF anymore because of transplantation or a switch to peritoneal dialysis.[17] Second, as the present *post hoc* analysis should be viewed as an observational study, residual confounding may play a role, even if we correct for all known confounders. The most important strength of the present analysis is its prospective, concise and meticulous data collection, which improves reliability considerably. Furthermore, the large sample size (n=700) with the long follow-up period (mean follow-up 2.27 year) and the high number of casualties (n=224) enhances its consistency.

In conclusion, the present analysis clearly shows that the survival benefit of high-volume HDF over low-flux HD in CONTRAST is independent of treatment time.

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