Clinical Predictors of Decline in Nutritional Parameters over Time in ESRD

Claire H. den Hoedt,†† Michiel L. Bots,‡ Muriel P.C. Grooteman,§‖ Neelke C. van der Weerd,¶ E. Lars Penne,§ Albert H.A. Mazairac,† Renée Levesque,** Peter J. Blankestijn,† Menso J. Nubé,§‖ Piet M. ter Wee,§‖ and Marinus A. van den Dorpel,* for the CONTRAST Investigators*

Summary

Background and objectives Inflammation and malnutrition are important features in patients with ESRD; however, data on changes in these parameters over time are scarce. This study aimed to gain insight into changes over time in serum albumin, body mass index, high-sensitivity C-reactive protein, and IL-6 in patients with ESRD and aimed to identify clinical risk factors for deterioration of these parameters.

Design, setting, participants, & measurements Data were analyzed from the Convective Transport Study, a randomized controlled trial conducted from June 2004 to January 2011, in which 714 patients with chronic ESRD were randomized to either online hemodiafiltration or low-flux hemodialysis. Albumin and body mass index were measured up to 6 years and predialysis C-reactive protein and IL-6 were measured up to 3 years in a subset of 405 participants. Rates of change in these parameters over time were estimated across strata of predefined risk factors with linear mixed-effects models.

Results Albumin and body mass index decreased and C-reactive protein and IL-6 increased over time. For every incremental year of age at baseline, the yearly excess decline in albumin was 0.003 g/dl (−0.004 to −0.002; $P<0.001$) and the excess decline in body mass index was 0.02 kg/m^2 per year (−0.02 to −0.01; $P<0.001$). In patients with diabetes mellitus, there was a yearly excess decline of 0.05 g/dl in albumin (−0.09 to −0.02; $P=0.002$). Compared with women, men had an excess decline of 0.03 g/dl per year in albumin (−0.06 to −0.001; $P=0.05$) and an excess increase of 11.6% per year in IL-6 (0.63%–23.6%; $P=0.04$).

Conclusions Despite guideline-based care, all inflammatory and nutritional parameters worsened over time. The deterioration of some of these parameters was more pronounced in men, older patients, and patients with diabetes mellitus. Special focus on the nutritional status of at-risk patients by individualizing medical care might improve their prognosis.

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*Department of Internal Medicine, Maasstad Hospital, Rotterdam, The Netherlands; †Department of Nephrology and ‡Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands; §Department of Nephrology and ‖Institute for Cardiovascular Research, VU Medical Center, Amsterdam, The Netherlands; ¶Academic Medical Center, Amsterdam, The Netherlands; and **St. Luc Hospital, Montréal, Quebec, Canada

Correspondence: Dr. Marinus A. van den Dorpel, Department of Internal Medicine, Maasstad Hospital, 1 K2 038, PO Box 9119, 3007 AC Rotterdam, The Netherlands. Email: dorpelm@maasstadziekenhuis.nl

Introduction

Systemic inflammation and poor nutritional status are strong predictors for mortality in patients with ESRD (1). Several factors contribute to systemic inflammation in hemodialysis patients, such as bioincompatibility of dialyzers, dialysate contamination, vascular access–related complications, uremia, and intercurrent clinical events (2,3). Many studies reported that systemic inflammation and protein energy wasting measured once relate to mortality in ESRD patients (1,4,5). Yet few studies reported longitudinal changes in these parameters. The Hemodialysis (HEMO) study showed a decline in various nutritional parameters in 1864 hemodialysis patients over 3 years of follow-up (6). In another study of 64 prevalent hemodialysis patients, albumin improved and body weight and C-reactive protein (CRP) remained stable during 36 months of follow-up (7). IL-6 increased over time in a study of 85 prevalent hemodialysis patients (8). Other studies with multiple measurements of CRP in ESRD patients focused on predictive power (9–11).

Factors that influence long-term changes over time in inflammatory and nutritional parameters in ESRD patients have not been thoroughly studied. Almost all studies focused on predictors of albumin, reporting that activation of the acute phase response, age, and vascular access (graft or catheter) related to lower albumin levels (12–14).

Because data on the natural history of inflammation and nutritional markers are limited, we assessed their longitudinal changes in patients participating in the Convective Transport Study (CONTRAST) (15). In a previous CONTRAST communication, we reported that compared with hemodialysis, online hemodiafiltration had no effect on the rate of change in albumin and led to a small amelioration of CRP and IL-6 during follow-up (C.H. den Hoedt et al., unpublished observations).

This analysis aimed to gain insight into the changes over time in serum albumin, body mass index (BMI),

CRP, and IL-6 in our ESRD population during long-term follow-up and to identify clinical risk factors for their deterioration.

Materials and Methods

General Methods and Patients

CONTRAST (ISRCTN38365125) was a randomized controlled trial in which patients were randomized to either hemodiafiltration or low-flux hemodialysis. The primary endpoint was mortality (15,16). The study was conducted in 29 dialysis centers in The Netherlands (n=26), Canada (n=2), and Norway (n=1). Patients were eligible if they were treated with hemodialysis two or three times a week, for at least 2 months, with a minimum dialysis single pool $Kt/V_{urea} \geq 1.2$. Kt/V_{urea} is a measure of urea removal, where K is the dialyzer clearance, t is the dialysis session length, and V is the adjustment for the urea distribution volume of the patient. Exclusion criteria were age<18 years, treatment by hemodiafiltration or high-flux hemodialysis in the 6 months preceding randomization, severe noncompliance defined as nonadherence to the dialysis prescription, a life expectancy <3 months due to causes other than kidney disease, and participation in another clinical intervention study evaluating cardiovascular outcome. Randomization was stratified by participating center. From June 2004 until January 2010, 714 patients were enrolled in CONTRAST; follow-up took place until January 2011. The study was conducted in accordance with the Declaration of Helsinki and was approved by the medical ethics review boards of all participating hospitals. Written informed consent was obtained from all patients before randomization. Primary renal diagnoses were as follows: renal vascular disease (29%), diabetes mellitus (19%), primary glomerulopathy or GN (12%), interstitial nephropathy (9%), cystic kidney disease (7%), multisystem disease (4%), other (12%), or unknown (8%).

Analyses of CRP and IL-6 levels were performed in 405 CONTRAST participants enrolled in hospitals where storage of extra blood samples for nonroutine laboratory assessments was logistically feasible (16 Dutch centers and 1 Norwegian center). Analyses of albumin levels and BMI were performed for all 714 patients.

Dialysis Procedures

Treatment times were fixed during follow-up in both treatment arms, unless single pool Kt/V_{urea} was <1.2. Online hemodiafiltration was performed in the postdilution mode; the target volume was 6 L/h. The following synthetic high-flux dialyzers were used for hemodiafiltration: FX80 (24%), FX100 (12%), and Optiflux F200NR (9%) (Fresenius Medical Care, Bad Homburg, Germany); Polyflux 170H (20%) and Polyflux 210H (30%) (Gambro AB, Stockholm, Sweden); or other dialyzers (4%) at the 3-month visit. Hemodialysis patients were treated with the following synthetic low-flux dialyzers: F6HPS (4%), F8HPS (46%), and Optiflux 18NR (11%) (Fresenius Medical Care); Polyflux 14L (4%), Polyflux 17L (25%), and Polyflux 21L (4%) (Gambro AB); or other (6%) at the 3-month visit. All patients were treated with ultrapure dialysis fluid, defined as <0.1 colony-forming units per milliliter and <0.03 endotoxin units per milliliter. Routine patient care was performed according to national and international quality of care guidelines.

Data Collection

At baseline, standardized forms were used to collect demographic, clinical, and laboratory data. The type of vascular access, dialysis duration (dialysis vintage), and medical history (presence of diabetes mellitus [DM] and previous cardiovascular disease [CVD]) were documented. CVD was defined as a history of angina pectoris, myocardial infarction, prior coronary revascularization, stroke, or transient ischemic attack, and/or peripheral vascular disease. Dialysis vintage was determined as the sum of time patients were treated with hemodialysis or peritoneal dialysis before inclusion. The mean of three consecutive postdialysis weights was used to calculate BMI. At each 3-month visit, data on clinical events, clinical characteristics, dialysis treatment, medication, and laboratory values were recorded. Blood samples for CRP and IL-6 were drawn before dialysis at baseline and after 6 months, 1 year, 2 years, and 3 years. Samples were placed on ice, centrifuged within 30 minutes at $1500 \times g$ for 10 minutes, and stored at −80°C until assayed. Blood samples for albumin were taken every 3 months during the whole study follow-up period. Patients with urine production <100 ml/d were considered anuric. Interdialytic 24-hour urine samples were collected only in patients with a residual diuresis of >100 ml/d.

Laboratory Measurements

High-sensitivity CRP and IL-6 levels were measured centrally. CRP was measured with a particle-enhanced immunoturbidimetric assay on a Roche-Hitachi analyzer (Roche Diagnostics GmbH, Mannheim, Germany), with a lower quantification limit of 0.1 mg/L. IL-6 was measured with an ELISA (Sanquin, Amsterdam, The Netherlands), with a lower quantification limit of 0.35 pg/ml. Serum albumin was measured in local hospitals using either the bromcresol green method or the bromcresol purple method. Bromcresol purple levels were converted to bromcresol green levels as follows: bromcresol green=-bromcresol purple+0.55 (in grams per decaliter) (17). Other laboratory measurements were performed in the hospitals using standard techniques.

Outcomes

The primary study outcome of this analysis was the annual rate of change in albumin, BMI, CRP, and IL-6 based on data obtained during 6 years (for albumin and BMI) or 3 years (for CRP and IL-6) of follow-up. The secondary study outcome was the influence of age, sex, dialysis vintage, and presence of DM, CVD, and residual kidney function (RKF) on the rate of change in parameters over time.

Statistical Analyses

Data are reported as the means±SDs or with 95% confidence intervals, medians with interquartile ranges, or proportions when appropriate. Unadjusted linear mixed-effects models with a random intercept and random slope were used to model changes in parameters over

time. In addition, relationships between changes in the four measured parameters were assessed. A similar model was used to study whether the rates of change differed across strata of the conventional risk factors. This was tested using interaction terms (age and dialysis vintage were used as continuous variables). In these linear mixed-effect models, adjustments were made for other baseline risk factors and randomization group by entering them as fixed effects. Cut-off points for stratified analyses on age and vintage were based on the median.

The natural logarithms of CRP and IL-6 (LnCRP and LnIL-6) were used for the analyses to improve the model fit. Percentage change was calculated by $e^{\Delta LnCRP}$ for CRP and by $e^{\Delta LnIL6}$ for IL-6. Missing values were not imputed. The analyses were conducted with R software (version 2.9.2; The R Project for Statistical Computing, Vienna, Austria).

Results

Characteristics of the study population are shown in Table 1.

Rates of Change in Albumin, BMI, CRP, and IL-6 over Time

Albumin decreased annually (0.08 g/dl; −0.09 to −0.06 g/dl; $P<0.001$) during 6 years of follow-up, as did BMI (0.15 kg/m^2; −0.23 to −0.07; $P<0.001$). CRP increased annually (10.0%; 2.5%–18.5% per year; $P=0.01$) during 3 years of follow-up, as did IL-6 (9.1%; 3.8%–15.0% per year; $P<0.001$).

Relationships between the Changes in Inflammatory and Nutritional Markers

Changes in CRP and IL-6 were inversely related to changes in albumin. A multiplication of CRP by 2.72 per year (increase LnCRP=1) was related to a decline of −0.08 g/dl per year (−0.10 to −0.06; $P<0.001$) in albumin, whereas a multiplication of IL-6 by 2.72 per year was related to a decline of −0.05 g/dl per year (−0.08 to −0.02; $P<0.001$) in albumin. Changes in CRP and IL-6 were not related to changes in BMI, with CRP × 2.72 → BMI −0.02 ($P=0.70$) and IL-6 × 2.72 → BMI −0.05 ($P=0.39$). Changes in albumin and changes in BMI were positively related. A decrease of 0.1 g/dl per year in albumin was associated with a decrease of 0.03 kg/m^2 per year in BMI (0.02–0.04; $P<0.001$).

Interactions of Conventional Risk Factors with Changes over Time in Albumin

Albumin showed a greater decline over time in older patients. For every incremental year of baseline age, there was an excess decline of 0.003 g/dl in albumin per year (−0.004 to −0.002; $P<0.001$). In addition, albumin showed a greater decline in patients with DM compared with patients without DM, with an excess albumin decline of 0.05 g/dl per year (−0.09 to −0.02; $P=0.002$). Albumin showed a greater decline in men compared with women, with an excess albumin decline of 0.03 g/dl per year (−0.06 to −0.001; $P=0.05$). The slopes of albumin in the strata of conventional risk factors are shown in Table 2.

Interactions of Conventional Risk Factors with Changes over Time in BMI

Older patients showed a greater decline in BMI, with an excess decline of 0.02 kg/m^2 in BMI per year (−0.02 to −0.01; $P<0.001$). The decline in BMI was not statistically different between patients with and without DM (−0.12 kg/m^2 per year; −0.30 to 0.07; $P=0.21$). Patients with CVD had an excess decline of 0.27 kg/m^2 in BMI compared with patients without CVD (−0.43 to −0.11; $P<0.001$). The slopes of BMI over time across strata of conventional risk factors are shown in Table 3.

Interactions of Conventional Risk Factors with Changes over Time in CRP and IL-6

The increase in CRP was similar in men and women (+14.4% per year; −9.8% to 32.3%; $P=0.07$). The increase in IL-6 per year was greater in men (excess increase of 11.5% per year; 0.63%–23.6%; $P=0.04$). In patients treated with low-flux hemodialysis, the increase in CRP was significantly larger in patients without RKF compared with patients with RKF. The same trend was found for changes in IL-6. The rates of change of CRP and IL-6 across the strata of conventional risk factors are shown in Tables 4 and 5. The rates of change in CRP and IL-6 were similar, irrespective of age, presence of DM, previous CVD, and vintage.

Discussion

Our results indicate that albumin and BMI measurements decreased during long-term follow-up of ESRD patients, whereas CRP and IL-6 measurements increased over time. Furthermore, deterioration of one or more of these parameters over time was more pronounced in men, older patients, patients with DM, and patients with CVD.

Studies of changes in nutritional and inflammatory parameters over time in ESRD patients have been performed in United States and small European populations (6,7,12,14,18). Because of the high prevalence of catheter and graft use in the United States, European and United States studies are difficult to compare. The negative effect of catheters and grafts on albumin levels as well as the incidence of infection, and thus concomitantly higher CRP and IL-6 levels, is well known (12,14,19,20). Interestingly, both the prevalence of catheter use and the decrease in albumin and BMI in the US HEMO study were comparable with CONTRAST (6). Comparison of our results with two smaller European studies is hampered by the fact that one study (18) comprised incident dialysis patients, and the other reported only on those participants who survived 3 years (7). The latter may have biased their findings (*i.e.*, stable CRP levels over time). Increasing IL-6 levels over time are in accordance with data from two HEMO study centers as well as a recent Israeli study (8,21). The inverse relationships between changes in CRP and IL-6 with albumin are in accordance with other studies, reflecting a negative influence of inflammation on albumin synthesis (12,13). The deterioration of inflammatory and nutritional parameters over time might be a result of vascular damage accompanying a longer dialysis vintage, repeated exposure to bioincompatible dialyzers, and/or an increased incidence of infectious and cardiovascular events.

Table 1. Baseline patient characteristics

Patient Characteristics	Total Cohort (*N*=714)	Inflammation Cohort(*n*=405)[a]
Patient characteristics		
Age (yr)	64.1±13.7	63.7±13.9
Men	445 (62)	252 (62)
Region		
The Netherlands	597 (84)	390 (96)
Norway	15 (2)	15 (4)
Canada	102 (14)	NA
History of cardiovascular disease	313 (44)	177 (44)
Diabetes mellitus	170 (24)	85 (21)
Dialysis vintage (yr)	2 (1–4)	1.8 (0.9–3.4)
Systolic BP (mmHg), predialysis	147±21	142±18
Diastolic BP (mmHg), predialysis	75±12	73±11
Body weight (kg), postdialysis	72.4±14.4	71.7±14.6
Body mass index (kg/m^2), postdialysis	25.4±14.4	25.0±4.8
Subjective global assessment classification		
Well nourished	580 (81)	345 (81)
Mild-to-moderate malnutrition	123 (17)	71 (18)
Severe malnutrition	1 (0)	1 (0)
Residual kidney function (defined as urine output>100 ml/24 h)	376 (53)	230 (57)
Estimated GFR (ml/min per 1.73 m^2)	3.2 (1.3–5.5)	2.6 (1.2–5.1)
Treatment characteristics		
Treatment frequency		
3×/wk	668 (94)	375 (93)
2×/wk	44 (6)	30 (7)
Duration of a dialysis session (min)	226±23	227±23
Blood flow (ml/min)	300 (300–348)	300 (300–325)
Dialysis access		
Fistula	567 (80)	339 (84)
Graft	100 (14)	53 (13)
Central venous catheter	47 (6)	10 (3)
Single pool Kt/V_{urea}	1.40±0.22	1.39±0.20
Laboratory parameters		
Hemoglobin (g/dl)	11.8±1.25	11.9±1.25
Phosphorus (mg/dl)	5.08±1.53	5.16±1.59
Albumin (g/dl)[b]	4.0±0.38	4.0±0.41
Creatinine (mg/dl), predialysis	9.74±2.89	9.80±2.83
Cholesterol (mg/dl)	142±37	142±39
High-sensitivity C-reactive protein (mg/L)	NA	3.93 (1.38–10.40)
IL-6 (pg/ml)	NA	2.06 (1.21–3.82)

Data are presented as the mean±SD, *n* (%), or median (interquartile range). To convert albumin in g/dl to g/L, multiply by 10. NA, not applicable.

[a]Subpopulation of the 714 patients in which CRP and IL-6 measurements were done.

[b]Albumin concentrations measured with the bromcresol purple method were converted to bromcresol green concentrations.

Older age and a faster decline in albumin and BMI were reported previously, yet only over a 1-year period (14). We now expand the evidence over a 6-year period. Other researchers also identified age as a risk factor for stable high or increasing CRP levels (9,10). These findings might reflect an increased incidence of events and a slower recovery of events in elderly patients or a more severe course of infection in older patients (22).

Worsening of some of the studied parameters over time was more pronounced in men than in women. This may be compatible with reports that men with ESRD are more prone to suffer from anorexia (23) and men on hemodialysis who suffer from inflammation have a worse prognosis than women who suffer from inflammation (24).

In this study, the annual decrease in albumin in patients with DM was almost twice the decrease in patients without DM. This might be explained by an accelerated loss of lean body mass in incident dialysis patients with DM (25). No effect of the presence of DM on the rate of change of albumin was found in a US Renal Data System study, likely because follow-up was limited to 1 year (14). The nutritional status of patients with DM might be more vulnerable, due to increased inflammation and an increased number of events.

The increase in CRP over time was larger in patients without RKF compared with patients with RKF, possibly due to decreased removal of uremic toxins leading to increased inflammatory activity or decreased renal clearance

Table 2. Annual rate of change in serum albumin (g/dl) in various clinical strata

Stratum	Estimate Slope[a]	95% Confidence Interval	*P* Value Slope	*P* Interaction Term
Age<66.8 yr	−0.05	−0.06 to −0.03	<0.001	Age×time
Age≥66.8 yr	−0.12	−0.14 to −0.09	<0.001	<0.001
Men	−0.09	−0.11 to −0.07	<0.001	Sex×time
Women	−0.06	−0.08 to −0.03	<0.001	0.05
DM	−0.11	−0.14 to −0.08	<0.001	DM×time
No DM	−0.07	−0.08 to −0.05	<0.001	0.002
CVD	−0.09	−0.12 to −0.07	<0.001	CVD×time
No CVD	−0.07	−0.09 to −0.05	<0.001	0.20
RKF	−0.08	−0.10 to −0.06	<0.001	RKF×time
No RKF	−0.07	−0.09 to −0.05	<0.001	0.81
Vintage below median	−0.07	−0.10 to −0.05	<0.001	Vintage×time
Vintage at and above median	−0.08	−0.10 to −0.06	<0.001	0.72

All analyses on strata were adjusted for age, sex, dialysis vintage, randomized group (excluding the conventional risk factor of the stratum under study), and presence of DM, CVD, and RKF. Estimates in this table may differ slightly from estimates in the text of the Results, because estimates in this table are derived from models performed in the subgroups separately. DM, diabetes mellitus; CVD, cardiovascular disease; RKF, residual kidney function.
[a]Estimate slope indicates mean longitudinal change per year in serum albumin levels associated with the presence or absence of the conventional risk factor.

Table 3. Annual rate of change in BMI (kg/m^2) in various clinical strata

Stratum	Estimate Slope[a]	95% Confidence Interval	*P* Value Slope	*P* Value Interaction Term
Age<66.8 yr	0.03	−0.08 to 0.13	0.59	Age×time
Age≥66.8 yr	−0.35	−0.47 to −0.23	<0.001	<0.001
Men	−0.20	−0.30 to −0.11	<0.001	Sex×time
Women	−0.07	−0.21 to 0.07	0.30	0.11
DM	−0.24	−0.43 to −0.06	0.01	DM×time
No DM	−0.12	−0.21 to −0.04	0.004	0.21
CVD	−0.31	−0.43 to −0.19	<0.001	CVD×time
No CVD	−0.04	−0.14 to 0.07	0.48	<0.001
RKF	−0.22	−0.33 to −0.12	0.23	RKF×time
No RKF	−0.07	−0.19 to 0.05	<0.001	0.07
Vintage below median	−0.09	−0.20 to 0.03	0.14	Vintage×time
Vintage at and above median	−0.23	−0.34 to −0.12	<0.001	0.60

All analyses on strata were adjusted for age, sex, dialysis vintage and randomized group (excluding the conventional risk factor of the stratum under study), and presence of DM, CVD, and RKF. Estimates in this table may differ slightly from estimates in the text of the Results, because estimates in this table are derived from models performed in the subgroups separately. BMI, body mass index.
[a]Estimate slope indicates mean longitudinal change per year in BMI associated with the presence or absence of the conventional risk factor.

of inflammatory markers in anuric patients. Other researchers also found lower CRP and IL-6 concentrations in patients with residual urine output (26).

Despite the fact that our patients were well nourished at baseline according to subjective global assessment measurements, their biomarkers worsened over time. The deterioration occurred despite guideline-based clinical care. Patients were given close nutritional support by dietitians, meals were provided at the dialysis department, infection prevention was performed, and a high proportion of patients had an autologous vascular access. Dialysis efficiency by increasing Kt/V_{urea} and dialysis modality appeared to have no effect on this deterioration (6,15).

The main limitation of this analysis is the relatively small sample size for CRP and IL-6 measurements, which restricts our power for demonstrating differences in the rate of change across subgroups. In addition, only a small subset of inflammatory and nutritional parameters was included in this study. The high attrition rate in a dialysis cohort like ours is generally seen as a study limitation. However, the use of linear mixed-effect models has been shown to yield valid and precise estimates of the rate of change in such datasets. The strengths of our study include concise and prospective data collection and concomitant analysis of four clinically important parameters over a long follow-up period. Furthermore, this study

Table 4. Annual rate of change in LnCRP [Ln(mg/L)] over time in various clinical strata

Stratum	Estimate Slope[a]	95% Confidence Interval	*P* Value Slope	*P* Value Interaction Term
Age<65.9 yr	0.12	0.02 to 0.22	0.02	Age×time
Age≥65.9 yr	0.06	−0.04 to 0.16	0.26	0.72
Men	0.15	0.06 to 0.24	0.002	Sex×time
Women	0.01	−0.09 to 0.12	0.80	0.07
DM	0.21	0.07 to 0.35	0.004	DM×time
No DM	0.07	−0.02 to 0.15	0.11	0.12
CVD	0.07	−0.04 to 0.17	0.21	CVD×time
No CVD	0.12	0.02 to 0.22	0.02	0.52
RKF	0.06	−0.03 to 0.15	0.17	
No RKF	0.15	0.03 to 0.26	0.01	
No RKF hemodialysis	0.27	0.11 to 0.42	<0.001	0.04[b]
No RKF hemodiafiltration	−0.01	−0.18 to 0.17	0.93	0.53[b]
Vintage below median	0.07	−0.02 to 0.17	0.14	Vintage×time
Vintage at and above median	0.12	0.02 to 0.21	0.01	0.16

All analyses on strata were adjusted for age, sex, dialysis vintage, randomized group (excluding the conventional risk factor of the stratum under study), and presence of DM, CVD, and RKF. Estimates in this table may differ slightly from estimates in the text of the Results, because estimates in this table are derived from models performed in the subgroups separately. LnCRP, natural logarithm of C-reactive protein.

[a]Estimate slope indicates the mean longitudinal change per year in LnCRP levels associated with the presence or absence of the conventional risk factor, the percent change per year calculated by $e^{\Delta LnCRP}$.

[b]Versus RKF (no difference hemodialysis and hemodiafiltration)

Table 5. Annual rate of change in LnIL-6 [Ln(pg/ml)] in various clinical strata

Stratum	Estimate Slope[a]	95% Confidence Interval	*P* Value Slope	*P* Value Interaction Term
Age<65.9	0.07	−0.01 to 0.14	0.07	Age×time
Age≥65.9	0.09	0.03 to 0.16	0.01	0.21
Men	0.13	0.07 to 0.20	<0.001	Sex×time
Women	0.02	−0.06 to 0.09	0.63	0.04
DM	0.16	0.07 to 0.26	0.001	DM×time
No DM	0.07	0.01 to 0.12	0.03	0.12
CVD	0.11	0.04 to 0.18	0.002	CVD×time
No CVD	0.07	0.001 to 0.14	0.05	0.58
RKF	0.08	0.02 to 0.14	0.01	
No RKF	0.10	0.02 to 0.18	0.02	
No RKF hemodialysis	0.19	0.08 to 0.30	<0.001	0.09[b]
No RKF hemodiafiltration	−0.02	−0.15 to 0.10	0.69	0.16[b]
Vintage below median	0.09	0.02 to 0.16	0.01	Vintage×time
Vintage at and above median	0.09	0.02 to 0.16	0.01	0.70

All analyses on strata were adjusted for age, sex, dialysis vintage, allocated treatment (excluding the conventional risk factor of the stratum under study), and presence of DM, CVD, and RKF. Estimates in this table may differ slightly from estimates in the text of the Results, because estimates in this table are derived from models performed in the subgroups separately. LnIL-6, natural logarithm of IL-6.

[a]Estimate slope indicates the mean longitudinal change per year in LnIL-6 levels associated with the presence or absence of the conventional risk factor, the percent change per year calculated by $e^{\Delta LnIL6}$.

[b]Versus RKF (no difference hemodialysis and hemodiafiltration).

was performed in a representative European ESRD population in which all patients were treated with ultrapure dialysis fluids.

Despite best efforts of care, all inflammatory and nutritional parameters worsened over time and are a point of concern in this patient population. Deterioration of one or more of these parameters was more pronounced in men, older patients, and patients with DM.

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The local CONTRAST investigators are as follows: *Canada:* M. Dorval (Georges-L Dumont Regional Hospital, Moncton) and R. Lévesque (CHUM St Luc Hospital, Montréal); *The Netherlands:* M.G. Koopman (Academic Medical Center, Amsterdam), C.J.A.M. Konings (Catharina Hospital, Eindhoven), W.P. Haanstra (Dialysis Clinic Noord, Beilen), M. Kooistra and B. van Jaarsveld (Dianet Dialysis Centers, Utrecht), T. Noordzij (Fransiscus Hospital, Roosendaal), G.W. Feith (Gelderse Vallei Hospital, Ede), H.G. Peltenburg (Groene Hart Hospital, Gouda), M. van Buren (Haga Hospital, The Hague), J.J.G. Offerman (Isala Clinics, Zwolle), E.K. Hoogeveen (Jeroen Bosch Hospital, 's-Hertogenbosch), F. de Heer (Maasland Hospital, Sittard), P.J. van de Ven (Maasstad Hospital, Rotterdam), T.K. Kremer Hovinga (Martini Hospital, Groningen), W.A. Bax (Medical Center Alkmaar, Alkmaar), J.O. Groeneveld (Onze Lieve Vrouwe Gasthuis, Amsterdam), A.T.J. Lavrijssen (Oosterschelde Hospital, Goes), A.M. Schrander-Van der Meer (Rijnland Hospital, Leiderdorp), L.J.M. Reichert (Rijnstate Hospital, Arnhem), J. Huussen (Slingeland Hospital, Doetinchem), P.L. Rensma (St. Elisabeth Hospital, Tilburg), Y. Schrama (St. Fransiscus Gasthuis, Rotterdam), H.W. van Hamersvelt (University Medical Center St. Radboud, Nijmegen), W.H. Boer (University Medical Center Utrecht, Utrecht); W.H. van Kuijk (VieCuri Medical Center, Venlo), M.G. Vervloet (VU University Medical Center, Amsterdam), and I.M.P.M.J. Wauters (Zeeuws-Vlaanderen Hospital, Terneuzen); and *Norway:* I. Sekse (Haukeland University Hospital, Bergen).

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