Chapter 7 |

The course of decline of renal function before and after the start of dialysis

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Abstract

Preservation of renal function is associated with improved quality of life and survival in dialysis patients. We explored the course of the glomerular filtration rate GFR (calculated as the mean of urea and creatinine clearance, corrected for body surface area) in 1861 patients in the year before until one year after the start of hemodialysis (HD) and peritoneal dialysis (PD). Decline of GFR was estimated using linear mixed models and adjusted for age, sex, primary kidney disease, cardiovascular disease, and diabetes. The decline attenuated from -0.53 mL/min/1.73m^2/month (95% CI -0.58;-0.48) to -0.12 (95%CI -0.20;-0.04) at 2-4 months of dialysis. The decline in HD attenuated from -0.51 (95%CI -0.57;-0.44) to -0.14 (95%CI -0.26;-0.02); in PD from -0.55 (95%CI -0.62;-0.48) to -0.11 (95%CI -0.23;0.01). In patients with GFR equal or above the median GFR at the start of dialysis the decline attenuated at 3 months from -0.70 (95%CI -0.78;-0.62) to -0.21 (95%CI -0.36;-0.05). In patients with GFR lower than the median GFR at start the decline attenuated at 1 month from -0.73 (95%CI -0.88;-0.58) to -0.04 (95%CI -0.27;0.19). In conclusion, the apparent decline of GFR in the year before until one year after the start of dialysis slows down after 2-4 months of dialysis. This is similar in HD and PD patients, although at a different level of GFR. Dialytic removal of urea and creatinine may be an explanation for this. Further studies are needed to examine alternative explanations.

Introduction

Preservation of renal function has important clinical consequences. For example, in dialysis patients the presence of residual renal function is associated with better quality of life and prolonged survival.[1-3] Residual renal function reflects not only remaining glomerular filtration rate (GFR) and urine production, but also contributes to the removal of uremic toxins by tubular secretion. Furthermore, it is associated with lower concentrations of serum markers of inflammation, and with prevention of the development of left ventricular hypertrophy.[4-7]

Several studies showed that the decline of residual renal function in hemodialysis (HD) patients is faster than in peritoneal dialysis (PD) patients.[8-11] In addition, it has been suggested that urea clearance declines with a constant rate in the months preceding the start of dialysis, but acutely decreases with ~2 mL/min at the time of the start of dialysis.[12] It is unclear whether this abrupt deterioration was real or just artificially introduced by the method used to model the decline of renal function. Furthermore, it might be questioned whether this change in the rate of decline of renal function, if present, takes place immediately at the start of dialysis or whether this takes some time to develop.

The aim of this study was to explore the course of GFR before and after the start of dialysis using data from the NEtherlands COoperative Study on the Adequacy of Dialysis (NECOSAD) cohort. More specifically, we examined whether the decline of GFR is constant from the year before until one year after the start of dialysis, or attenuates at some point during this follow-up period. To that end, linear mixed effects models were used to estimate the rate of decline of GFR for the total time window and these were compared with linear mixed effects models allowing attenuation in the decline of renal function at different time points during follow-up. In addition, it was investigated whether the course of decline of renal function was influenced by dialysis modality or by the level of GFR at start of dialysis.

Methods

Study design

NECOSAD is a multicenter prospective cohort study of incident dialysis patients from 38 dialysis centers in The Netherlands. At start as well as at three months, six months, and subsequently every six months after the start of dialysis, blood and timed urine collections were taken. The collection period was 24 hours for pre-dialysis and PD patients, and comprised the whole interdialytic interval in HD patients. Patients were followed till time of death or censoring because of kidney transplantation, recovery of renal function, withdrawal from the study or a transfer to a non-participating dialysis center. In a sample of NECOSAD patients, included before April 2003, trained research nurses followed the clinical course during pre-dialysis through medical charts for a maximum of one year before the start of dialysis. In these medical charts, the start of pre-dialysis care was defined as the first time a patient was informed about the need to prepare for dialysis therapy. From the pre-dialysis period up to a maximum of ten assessments of creatinine and urea in plasma and 24-hour urine were recorded. These data have been added to the NECOSAD database 'post-hoc'. For all patients included in the study, start of

dialysis was regarded as the baseline measurement even if pre-dialysis data were available. Medical ethics committees of all participating hospitals gave their approval for the NECOSAD study.

Patients

To be eligible for inclusion in NECOSAD adult patients (at least 18 years of age) had to start with dialysis as their first renal replacement therapy and should have provided their written informed consent prior to study inclusion. For the present analysis, patients with at least one GFR measurement in the year before until one year after the start of dialysis were included and follow-up was restricted to one year after start dialysis.

Data collection

For all patients the following baseline data were collected between four weeks prior to and two weeks after the start of dialysis: age, sex, body mass index, dialysis modality, and blood pressure. Primary kidney disease was classified using the codes of the European Renal Association-European Dialysis and Transplantation Association.[13] Comorbidities were recorded as doctors' diagnosis of diabetes mellitus or cardiovascular disease. The severity of comorbidities was reflected by the Davies comorbidity score, which is based on the presence or absence of seven comorbid conditions (malignancy, ischemic heart disease, peripheral vascular disease, left ventricular dysfunction, diabetes mellitus, systemic collagen vascular disease, and other significant pathology e.g. chronic obstructive airways disease), giving rise to three risk groups: low risk (without any comorbid condition), medium risk (one or two comorbid conditions), and high risk (three or more comorbid conditions).[14]

Outcome: decline of renal function

Creatinine and urea levels were determined in plasma and 24-hour urine samples. GFR was calculated as the mean of creatinine and urea clearance, and corrected for body surface area (mL/min/1.73m^2). If urine production was less than 200 mL/24-hr GFR was set at 0 mL/min/1.73m^2. Furthermore, patients were considered anuric at the first of two subsequent time points with GFR=0 mL/min/1.73m^2.

Statistical analyses

Baseline characteristics were expressed as mean and standard deviation or percentage. The rate of decline of renal function was estimated using linear mixed effects models. Here the GFR is modeled as a linear function of follow-up times; with per subject a random intercept and a random time effect. The fixed regression coefficient for time (β1) estimates the rate of decline of GFR per month. To allow for a change in the slope before and after a certain change point an additional covariate was added, being equal to 0 for measurements taken before the change point and being equal to (time-change point) for measurements taken after the change point. The regression coefficient for this covariate (β2) measures the difference in slope before and

after the change point. Different change points (-11 months, -10 months up to 11 months after the start of dialysis) were considered, resulting in 23 different models. Akaike's Information Criterion (AIC), which is based on the value of the maximum likelihood and on the number of parameters in the model, was used to select the model with the best fit: a lower AIC indicates a better model fit. The change point model with the best fit was then fitted by restricted maximum likelihood to estimate the monthly decline of GFR. In this model, β1 reflects the monthly decline of renal function *before* the change point, while β2 indicates whether the rate of decline changes after the change point and (β1+β2) reflects the decline *after* the change point. Models were adjusted for age, sex, primary kidney disease, cardiovascular disease, and diabetes at start of dialysis. In addition, to study whether the course of decline of renal function differs between HD and PD patients, modality at start of dialysis was added as a covariate. The analyses were based on the intention-to-treat principle meaning that modality switches during follow-up were ignored. To study possible differences in decline between HD and PD patients, interaction terms were added to the model (time1*modality and time2*modality). The first interaction term reflected whether the rate of decline in HD patients differed from decline in PD patients before the change point, while the second interaction term reflected whether the change in the rate of decline of GFR after the change point was different between HD and PD patients. Finally, it was investigated whether the course of renal function was dependent on the level of GFR at start of dialysis. To that end, an extra covariate indicating whether a patient had a GFR level equal/above or below the median GFR level at start of dialysis was added and interaction terms were compared. All statistical analyses were performed with SPSS version 17.0.

Results

Study population

The NECOSAD study included 2051 incident patients with end-stage renal disease, who started dialysis between August 1996 and February 2007. At the start of dialysis, as well as at three months, six months, and subsequently every six months thereafter, blood and 24-hour urine samples were taken. In addition, in a subset of the patients included (n=1130), pre-dialysis data were collected retrospectively from medical records. For the present analysis, 1861 patients with at least one GFR measurement available in the year before until one year after the start of dialysis were included. Characteristics at the start of dialysis of these 1143 HD and 718 PD patients are shown in Table 1.

Follow-up

Median (interquartile range) follow-up in the period of one year before and one year after the start of dialysis was 1.00 (1.00; 1.13) years. During the one year after the start of dialysis, 228 (12.3%) patients became anuric, i.e. GFR was 0 mL/min/1.73m^2 at two subsequent time points. Furthermore, 194 (10.4%) patients were censored for death, 83 (4.5%) patients for transplantation, 56 (3.0%) patients for refusal of further treatment, 20 (1.1%) patients for

recovery of renal function, and 22 (1.2%) patients for other reasons. Hence, one year after the start 1486 (79.8%) patients were still on dialysis.

Table 1. Characteristics of NECOSAD patients with at least one glomerular filtration rate (GFR) measurement in the period of one year before and one year after start of dialysis (N=1861) at start of dialysis.

	HD (N=1143)	PD (N=718)
Age *year*	63.5 (13.9)	53.5 (14.9)
Sex *% male*	59.8	66.2
Primary kidney disease *%*		
Renal vascular disease	20.6	12.8
Diabetes mellitus	14.5	14.2
Glomerulonephritis	8.6	19.1
Other	56.3	53.9
Davies comorbidity score *%*		
Low	43.0	60.3
Medium	45.9	33.4
High	11.1	6.3
Comorbidities *%*		
Cardiovascular disease [n=1704]	42.4	26.3
Diabetes mellitus* [n=1703]	23.0	19.5
Body mass index kg/m^2 [n=1852]	25.0 (4.4)	24.9 (4.8)
Systolic blood pressure *mmHg* [n=1850]	149.8 (24.2)	148.1 (23.2)
Diastolic blood pressure *mmHg* [n=1850]	80.7 (12.6)	86.3 (13.5)
GFR $mL/min/1.73m^2$ [n=1147]	4.9 (3.8)	5.7 (3.3)
Medication use *%*		
ACE Inhibitors	15.0	21.0
ARBs	4.3	7.2
B-blockers	20.1	21.3
Diuretics	20.4	20.9

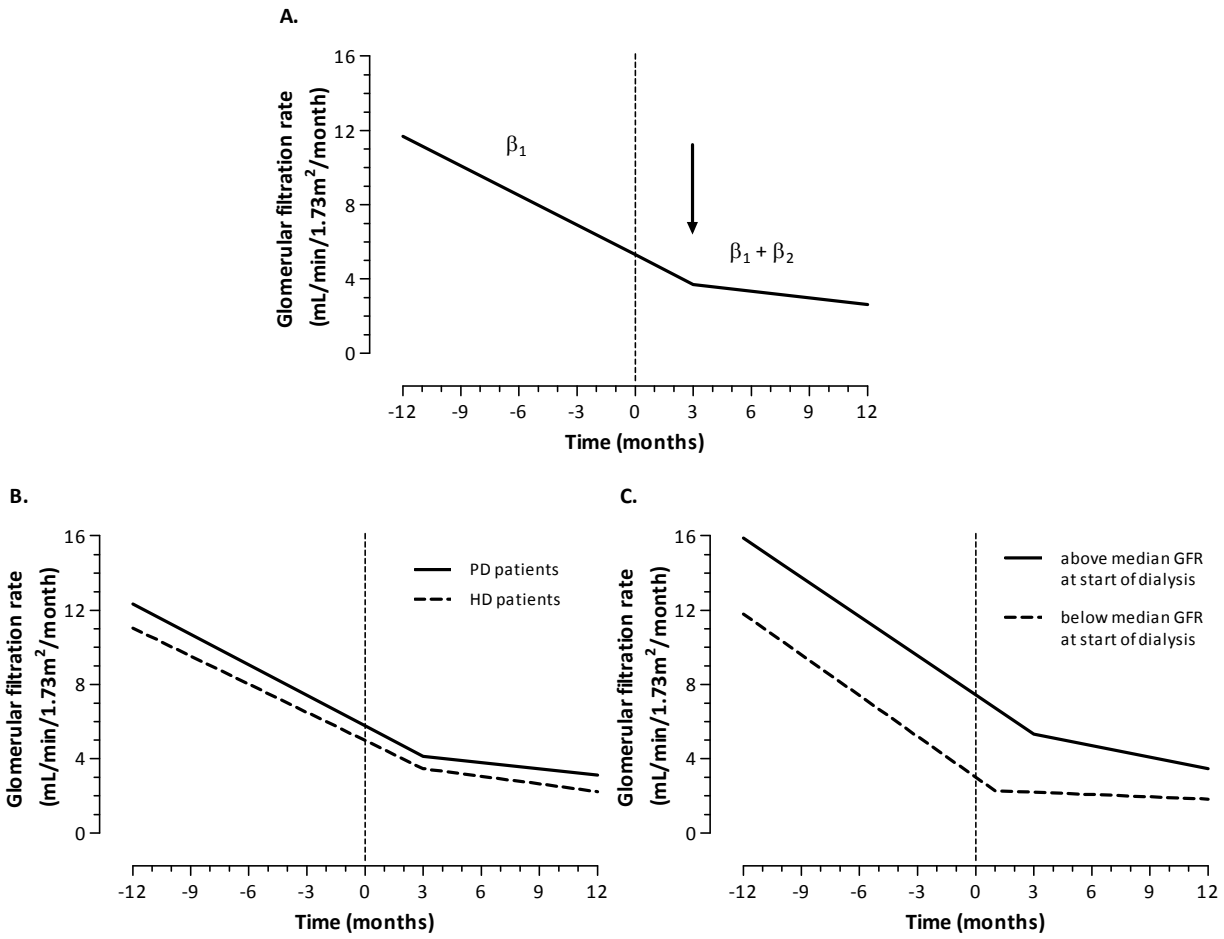
Values are given as mean (standard deviation) or percentage, as appropriate; values between square brackets indicate the number of patients for whom data were available on that particular parameter; HD, hemodialysis; PD, peritoneal dialysis; ACE: angiotensin I converting enzyme; ARB: angiotensin II receptor blocker; *including diabetes mellitus as primary kidney disease.

The best fitting models for the course of renal function

Decline of GFR was estimated using linear mixed effects models. The best fitting model to describe the course of renal function with a possible change in decline was selected based on the Akaike's Information Criterion (AIC),[15] whereby a lower AIC indicated a better model fit. The model which fitted best in all patients was the model which allowed for a change in the rate of decline three months after the start of dialysis (Figure 1A). This model was significantly better as compared to the model that fitted a constant linear decline (i.e. a model without change point). In HD and PD patients the best fitting models were the models with a change in the rate

of decline at three months after the start of dialysis (Figure 1B). In patients who started dialysis when their GFR was equal or above the median GFR level at start of dialysis, the rate of decline of renal function changed after three months of dialysis. In patients who started dialysis when their GFR level was below the median GFR level at start of dialysis, the rate of decline changed after one month of dialysis (Figure 1C).

Figure 1. Schematic representation of the course of decline of GFR before and after the start of dialysis in 1861 dialysis patients (panel A), in 1143 HD and 718 PD patients separately (panel B), and in 573 patients with GFR at start of dialysis below and 574 patients with GFR at start of dialysis equal/above the median GFR at start of dialysis (panel C). The courses of decline were estimated by linear mixed effects models adjusted for possible confounders (age, sex, primary kidney disease, cardiovascular disease, and diabetes mellitus) whereby decline attenuates a few months after the start of dialysis (change point, indicated by arrow in panel A). In these figures, population averages of the covariates were used. β_1 represents decline before the change point, $\beta_1 + \beta_2$ decline after the change point. The dashed line at 0 months indicates the start of dialysis.



Rates of decline of renal function

Estimates for the rates of decline of GFR derived from the best fitting models are shown in Table 2. It shows that the rate of decline attenuated to a slower rate after a few months of dialysis. To

investigate whether the course of decline of renal function was dependent on the level of GFR at start of dialysis, patients with an available GFR measurement at the start of dialysis (n=1147) were stratified on whether their GFR level was equal/above or below the median GFR level at start of dialysis. Both categories show attenuation to a slower rate of decline after a few months of dialysis. (Table 3)

Table 2. Course of decline of glomerular filtration rate (GFR) in 1143 hemodialysis (HD) and 718 peritoneal dialysis (PD) patients in the period of one year before until one year after the start of dialysis.

	Time[1]	Crude		Adjusted[2]	
		Decline per month (95% CI)[3]		Decline per month (95% CI)[3]	
		Before	After	Before	After
All	2 months	-0.61 (-0.67;-0.54)	-0.15 (-0.26;-0.04)	-0.62 (-0.69;-0.56)	-0.15 (-0.26;-0.05)
	3 months	-0.52 (-0.57;-0.47)	-0.12 (-0.21;-0.03)	**-0.53 (-0.58;-0.48)**	**-0.12 (-0.20;-0.04)**
	4 months	**-0.48 (-0.53;-0.43)**	**-0.05 (-0.14;0.04)**	-0.48 (-0.53;-0.44)	-0.07 (-0.16;0.01)
HD	2 months	-0.57 (-0.67;-0.47)	-0.15 (-0.32;0.02)	-0.60 (-0.69;-0.50)	-0.16 (-0.32;-0.01)
	3 months	**-0.49 (-0.57;-0.41)**	**-0.12 (-0.25;0.01)**	**-0.51 (-0.57;-0.44)**	**-0.14 (-0.26;-0.02)**
	4 months	-0.46 (-0.53;-0.39)	-0.06 (-0.20;0.08)	-0.47 (-0.53;-0.40)	-0.08 (-0.21;0.04)
PD	2 months	-0.63 (-0.71;-0.55)	-0.15 (-0.28;-0.01)	-0.64 (-0.73;-0.56)	-0.14 (-0.28;0.00)
	3 months	-0.54 (-0.61;-0.48)	-0.12 (-0.23;0.00)	**-0.55 (-0.62;-0.48)**	**-0.11 (-0.23;0.01)**
	4 months	**-0.50 (-0.56;-0.44)**	**-0.06 (-0.17;0.05)**	-0.50 (-0.56;-0.44)	-0.06 (-0.17;0.06)

Results of the best fitting models are shown in bold; [1]Timepoint (months after the start of dialysis) at which the decline per month was allowed to change; [2]Adjusted for age, sex, primary kidney disease, and comorbidities (diabetes mellitus and cardiovascular disease); [3]Decline of GFR in mL/min/1.73m^2/month in the period before and after the change point.

Table 3. Course of decline of glomerular filtration rate (GFR) in 574 patients who started dialysis when their GFR level was equal/above and in 573 patients who started dialysis when their GFR level was below the median GFR level at start of dialysis.

	Time[1]	Crude		Adjusted[2]	
		Decline (95% CI)[3]		Decline (95% CI)[3]	
		Before	After	Before	After
Above median GFR	3 months	-0.73 (-0.82;-0.64)	-0.21 (-0.37;-0.05)	-0.70 (-0.78;-0.62)	-0.21 (-0.36;-0.05)
Below median GFR	1 month	-0.75 (-0.90;-0.60)	-0.02 (-0.25;0.20)	-0.73 (-0.88;-0.58)	-0.04 (-0.27;0.19)

[1]Timepoint (months after the start of dialysis) at which the decline per month was allowed to change; [2]Adjusted for age, sex, primary kidney disease, and comorbidities (diabetes mellitus and cardiovascular disease); [3]Decline of GFR in mL/min/1.73m^2/month in the period before and after the change point.

Differences in the decline of GFR between HD and PD patients

Differences in the rate of decline of GFR between HD and PD patients were estimated using a model that allowed a change in the rate of decline after three months of dialysis. The decline of GFR before the change point was similar for PD and HD patients (mean difference: 0.004 mL/min/1.73m^2/month [95% CI -0.10; 0.11]), also after adjustment for possible confounders (mean difference 0.02 mL/min/1.73m^2/month [95% CI -0.08; 0.12]). After the change point no

difference in the unadjusted rate of decline of GFR was found between HD and PD patients (mean difference 0.03 mL/min/1.73m^2/month [95% CI -0.11; 0.18]). After adjustment for possible confounders the mean difference in decline in GFR between HD and PD patients was -0.02 mL/min/1.73m^2/month (95% CI -0.16; 0.12).

Post-hoc analyses

To investigate the robustness of the results, analyses were repeated restricted to patients with specific reasons for censoring. These analyses showed that the decline of renal function was not different in patients who died within the first year of dialysis or who were transplanted during follow-up. Furthermore, it was investigated whether the mean rate of decline of GFR was influenced by the decline in patients who became anuric during follow-up. This analysis showed that the decline of renal function in all patients was similar to the decline in patients who maintained some level of GFR and did not become anuric during follow-up.

Discussion

This large study showed that in both HD and PD patients the rate of decline of GFR is not constant, but attenuates at two to four months after the start of dialysis. Before this 'change point' the rate of decline of GFR was faster as compared to thereafter. The time of attenuation of the decline of GFR may depend on the level of GFR at the start of dialysis. No evidence was found for a faster decline of GFR in patients on HD as compared to PD; neither before, nor after the change point.

More than twenty-five years ago, a faster decline of renal function in patients on HD as compared to PD has been observed.[8] This finding has been confirmed by others[9;16;17] even with improved statistical procedures accounting for dependency among observations and informative censoring.[10;11] In contrast to the present analysis, these studies did not include the course of decline of GFR during pre-dialysis. Furthermore, many of the previous studies calculated the decline of GFR relative to the GFR at start of dialysis, without accounting for differences in GFR between HD and PD patients at start. Since GFR at start of dialysis in PD patients in general is higher as compared to HD patients, an equal amount of (absolute) decline of GFR in HD and PD patients will lead automatically to a larger relative decline of GFR in HD as compared to PD. The results of the present study show that the rate of decline of renal function in HD and PD patients is similar, although at a different level of GFR.

One study found that the decline of urea clearance in patients treated with high-flux biocompatible HD was similar to the decline in patients treated with continuous ambulatory PD.[12] It was also found that the rate of decline of urea clearance was similar before and after the start of dialysis, although a step-decline of about 2 mL/min was observed at start of dialysis. In the present analysis we did not observe a step-decline of GFR at the start of dialysis. This can be explained as follows: In the previous analysis, decline of urea clearance was estimated by fitting two separate linear regression models: one model for decline in the period preceding the start of dialysis, the other model for decline in the period after the start of dialysis. As a result, if a

difference (step-decline) in the rates of decline would have been present, it should have been observed at start of dialysis by definition. An advantage of the present analysis is that both the period before and after the start of dialysis was taken into account in the same regression model to estimate the decline of GFR.

Several methodological issues should be considered. First, there were missing GFR measurements. Restricting the analyses to complete cases might result in biased estimates. It is likely that GFR values were missing for observed reasons, i.e. missing at random. The present analyses were performed with linear mixed effects models, which are able to deal with data missing at random, without restricting the analyses to complete cases. Second, data on decline of renal function before the start of dialysis were collected retrospectively. The present results can thus (only) be generalized to patients who start dialysis. Finally, for the present analysis it was assumed that decline of renal function progresses linearly. Alternatively the decline of renal function could follow a different pattern like for example an exponential pattern. Therefore, we examined the residuals of our best fitted linear mixed effects model (i.e. the model with a change point at three months). The residuals of that model showed an approximately normal distribution. Furthermore, previous studies also observed a linear decline of estimated GFR.[18] Therefore, the assumption of linear decline seems reasonable.

A possible explanation for attenuation in the rate of decline of GFR after the start of dialysis is that the reduced decline rate of GFR might be due to the dialysis procedure itself, during which urea and creatinine are removed from the extracellular compartment. When the generation rates of both solutes would remain unaltered, their removal would result in lower plasma concentrations. As the plasma concentration is in the denominator of the clearance formula, this would result in a relatively higher value of GFR, calculated from urea and creatinine clearances. It would also imply that residual GFR calculations in dialysis patients are to some extent influenced by dialytic removal of low molecular weight solutes. When this is the case, the observed decline rate may be an artifact and the real glomerular filtration rate is not necessarily affected. Another possibility is that the start of dialysis may be accompanied with specific treatment and lifestyle changes such as changes in medication and diet. These changes may have a beneficial effect on preservation of the GFR that might get apparent only a few months after the start of dialysis.

The results of the present study show that the rate of decline of GFR decreases after a few months of PD or HD treatment. Preservation of renal function is associated with a more adequate dialysis therapy, improved quality of life, and consequently reduced morbidity and mortality, as has been shown by previous observational studies.[1-3] These studies also demonstrated that dialysis is started at a wide variety of kidney functions, indicating that other (additional) criteria are used for the decision on when to start dialysis.[19] Therefore, the debate on the advantages of an earlier start of dialysis is still going on. Recently, the results of the Initiation Dialysis Early and Late (IDEAL) Study, the first randomized controlled trial in which patients were randomly assigned to either early or late start of dialysis, have been published. The results of this trial did not show differences in the risk of mortality or adverse events

(cardiovascular events, infections or complications of dialysis) between patients with early *versus* late start of dialysis.[20] In the IDEAL study the estimated glomerular filtration levels (by the Cockroft and Gault equation) at the start of dialysis were 12.0 mL/min for the early-start group and 9.8 mL/min for the late-start group, while it was as low as 5.2 mL/min/1.73m^2 in the present study. Whether the subsequent course in decline in GFR after start of dialysis at the levels of GFR as observed in IDEAL is comparable to the present study needs to be awaited since data on decline of renal function in the IDEAL Study have not yet been published.

In conclusion, the present study shows that the rate of decline of renal function is not constant from pre-dialysis until one year after the start of dialysis, but changes after two to four months of dialysis. This pattern was observed in both dialysis modalities. The observation that the apparent decline of renal function attenuates somewhat earlier when the GFR level at start of dialysis is lower, might suggest that the attenuation in the rate of decline of renal urea and creatinine clearance depends at least partly on the level of remaining renal function. In addition, it was shown that the attenuation in the rate of decline of these parameters was not different for patients who were finally censored because of death, kidney transplantation or who did not become anuric during follow-up. Further studies are needed to examine possible explanations for the attenuation in the rate of decline of GFR after the start of dialysis.

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Disclosure

The authors have had no involvements that might raise the question of bias in the work reported, in the conclusions, implications, or opinions stated. The results presented in this paper have not been published previously in whole or in part, except in abstract format.

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