

Relative Contribution of Residual Renal Function and Different Measures of Adequacy to Survival in Hemodialysis Patients: An analysis of the Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD)-2

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Abstract. A high delivered Kt/V_{urea} (dKt/V_{urea}) is advocated in the U.S. National Kidney Foundation Dialysis Outcomes Quality Initiative guidelines on hemodialysis (HD) adequacy, irrespective of the presence of residual renal function. The contribution of treatment adequacy and residual renal function to patient survival was investigated. The Netherlands Cooperative Study on the Adequacy of Dialysis is a prospective multicenter study that includes incident ESRD patients older than 18 yr. The longitudinal data on residual renal function and dialysis adequacy of patients who were treated with HD 3 mo after the initiation of dialysis ($n = 740$) were analyzed. The mean renal Kt/V_{urea} (rKt/V_{urea}) at 3 mo was 0.7/wk (SD 0.6) and the dKt/V_{urea} at 3 mo was 2.7/wk (SD 0.8). Both components of urea clearance were associated with a better survival (for each

increase of 1/wk in rKt/V_{urea} , relative risk of death = 0.44 [$P < 0.0001$]; dKt/V_{urea} , relative risk of death = 0.76 [$P < 0.01$]). However, the effect of dKt/V_{urea} on mortality was strongly dependent on the presence of rKt/V_{urea} , low values for dKt/V_{urea} of <2.9 /wk being associated with a significantly higher mortality in anuric patients only. Furthermore, an excess of ultrafiltration in relation to interdialytic weight gain was associated with an increase in mortality independent of dKt/V_{urea} . In conclusion, residual renal clearance seems to be an important predictor of survival in HD patients, and the dKt/V_{urea} should be tuned appropriately to the presence of renal function. Further studies are required to substantiate the important role of fluid balance in HD adequacy.

The results of the National Cooperative Dialysis Study (NCDS) have led to the development of Kt/V_{urea} to quantify the dialysis dose in ESRD patients who are treated with he-

modialysis (HD) (1,2). In various studies, it was found that the Kt/V_{urea} (or the urea reduction ratio as equivalent parameter) is an important predictor of morbidity and mortality (3–9). In the National Kidney Foundation-Dialysis Outcomes Quality Initiative (NFK-DOQI) guidelines (1997), new high clearance targets in terms of delivered Kt/V_{urea} were advocated (10).

In a number of recent studies among peritoneal dialysis patients, however, it was found that a high delivered Kt/V_{urea} does not necessarily improve patient outcome and that the influence of residual renal clearance on survival is much more important (11–13). The residual renal function is probably an important predictor of outcome in HD patients as well (14,15). However, the relative contribution of residual renal Kt/V_{urea} (rKt/V_{urea}) versus delivered Kt/V_{urea} (dKt/V_{urea}) to patient outcome remains to be established for HD patients. In most studies reporting on mortality as a function of urea clearance in HD patients, it was assumed that residual renal function was negligible and only one value for the delivered Kt/V_{urea} was calculated (8,9,16). In view of the increasing emphasis on an early start during recent years, a substantial residual renal clearance may be present in HD patients, and the prescribed

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dKt/V_{urea} probably depends on the further decline in rKt/V_{urea} after initiation of renal replacement therapy (17).

Furthermore, it has been suggested that a short duration of dialysis session will lead to an overestimation of the delivered Kt/V_{urea} , an impaired control of fluid balance, and a lower clearance of the so-called middle molecules (16,18–22). These factors are not covered by the Kt/V_{urea} index but are possibly important characteristics of dialysis treatment and independent predictors of patient outcome as well.

The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) is a large, prospective, observational, multicenter cohort study in incident ESRD patients in the Netherlands. We analyzed the contribution of rKt/V_{urea} , dKt/V_{urea} , and other treatment characteristics, such as duration of treatment and ultrafiltration, to survival in HD patients. A randomized, controlled trial, such as the Hemodialysis (HEMO) Study (23), seems to be the best way to investigate the independent influence of dKt/V_{urea} in a range of high values, *i.e.*, values beyond the DOQI targets. However, examining the influence of adequacy in a range of values below the DOQI targets cannot be done in a randomized, controlled trial because of obvious ethical reasons. For this reason, observational data, when analyzed with multivariate techniques and interpreted cautiously, may yield useful information.

We hypothesized that residual renal function in the low range of values that are encountered in ESRD patients has a strong influence on outcome. Furthermore, it was hypothesized that a dKt/V_{urea} below the DOQI target may be sufficient when residual renal function is still present and that other characteristics of HD treatment may independently contribute to outcome as well.

Materials and Methods

Patients

The NECOSAD study is a multicenter, prospective, observational cohort study in which ESRD patients are consecutively included at the time of initiation of dialysis and followed at 3-mo and at 6-mo intervals until transplantation or death. All patients who are older than 18 yr and start chronic dialysis as the first renal replacement therapy are eligible. For the present analysis, we selected patients who survived the first 3 mo of dialysis and who were treated with HD at the 3-mo visit ($n = 947$) and for whom a complete data set on nutritional parameters, rKt/V_{urea} , and dKt/V_{urea} at the 3-mo visit (baseline) was available ($n = 740$). A higher mortality was found among the patients with missing data, which indicates that their exclusion was not completely at random. However, similar results were found in a sensitivity analysis in which the number of excluded patients could be substantially reduced by using recorded data from the 0-mo or 6-mo visit, whenever possible (percentage exclusion <10%; data not shown in the Results section).

Data Collection Procedures

Data on demography, primary kidney disease, and comorbidity were collected at the time of entry in the study. Data on residual renal function (rKt/V_{urea} and urine production), nutritional status, biochemistry, and dialysis characteristics (current modality, dKt/V_{urea} , ultrafiltration, duration of a treatment session, weekly number of sessions) were collected 3 mo after the initiation of dialysis (baseline visit) and at 6-mo intervals.

Primary kidney disease was classified according to the codes of the European Renal Association–Dialysis and Transplantation Association (24). On the basis of the number of comorbid conditions, a patient was classified according to the Davies' comorbidity index as having no, intermediate, or severe comorbidity (25,26).

For monitoring renal function, both urea and creatinine were measured in the urinary volume that was collected during the long interdialytic interval. For the calculation of the rKt/V_{urea} , the mean of the urea concentration in a blood sample collected immediately after the HD session that preceded this interval and the urea concentration in a sample collected before the next HD session was used. The rKt/V_{urea} was calculated as the renal urea clearance per week adjusted for the urea distribution volume (V_{urea}), which was determined according to Watson *et al.* (27) (see Appendix 1). The contribution of renal function to fluid balance was calculated as the urinary volume produced in the long interdialytic interval divided by its duration and expressed as volume per day (L/d). The single-pool Kt/V_{urea} delivered by HD (sp- dKt/V_{urea}) was estimated according to the second-generation Daugirdas formula on the basis of one plasma urea measurement before and one immediately after the dialysis session, the ultrafiltration, and the duration of the session (see Appendix 1) (10,28).

The difference between the ultrafiltration during a session and the interdialytic weight gain during the preceding interdialytic interval was calculated during a number of successive dialysis sessions and was called the "net fluid balance" for that session. Each dialysis center was requested to register for each participating patient the weight before and the weight at the end of an HD session for a maximum of eight consecutive HD sessions that preceded the session of the NECOSAD visit. An individual mean fluid balance during the weeks before a baseline or a follow-up visit was calculated and expressed as milliliters per week. By calculating such an individual mean difference from a number of successive sessions, a more stable estimate for an individual patient at the time of a NECOSAD visit was obtained. These weights before and after sessions that preceded the baseline or follow-up visits were sometimes missing. As a consequence, the number of sessions from which an average fluid balance for the weeks that preceded a NECOSAD visit could be calculated was variable. The number of calculated fluid balances included in the estimation of the weekly mean fluid balance ranged from one (two registered sessions) to eight (nine registered sessions) per patient (average, 4.5). However, the percentage of patients with only one or two registered "fluid balances" for a certain time point was small (on average 5%). A negative value for the (mean) fluid balance (ml/wk) indicates a fluid removal by HD that exceeded the interdialytic weight gain; a positive value indicates a fluid removal that was below the level required to keep the patient in balance.

The nutritional status was scored on the seven-point scale of the subjective global assessment (SGA), which is a standardized method based on the clinical judgment of the dialysis nurse (29). Albumin was assessed with the method used locally in the dialysis centers, such as a bromocresol green or a bromocresol purple assay. In a few centers, an immunonephelometric assay was used. The protein catabolic rate (nPCR) was calculated on the basis of total urea removal by dialysis, residual renal urea clearance, and protein loss in urine and was normalized to actual body weight (see Appendix 1).

Statistical Analyses

Renal versus delivered Kt/V_{urea} and patient survival. A multivariate Cox proportional-hazards model was used to examine determinants of patients' survival time, which was calculated from the 3-mo visit onward. The survival time of a participant was censored at

the time of transplantation, transfer to peritoneal dialysis, withdrawal from the study or at the end of the study period (September 1, 2002). The multivariate model contained age, Davies' comorbidity score, primary kidney disease, serum albumin, and SGA beforehand. In this way, adjustments were made for important patient characteristics that are known to influence outcome and, thus, have the potential to confound the relationships of major interest, *i.e.*, the effects of residual renal function and adequacy on survival. The rKt/V_{urea} and dKt/V_{urea} were entered as time-dependent covariates (30). This means that an event was attributed to the levels of rKt/V_{urea} and dKt/V_{urea} recorded at the preceding visit. In case of a missing value for either the rKt/V_{urea} or the dKt/V_{urea} , the value recorded at the visit before the preceding visit was included in the estimation procedure. A time-dependent Cox-regression analysis makes it possible to take into account the decline of residual renal function since baseline and the changes in dialysis dose by including in the estimation procedure all registered values for residual renal function and adequacy in the course of the patient's follow-up. The " V_{urea} " in the ratio Kt/V_{urea} is strongly associated with the body mass index (BMI), which has survival-determining properties in itself. The BMI was included as a (time-dependent) variable as well, as disregarding body size may lead to an attenuation of the estimated association between dKt/V_{urea} and mortality (8,31,32). For adjustment of comorbidity and nutritional status, the values recorded at the 3-mo visit were used in the estimation procedure, instead of values recorded at later visits. This was done to bypass the analytical problem arising from the inclusion of variables that may be intermediate factors in the causal pathway between adequacy and outcome. Variables that were not statistically significantly associated with survival were excluded from the model ("backward selection"). In a next step, interaction terms of dKt/V_{urea} -by- rKt/V_{urea} were included to investigate whether the relationship between dKt/V_{urea} and mortality was modified by the presence of residual renal function. A patient was regarded as anuric when the recorded urine output was 100 ml/d or less ($rKt/V_{urea} = 0$).

Other potentially important clinical and biochemistry parameters at baseline (systolic and diastolic BP after a dialysis session, hemoglobin, plasma phosphate, plasma calcium, and nPCR) were entered separately to examine whether the associations of interest were modified. These variables were not included beforehand, as they might be strongly associated with comorbidity, renal function, and nutritional parameters, determinants that already were included in the multivariate model. Furthermore, they may be intermediate factors in the pathway between adequacy or renal Kt/V_{urea} and outcome.

Alternative measures of HD adequacy and patient survival. The duration of the HD treatment (hr/wk), the weekly frequency of treatment session, the ultrafiltration, and the net fluid balance were added to the multivariate Cox regression model as time-dependent covariates.

All analyses were performed with SAS statistical software, version 8.0 for Windows. $P \leq 0.05$ was regarded as statistically significant.

Results

In Table 1, the baseline characteristics of the 740 included patients are shown. The majority of patients were older than 60 yr. The mean age was 62.3 yr (SD 13.9). Diabetes and renal vascular disease were often recorded as the primary cause of the renal disease. The majority of patients were in a comparatively favorable nutritional status, as assessed by means of the SGA (score 6 or 7).

In Table 2, the characteristics of HD treatment and the residual renal function in the course of follow-up are shown.

Table 1. Patient characteristics at baseline^a

	n or Mean	% or SD
Age (yr; n [%])		
<45	89	12.0
45 to 60	185	25.0
60 to 70	203	27.4
>70	263	35.5
Gender (n [%])		
male	425	57.4
female	315	42.6
Primary kidney disease (n [%])		
Diabetes	111	15.0
Glomerulonephritis	76	10.3
Renal vascular cause	157	21.2
All other	396	53.5
Davies' comorbidity score (n [%])		
no	296	40.0
intermediate	361	48.8
high	83	11.2
SGA score (n [%])		
≤4	108	14.6
5	138	18.7
6	282	38.1
7	212	28.7
No. of patients treated with EPO (n [%])	669	90.4
Albumin (g/dl ^b ; mean [SD])	3.66	0.48
Hemoglobin (g/dl ^b)	10.7	1.4
BMI (kg/m ²)	24.6	4.5
nPCR (g/kg per d)	1.00	0.23
Calcium (mg/dl) ^c	9.36	1.0
Phosphorus (mg/dl) ^d	5.85	1.76
Systolic BP (mmHg, before/after session)	154/142	21/21
Diastolic BP (mmHg, before/after session)	82/78	11/11

^a EPO, erythropoietin; BMI, body mass index; nPNA, nPCR, normalized protein catabolic rate.

^b To convert from g/dl to g/L, multiply by 10.

^c To convert from g/dl to mmol/L, multiply by 0.25; to mEq/L, multiply by 0.5.

^d To convert from g/dl to mmol/L, multiply by 0.323.

The rKt/V_{urea} declined from 0.70/wk at the 3-mo visit (baseline) to 0.32/wk at the 36-mo visit. A tendency toward a higher weekly number of HD sessions and treatment hours and a higher mean $sp-dKt/V_{urea}$ was observed alongside the decline in rKt/V_{urea} . Both the mean interdialytic weight gain and the mean fluid removal by dialysis (ultrafiltration) increased during follow-up, and no trend in the mean difference between interdialytic weight gain and ultrafiltration (the mean net fluid balance) was found. However, huge ranges of values for the net fluid balance around the mean were observed, which indicates that for a number of patients, the ultrafiltration was in excess or too low in comparison with the interdialytic weight gain.

Table 2. Follow-up data on residual renal function and adequacy measures

	Visit								
	3 Month	6 Month	12 Month	18 Month	24 Month	30 Month	36 Month		
No. of patients at risk	740	696	571	476	372	299	233		
No. of patients with data on adequacy (dialysis Kt/V _{urea})	740	636	522	405	321	251	195		
Dialysis sp-Kt/V _{urea} (/wk)	2.72	2.96	3.19	3.37	3.50	3.53	3.59		
coefficient of variation (%) ^b	30	28	29	24	24	24	22.3		
Renal Kt/V _{urea} (/wk)	0.70	0.61	0.48	0.43	0.34	0.32	0.32		
coefficient of variation (%)	83	101	104	114	136	130	172		
Prevalence of anuric patients (%)	11.5	18.6	25.5	35.1	44.5	52.2	58.1		
Mean no. of weekly hours of HD ^a	9.3	9.6	10.0	10.4	10.7	10.8	11.0		
5 to 95% percentiles	6–12	6–12	7–12	7–12	8–13.5	8–13.5	8–13.5		
HD frequency: ≥3 versus ≤2 (/wk; %)	57	62	68	75	79	80	82		
Interdialytic weight gain (ml/wk)	3,756	4,108	4,542	4,950	5,585	5,375	5,481		
coefficient of variation (%)	78	66	64	63	50	46	51		
Ultrafiltration (ml/wk)	3,756	4,147	4,550	4,940	5,505	5,410	5,539		
coefficient of variation (%)	78	66	63	63	49	44	50		
Net fluid balance (ml/wk) ^c	0	-40	-8	+10	+80	-36	-58		
5 to 95% percentiles	-800–+800	-750–+700	-625–+600	-550–+700	-450–+800	-1000–+700	-1000–+800		

^a HD, hemodialysis.

^b Coefficient of variation = SD/mean * 100%.

^c Net fluid balance = mean [interdialytic weight gain – ultrafiltration], expressed in ml/wk.

The median follow-up was 1.7 yr (5 to 95%; range, 0.21 to 4.5 yr). A total of 238 of the 740 patients died during follow-up. A total of 109 patients received a transplant and were censored at the time of transplantation. Thirty patients were transferred to peritoneal dialysis during follow-up and were censored 60 d thereafter. The survival times of the other patients were censored at September 1, 2002 ($n = 288$), or at the time of withdrawal ($n = 75$). The 2-yr patient survival was 73.0%; the 2-yr technique survival (*i.e.*, time until transfer to peritoneal dialysis) was 96% (Kaplan Meier-product-limit survival estimates).

Adjusted effects of renal Kt/V_{urea} versus delivered Kt/V_{urea} on survival

Both a higher rKt/V_{urea} and a higher $sp-dKt/V_{urea}$ were independently and significantly associated with a better survival (Table 3). Serum albumin at baseline was not independently associated with mortality. A significant effect of albumin on mortality was found when BMI and SGA were removed from the model ($0.97; P < 0.05$). This points to the fact that albumin is associated with these nutritional parameters, and power is lost by including closely related variables in the same multivariate model. The magnitude of the estimated relative risk of death (RR) associated with the rKt/V_{urea} and the one associated with the dKt/V_{urea} are hard to compare with each other in absolute terms. However, in statistical terms, the effect of rKt/V_{urea} seemed to be stronger than the effect of $sp-dKt/V_{urea}$ ($P < 0.0001$ versus $P = 0.0035$). The finding that the effect of rKt/V_{urea} on survival was present, whether the $sp-dKt/V_{urea}$ was included in the multivariate model or not, supported this. Conversely, the favorable effect of $sp-dKt/V_{urea}$

became apparent only when adjusting for the influence of rKt/V_{urea} . Similar results for rKt/V_{urea} and dKt/V_{urea} were obtained when SGA and serum albumin were also included as time-dependent variables.

The effect of $sp-dKt/V_{urea}$ on survival became only marginally less when the BMI was removed from the model (RR = 0.79, $P = 0.0080$). This means that the survival-predicting properties of V_{urea} itself did not confound the relationship between dKt/V_{urea} and outcome. Similar results were found when the equilibrated dKt/V_{urea} (see Appendix 1) was used instead of the $sp-dKt/V_{urea}$ or when excluding those values of dKt/V_{urea} for which the simultaneously measured rKt/V_{urea} to match was missing (*e.g.*, at 12 mo, $n = 68$; at 18 mo, $n = 74$). Furthermore, the observed effects of rKt/V_{urea} and dKt/V_{urea} on mortality were not substantially modified by inclusion of systolic BP, diastolic BP, hemoglobin, plasma calcium, plasma phosphate concentration, or nPCR at baseline.

The effect of delivered Kt/V_{urea} on mortality became only slightly less pronounced when the patients in whom the time lag between death and preceding visit was 30 d or less were excluded (RR = 0.79, $P = 0.0221$; data not in Table 3). This indicates that lessening the treatment intensity for reasons of convenience in patients who were dying and for whom every hope was given up by the nephrologist did not explain the higher risk of death associated with lower doses.

Effect of delivered Kt/V_{urea} by subcategories of renal Kt/V_{urea}

In Figure 1, the adjusted effect of $sp-dKt/V_{urea}$ (categorized in the quintiles as defined at the 3-mo visit) is shown by

Table 3. Multivariate Cox regression model on patient survival

	Adjusted Relative Risks of Death ($n = 740/238$ Death Events)		
	RR	95% CI	P Value
Age at entry (yr)	1.03	1.02 to 1.05	<0.0001
Male gender	0.84	0.64 to 1.10	0.2098
Davies' comorbidity score at entry			
high	4.74	3.04 to 7.40	<0.0001
intermediate	2.35	1.63 to 3.39	
low	1.00 ref		
Primary kidney disease			0.0855
diabetes	1.43	0.98 to 2.09	
glomerulonephritis	0.67	0.38 to 1.20	
renal vascular disease	1.18	0.86 to 1.62	
others	1.00 ref		
Albumin baseline (for each 0.1 g/dl increase) ^b	0.98	0.95 to 1.01	0.1355
SGA (scale 1–7) at baseline	0.89	0.80 to 0.99	0.0389
BMI (kg/m^2)	0.96	0.93 to 0.99	0.0252
Residual rKt/V_{urea} (/wk)	0.44	0.30 to 0.65	<0.0001
Dialysis $sp-dKt/V_{urea}$ (/wk)	0.76	0.64 to 0.92	0.0035

^a The residual renal function (rKt/V_{urea}) and dose of dialysis ($sp-dKt/V_{urea}$) were included as time-dependent variables. RR, relative risk; CI, confidence interval.

^b To convert albumin in g/dl to g/L, multiply by 10.

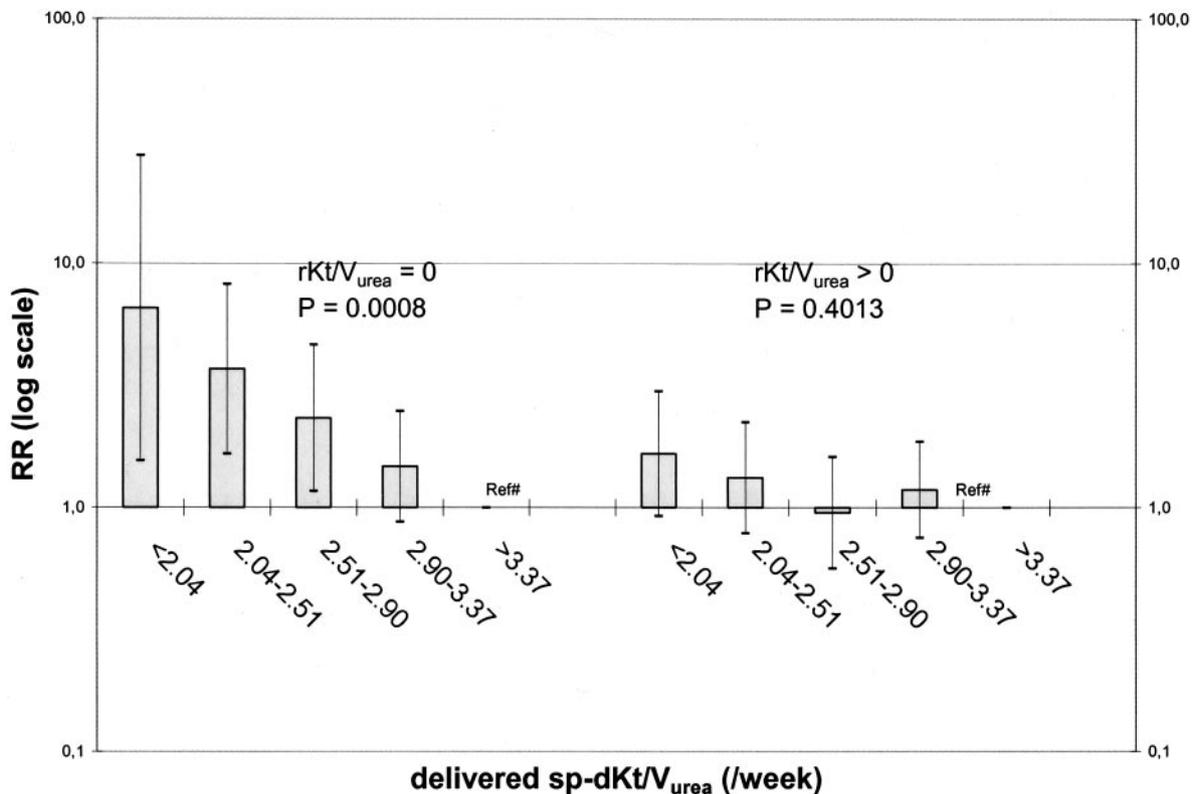


Figure 1. The effect of single-pool Kt/V_{urea} (sp-dKt/V_{urea}) on mortality by presence of residual renal function (rKt/V_{urea} = 0 [“anuric”] versus rKt/V_{urea} > 0). The rKt/V_{urea} and sp-dKt/V_{urea} were included as time-dependent variables. The relative risks are adjusted for age, Davies’ comorbidity score, primary kidney disease, subjective global assessment, and body mass index.

Table 4. Multivariate Cox regression models with residual renal Kt/V_{urea}, delivered Kt/V_{urea}, and the net fluid balance as independent predictors of survival^a

	Adjusted RR		
	RR	95% CI	P Value
rKt/V _{urea} (/wk)			<0.0001
0	17.66	4.98 to 62.61	
>0 to 0.84	1.67	1.06 to 2.64	
>0.84	1.0 ref		
sp-dKt/V _{urea} (/wk)			
if rKt/V _{urea} = 0	0.54	0.40 to 0.72	<0.0001
if rKt/V _{urea} > 0	0.90	0.72 to 1.12	0.3395
Net fluid balance (ml/wk) ^b			0.0021
≤ -300	2.17	1.46 to 3.22	
> -300 to ≤ -50	1.24	0.82 to 1.86	
> -50 to ≤ 67	1.00 ref		
> 67 to ≤ 300	1.31	0.85 to 2.00	
> 300	1.35	0.88 to 2.07	

^a The shown RR are adjusted for age, Davies’ comorbidity score, primary kidney disease, SGA, and BMI. The rKt/V_{urea}, the dKt/V_{urea}, and the net fluid balance were entered as time-dependent variables.

^b A negative value indicates an excessive ultrafiltration; a positive value indicates an ultrafiltration that is too low in comparison with the interdialytic weight gain.

presence of residual renal function. The RR that are shown all were estimated in one multivariate model, *i.e.*, terms of interaction between residual function and delivered Kt/V_{urea} were included.

Among anuric patients, a consistent decrease in mortality with higher levels of dKt/V_{urea} was found (overall *P* = 0.0008). The mortality figures associated with the three lowest dKt/V_{urea} quintiles (dKt/V_{urea} < 2.90/wk) were significantly higher than the mortality figure for the highest quintile (dKt/V_{urea} > 3.37/wk). Conversely, among patients with residual renal function, as defined by a urine output of at least 100 ml/d, the effect of dKt/V_{urea} was less pronounced. The mortality associated with the lowest dKt/V_{urea} quintile (dKt/V_{urea} < 2.04/wk) was borderline significantly higher than the mortality associated with the highest dKt/V_{urea} quintile (RR = 1.66, *P* = 0.0891). Among these patients, no significant survival benefit at higher levels of dKt/V_{urea} was found (overall *P* = 0.4013).

The strong influence of delivered Kt/V_{urea} on mortality among anuric patients was also found when the patients in whom the time lag between death and preceding visit was 30 d or less were excluded (for each increase of 1/wk, the RR was 0.57, *P* = 0.0005, data not in Table 4).

Delivered Kt/V_{urea} versus alternative measures of HD adequacy

The weekly number of treatment hours, the weekly frequency of dialysis sessions, and the ultrafiltration did not

contribute significantly to the prediction of patient survival, irrespective of inclusion of the $sp\text{-Kt}/V_{\text{urea}}$ in the multivariate model (P values ranged from 0.1315 to 0.9400; data not shown).

The difference between the interdialytic weight gain and ultrafiltration (*i.e.*, the net fluid balance) was significantly associated with mortality (Table 4). The mortality associated with the lowest quintile for the net fluid balance (<-300 ml/wk, *i.e.*, an excess of ultrafiltration) was significantly higher than the mortality associated with the intermediate quintile (*i.e.*, when the net fluid balance ≈ 0). The mortality rates associated with the other quintiles were not significantly higher than the mortality rate in the intermediate quintile ($P > 0.17$). However, a U-shape relationship between the fluid balance and mortality was suggested.

The unfavorable association of excessive ultrafiltration became slightly less pronounced (RR = 1.94, 95% confidence interval, 1.29 to 2.86) when SGA was included as a time-dependent covariate, which, as such, may be regarded as a marker of short-term deterioration of clinical condition. However, the relationship between fluid balance and mortality was still present and statistically significant ($P = 0.0211$ overall test, data not shown). Similar results for residual renal function, dKt/V_{urea} , and fluid balance were found when urine output was included as a measure of residual renal function, instead of rKt/V_{urea} . This finding indicates that urine output, like renal Kt/V_{urea} , reflects residual renal function, whereas, “net fluid balance” reflects a “concerted action” of fluid intake, ultrafiltration, and urine output and as such may be an independent component of adequacy.

Discussion

In the present study, the effects of residual renal function and dialysis adequacy on mortality in chronic HD patients were investigated. The prospective study design made it possible to take into account the decline of residual renal function and the related change in dialysis intensity in the course of follow-up. Both a higher rKt/V_{urea} and a higher dKt/V_{urea} were significantly and independently associated with a lower mortality. However, the beneficial effect of a higher dKt/V_{urea} on survival was more pronounced when residual renal function was absent. Furthermore, patient’s fluid balance was associated with survival independent of urea clearance.

Our finding of a positive association between delivered urea clearance and patient outcome confirms many other studies (3–9). However, the existence of and the definition of the threshold dKt/V_{urea} level beyond which there is no further benefit in patient outcome remains a matter of debate. In the secondary analysis of the NCDS data by Gotch and Sargent (2), the well-known step function between Kt/V_{urea} and outcome was demonstrated. A delivered $Kt/V_{\text{urea}} < 0.8$ /session in a thrice-weekly schedule was associated with a higher morbidity, whereas an increase in the range 0.9 to 1.5/session did not lead to a further improvement in patient outcome. Other studies thereafter indicated higher threshold values for the delivered Kt/V_{urea} (3,7,16). For example, Gotch *et al.* (16), using data from two large U.S. databases, found a steep decline in mor-

tality when the dialysis dose was increased up to an equilibrated Kt/V_{urea} of 1.05/session (which is approximately similar to a single-pool Kt/V_{urea} of 1.2/session and a urea reduction ratio of 65%). No further survival benefit could be established at higher doses. Different groups of patients may have differential sensitivity to the HD dose, and, as patients with demographic and clinical characteristics similar to a great part of later ESRD populations were not eligible for inclusion in the NCDS, this may explain differences in results on the dose–response relationship between adequacy and outcome (1,33,34). In other studies, the presence of a step function of patient outcome in relation to dose was questioned and a continuous dose–outcome association was suggested (9,33). In the recent study of Port *et al.* (9), a survival benefit in patients who were treated with a $sp\text{-Kt}/V_{\text{urea}} > 1.7$ /session could be established. Blood sampling within 1 min after dialysis and the use of high-efficiency or high-flux membranes lead to a higher urea rebound, which may hamper the comparison of results from recent studies with those from older studies (16,35). Furthermore, disregarding body size in survival analysis may lead to a flatter correlation between dose and outcome, which may wrongly suggest that no further improvement in patient outcome is present at higher doses (8,9).

The striking new observation in our study, which goes beyond previous reports, is that the relationship between delivered clearance and mortality is modified by the presence of residual renal function. In anuric patients, values for the $sp\text{-dKt}/V_{\text{urea}}$ in the range of low values of < 2.90 /wk were significantly associated with a higher mortality, and a consistent relationship between dose and outcome was found. No significant improvement in patient survival could be established in the Kt/V_{urea} range 2.90 to 3.40 *versus* > 3.4 /wk (Figure 1). Because a safety margin should always be used, the present NECOSAD data support the recommended Kt/V_{urea} of 3.6/wk by DOQI for patients without residual renal clearance. Furthermore, the observed relationship between dose and outcome might have been attenuated in our observational study design, especially in the range of higher Kt/V_{urea} values, as a more intense dialysis treatment may be prescribed to patients with a less favorable clinical condition and a higher risk of death. For this reason, other data are required to establish definitely whether a further improvement may be expected at doses higher than those recommended by the current U.S. guidelines. The primary results from the randomized controlled HEMO Study indicate no improvement of patient outcome at higher doses of dialysis in the range of 3.9 to 5.1 weekly $sp\text{-Kt}/V_{\text{urea}}$ (23). Patients with a residual renal clearance of 1.5 ml/min per 35 L ($rKt/V_{\text{urea}} = 0.43$ /wk) and higher were excluded from the HEMO study, which resulted in a minority of participants with some residual renal function at the time of randomization. As the distribution of values around the mean delivered urea clearance in both the experimental and the control groups was small, the HEMO study and the present NECOSAD analysis may be regarded as complementary to each other, as the influence of Kt/V_{urea} was explored in different dose ranges.

In patients with some residual renal function, only values for the $sp\text{-dKt}/V_{\text{urea}}$ in the lowest quintile range of < 2.04 /wk were

weakly associated with a higher mortality, but no consistent trend toward improvement in patient outcome at doses higher than 2.04/wk was observed. These results indicate that the threshold value for dKt/V_{urea} above which no further improvement in patient outcome may be expected is lower for patients with residual renal function, which is intuitively intelligible as the aim of dialysis treatment is to compensate for the loss of renal function. The observed strong and beneficial influence of residual renal function, even in the low range of values of ESRD patients, indicates that in prescribing dKt/V_{urea} , presence of residual renal function should be taken into account. This finding is probably important, especially in view of the trend toward an earlier initiation of dialysis treatment (17). This trend may be diminished in view of the results of recent studies that indicate that starting dialysis with a comparatively high residual renal function is not associated with a better survival (36,37). Our finding of a lessened benefit of dialysis dose with higher residual function may be regarded as supportive of these results.

The present NECOSAD analysis did not indicate that treatment duration itself may contribute to patient survival, which is in accordance with some other reports (1–3,7,33). However, an important drawback of the observational NECOSAD study is the restriction to treatment characteristics that are usually present in current dialysis practice. In the study of Charra *et al.* (19,20) in Tassin, France, an excellent survival was reported for a group of HD patients who were treated with a very long duration of dialysis (8 hr/session in a thrice-weekly schedule), which resulted in a high $eq\text{-}dKt/V_{\text{urea}}$ of 1.6/session. The data from Tassin have been widely quoted to support the hypothesis that a longer treatment duration is associated with a better outcome as a result of a better removal of the uremic toxins with a larger molecular weight and a better fluid balance control. However, the question on the independent effect of duration remains unresolved, as a study is needed in which the effect of high treatment duration is examined with urea clearance held constant and differences in case-mix are taken into account (16). A beneficial effect associated with an extreme long treatment time may be present, and this possibility does not contradict the absence of an effect in the range of treatment times used in our study (38).

The present NECOSAD study supports the notion that the fluid balance is an important characteristic of HD treatment and a predictor of mortality, which is operative independent of urea clearance. A U-shape relationship between the fluid balance and mortality was suggested and might be expected, as the amount of ultrafiltration has to match the interdialytic weight gain caused by failing of renal function. A fluid removal that is too much in comparison with the interdialytic weight gain seemed to be significantly associated with a higher mortality. Our findings concerning the fluid balance have to be interpreted with caution and require substantiation from other studies. A negative or positive fluid balance, as measured during a small number of consecutive dialysis sessions, probably cannot be representative for a longer period of months or years, as an unimaginable fluid disbalance would inevitably ensue. Measurements of dialysis adequacy were done when the

patient was clinically stable, but this does not preclude small variations in fluid balance that might be harmful to the patient. A temporary excess of ultrafiltration might be a serious threat to the cardiovascular system or residual renal function and lead to a short-term increase in death rate, as was searched for in our time-dependent Cox regression analysis. The relationship between net fluid balance and mortality was not substantially modified by inclusion of SGA as time-dependent variable, *i.e.*, when adjustments for a short-term deterioration of clinical condition as a possible motive for a well-intentioned excessive ultrafiltration were made. However, although adjustments for comorbidity and residual renal function were made in the multivariate model, we cannot exclude the possibility that the association between excessive ultrafiltration and patient death was due to the presence of patients with heart failure with a tendency to fluid overload. These patients might have been at increased risk of death as a result of their underlying cardiovascular problems and not because of the excessive ultrafiltration as well-intentioned treatment of their fluid overload. In addition, for other patients, an intentional excessive ultrafiltration may have followed a period of insidious growing fluid overload as a result of a chronic shortcoming ultrafiltration, which might have been the cause of the increased risk of death. The conclusion that close monitoring of the fluid balance is an important adequacy measure would still hold, anyway.

In conclusion, the presented NECOSAD data indicate that presence of residual renal clearance is an important predictor of survival in HD patients and that the dKt/V_{urea} should be tuned appropriately to the presence of residual renal function. In addition, our data suggest that close monitoring of the fluid balance is a measure of dialysis adequacy as well. However, further studies are required to substantiate the important role of fluid balance in HD adequacy.

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Appendix 1: Formulas

Formula for renal Kt/V_{urea} (rKt/V_{urea}):

$$\text{gfr}_{\text{ure}} = [\text{URE}/[(\text{Ct} + \text{Cc})/2]] * [1000/1440]$$

gfr_{ure} = renal urea clearance (in ml/min)

URE = urea output in interdialytic urine collection (mmol/d)

Ct = plasma concentration of urea at the beginning of interdialytic interval, *i.e.*, after the dialysis session of the NECOSAD visit (mmol/L)

C_c = plasma concentration of urea at the end of interdialytic interval, *i.e.*, before next dialysis session (mmol/L)

$$rKt/V_{\text{urea}}(/wk) = [gfr_{\text{urea}} * 1440 * 7] / [v * 1000]$$

v = urea distribution volume (in L), calculated according to Watson *et al.*:

$$\text{male: } v = 2.447 - 0.09516 * \text{age} + 0.1074 * \text{length} + 0.3362 * \text{weight}$$

$$\text{female: } v = -2.097 + 0.1069 * \text{length} + 0.2466 * \text{weight}$$

NB. Weight (in kg) was measured after the hemodialysis session of the NECOSAD visit.

Formula for single-pool Kt/V_{urea} delivered by dialysis (sp-d Kt/V_{urea}):

$$ktv_{hd} = -\ln\left[\frac{C_t}{C_o}\right] - [0.008 * t] + \left[\frac{4 - 3.5 * C_t/C_o}{UF * 0.58/v}\right]$$

ktv_{hd} = single-pool Kt/V_{urea} per HD session

C_o = plasma concentration of urea before session (mmol/L)

t = treatment time in hours

UF = ultrafiltration (in L), *i.e.*, weight before dialysis session minus weight after dialysis session of NECOSAD visit

$$sp-dKt/V_{\text{urea}} (/wk) = ktv_{hd} * [\text{weekly frequency of dialysis}]$$

Formula for equilibrated Kt/V_{urea} delivered by dialysis (eq-d Kt/V_{urea}):

$$eq-dKt/V_{\text{urea}} (/wk) = [sp-dKt/V_{\text{urea}} * [1 - 0.6/t] + 0.03]$$

Formula for normalized protein catabolic rate (nPCR):

$$PCR = 262 * \left[\frac{v * [C_c - C_t]}{\text{intdint}} + \frac{gfr_{\text{urea}} * [C_c + C_t]}{2000} \right] + [0.294 * v]$$

$$nPCR(\text{g/kg per d}) = PCR / [v * 0.58]$$

intdint = interdialytic interval (minutes)

urine protein = protein in urine output (g/d)

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