Longer treatment time and slower ultrafiltration in hemodialysis: Associations with reduced mortality in the DOPPS

R Saran[1], JL Bragg-Gresham[2], NW Levin[3], ZJ Twardowski[4], V Wizemann[5], A Saito[6], N Kimata[7], BW Gillespie[8], C Combe[9], J Bommer[10], T Akiba[7], DL Mapes[2], EW Young[11] and FK Port[2]

[1]Division of Nephrology and Kidney Epidemiology and Cost Center, University of Michigan, Ann Arbor, Michigan, USA; [2]University Renal Research and Education Association (URREA), Ann Arbor, Michigan, USA; [3]Renal Research Institute, New York, New York, USA; [4]Division of Nephrology, Department of Medicine, University of Missouri, Columbia, Missouri, USA; [5]Georg Haas Dialysezentrum, Giessen, Germany; [6]Tokai University School of Medicine, Isehara, Kanagawa, Japan; [7]Division of Blood Purification, Kidney Center, Tokyo Women's Medical University, Tokyo, Japan; [8]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA; [9]Département de Néphrologie, Centre Hospitalier Universitaire de Boredeaux and Université Victor Segalen Bordeaux , Bordeaux, France; [10]University of Heidelberg, Heidelberg, Germany and [11]Department of Veterans Affairs Medical Center, and Division of Nephrology, University of Michigan, Ann Arbor, Michigan, USA

Longer treatment time (TT) and slower ultrafiltration rate (UFR) are considered advantageous for hemodialysis (HD) patients. The study included 22 000 HD patients from seven countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS). Logistic regression was used to study predictors of TT > 240 min and UFR > 10 ml/h/kg bodyweight. Cox regression was used for survival analyses. Statistical adjustments were made for patient demographics, comorbidities, dose of dialysis (*Kt/V*), and body size. Europe and Japan had significantly longer ($P < 0.0001$) average TT than the US (232 and 244 min vs 211 in DOPPS I; 235 and 240 min vs 221 in DOPPS II). *Kt/V* increased concomitantly with TT in all three regions with the largest absolute difference observed in Japan. TT > 240 min was independently associated with significantly lower relative risk (RR) of mortality (RR = 0.81; $P = 0.0005$). Every 30 min longer on HD was associated with a 7% lower RR of mortality (RR = 0.93; $P < 0.0001$). The RR reduction with longer TT was greatest in Japan. A synergistic interaction occurred between *Kt/V* and TT ($P = 0.007$) toward mortality reduction. UFR > 10 ml/h/kg was associated with higher odds of intradialytic hypotension (odds ratio = 1.30; $P = 0.045$) and a higher risk of mortality (RR = 1.09; $P = 0.02$). Longer TT and higher *Kt/V* were independently as well as synergistically associated with lower mortality. Rapid UFR during HD was also associated with higher mortality risk. These results warrant a randomized clinical trial of longer dialysis sessions in thrice-weekly HD.

Correspondence: *R Saran, Division of Nephrology, Kidney Epidemiology and Cost Center, University of Michigan, 315 W. Huron, Suite 240, Ann Arbor, Michigan 48103-4262, USA. E-mail: rsaran@umich.edu*

Received 30 September 2005; revised 3 November 2005; accepted 16 November 2005; published online 15 February 2006

Kidney International (2006) **69,** 1222–1228. doi:10.1038/sj.ki.5000186; published online 15 February 2006

KEYWORDS: dialysis dose; dialysis session length; intradialytic hypotension; urea kinetic modeling; interdialytic weight gain; outcomes research

Hemodialysis (HD) patients continue to experience high mortality rates.[1] Several studies have suggested that longer duration of HD sessions is associated with a survival advantage.[2–6] A recent US study, however, failed to confirm this relationship.[7] Potentially, long, slow dialysis sessions may result in improved middle molecular clearance and better blood pressure and volume control, particularly if high-flux dialysis membranes are used.[8,9] The National Cooperative Dialysis Study suggested a survival advantage with longer treatment times.[10,11] This *clinically* important trend failed to capture the attention of the nephrology community, perhaps because of its *P*-value of 0.06. The recently completed Hemodialysis (HEMO) Study focused on dialysis dose as measured by urea kinetics (*Kt/V*) and membrane flux,[12] rather than the length of dialysis treatments.

Excessive interdialytic weight gain has been shown to be an independent predictor of mortality in a number of observational studies.[13,14] Although higher interdialytic weight gain is associated with better nutritional indices, it predisposes to volume overload, which causes abnormal ventricular remodeling resulting in heart failure.[15–17] Those with excessive interdialytic weight gain tend to receive a higher ultrafiltration rate (UFR) (i.e., rate of volume removal during HD), potentially resulting in increased frequency of intradialytic hypotension (IDH). IDH in turn could result in altered sensorium, myocardial ischemia and infarction, blindness, and even stroke.[18,19] Although it is not entirely clear that recurrent IDH is associated with higher mortality,[20]

it is plausible that a lower UFR would decrease its incidence and severity, thereby reducing the potential for recurrent hypotensive injury to vital organs.

This study examines the relationship between treatment time (TT) and UFR with patient outcomes in the Dialysis Outcomes and Practice Patterns Study (DOPPS), an international, prospective cohort study of HD patients and facilities.

RESULTS

Distribution of TT and UFR

Average facility TT was normally distributed across the DOPPS regions with the mean and median at 228 and 229 min, respectively (Figure 1a). Approximately half the patients were receiving a TT of 211–240 min (3.5–4 h), whereas 27.1% had TT > 240 min and 22.2% had TT < 211 min. Table 1 shows the average (±s.d.) TT in DOPPS I and II in each region at the patient level. In both DOPPS I and DOPPS II, mean TTs for Japan and Europe were significantly longer than those in the US after accounting for facility clustering effects. TT in the US increased significantly between DOPPS I and DOPPS II – from 211 to 221 min – whereas there was no significant change in mean TT in the other DOPPS regions.

Overall, the mean UFR was 8.9 ml/h/kg, whereas the median value was 9.0 ml/h/kg (Figure 1b). In DOPPS I, the average UFR was significantly lower in Japan and Europe than in the US (Table 1). In Japan, this rate increased significantly ($P<0.05$), from 8.2 in DOPPS I to 9.9±3.6 in DOPPS II.

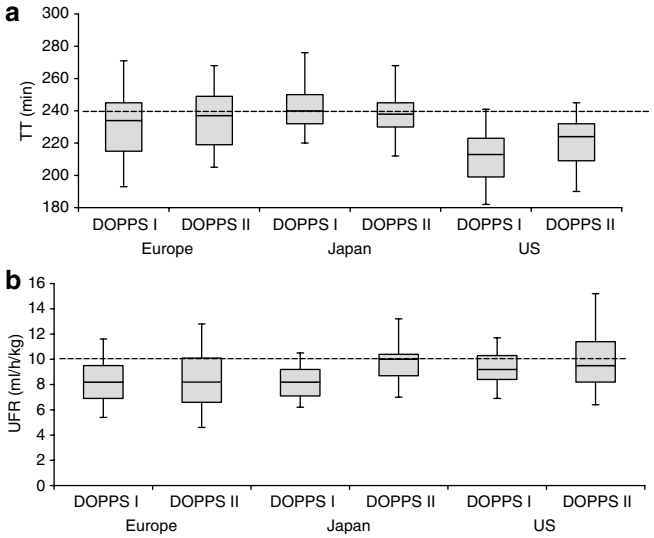

Figure 1 | (a) Distribution of facility mean TT, by region and phase of DOPPS (*n*=546 facilities). (**b**) Distribution of facility mean UFR, by region and phase of DOPPS ($n=531$ facilities).

Table 1 | Average (±s.d.) treatment time (TT) and ultrafiltration rate (UFR) by region and phase of study for a prevalent cross-section of patients[a]

	DOPPS I		DOPPS II	
Region	*n*	Mean	*n*	Mean
TT (min)				
Europe	2590	232[b]±41	2856	235[b]±38
Japan	2169	244[b]±32	1805	240[b]±33
US	3856	211±32	2260	221[c]±33
UFR (ml/h/kg)				
Europe	2590	8.3[b]±3.6	2856	8.4[b]±3.5
Japan	2169	8.2[b]±3.5	1805	9.9[c]±3.6
US	3856	9.2±3.9	2260	9.8±3.7

[a]Accounts for facility clustering.
[b]$P<0.05$ vs US within phase.
[c]$P<0.05$ comparing DOPPS II to DOPPS I within each country.

Relationship of TT and *Kt/V*

The mean (±s.d.) *Kt/V* values in Japan, Europe, and the US were 1.34±0.26, 1.36±0.25, and 1.41±0.26, respectively. The corresponding 10–90th percentile ranges were 1.03–1.67, 1.09–1.70, and 1.13–1.70, respectively. The mean *Kt/V* values at four different TT values (180, 210, 240, and 270 min) were examined by region. In Japan, the *Kt/V* values were 1.16±0.22, 1.23±0.23, 1.33±0.23, and 1.43±0.26, respectively, reflecting increasing *Kt/V* by increasing TT ($P<0.0001$). In Europe, the corresponding values were 1.29±0.25, 1.36±0.26, 1.38±0.26, and 1.36±0.21 ($P<0.0001$), respectively. In the US, they were 1.37±0.26, 1.43±0.27, 1.43±0.27, and 1.38±0.23 ($P<0.0001$), respectively. The unadjusted correlations of TT and *Kt/V* were therefore examined in each DOPPS region to assess the feasibility of testing the independent effects of each of the two variables in the Cox models. In Japan, the r^2 for the correlation was 0.14 ($P=0.0001$); in Europe it was 0.03 ($P=0.0001$); and in the US it was 0.01 ($P=0.0001$). For every 30 min longer TT, the *Kt/V* value was higher by 0.08 in Japan ($P<0.0001$), 0.03 ($P<0.0001$) in Europe, and 0.02 in the US ($P<0.0001$).

Factors associated with longer TT and higher UFR

Descriptive characteristics and statistically significant adjusted odds ratios from logistic regression models for two categories of TT (>240 min and ⩽240) and UFR (>10 and ⩽10 ml/h/kg) are shown in Table 2a and b.

Mortality risk and TT

Using TT > 240 min as the referent category, the relative risk (RR) of mortality for TT < 211 min was 1.34 ($P<0.0001$) and the RR of mortality for TT of 211–240 min was 1.19 ($P=0.01$) (Figure 2). Table 3 shows the unadjusted and adjusted RR of all-cause and cardiopulmonary mortality by TT > 240 min (vs ⩽240 min). After adjustment, TT longer than 240 min (vs ⩽240 min) was associated with a 19% lower RR of all-cause mortality ($P=0.0005$) and 16% lower RR of cardiopulmonary mortality ($P=0.03$). The differences between unadjusted and adjusted results are partly explained by the substantially younger age of patients treated with longer TT (Table 2a). Considering TT modeled as a continuous variable, for every 30 min longer dialysis session,

Table 2 | (a) Statistically significant predictors of having a treatment time >240 min (b) Statistically significant predictors of having UFR>10 ml/h/kg

(a) Statistically significant predictors of having a treatment time >240 min

Characteristic (reference for OR)	Mean or % TT>240 min (*n*=1980)	Mean or % TT⩽240 min (*n*=14 353)	OR (TT>240 vs ⩽240 min)[a]
Age (per 10 years)	56.4	62.0	0.83‡
Male (vs female)	70.1	56.1	1.59‡
Black (vs non-black)	11.4	15	1.54‡
Time on dialysis (per year)	7.2	3.56	1.07‡
Prior transplant (yes vs no)	7.8	5.4	0.58‡
Employed (yes vs no)	27.0	14.9	1.15
Disabled (yes vs no)	16.2	14.4	1.19‡
Comorbidities (yes vs no)			
Cardiac disease other than CAD or CHF	33.7	32.1	1.19‡
Diabetes	29.2	36.5	1.14†
Intradialytic weight loss >5.7% (yes vs no)	12.2	5.6	2.58‡
Height (per 1 cm)	168	165	1.02‡
Weight (per kg)	71.5	66.4	1.04‡
Kt/V (per 0.1)	1.43	1.33	1.20‡
Residual renal function (yes vs no)	15.3	23.8	0.62‡
UFR>10 ml/h/kg	27.1	36.3	0.62‡

(b) Statistically significant predictors of having UFR>10 ml/h/kg

Characteristic	Mean or % UFR>10 (*n*=5759)	Mean or % UFR⩽10 (*n*=10 599)	OR (UFR>10 vs ⩽10 ml/h/kg)[b]
Age (per 10 years)	59.9	62.0	0.91‡
Time on dialysis (per year)	4.8	3.5	1.02‡
Comorbidities (yes vs no)			
CHF	32.1	29.3	1.19‡
Cardiac disease (other than CAD or CHF)	34.3	31.2	1.12‡
Smoker	22.5	18.9	1.14†
Hypertension	77.2	76.5	1.12†
Diabetes	35.7	35.6	1.19‡
Kt/V (per 0.1)	1.4	1.31	1.06‡
Weight (per kg)	63.4	69.1	0.98‡
Intradialytic weight loss >5.7% (yes vs no)	18	0.2	79.1‡
Residual renal function (yes vs no)	17	25.9	0.68‡
TT>240 min	9.3	13.6	0.51‡
Catheter as vascular access	14.9	22.0	0.64‡

CAD, coronary artery disease; CHF, congestive heart failure; TT, treatment time; UFR, ultrafiltration rate.
†$0.01<P<0.05$. ‡$P<0.01$.
[a]OR adjusted for factors listed above and for ethnicity, 12 summary comorbid conditions, living status, marital status, depression, prior kidney transplant, catheter use as vascular access, geographical region, and DOPPS I vs DOPPS II. Accounts for facility clustering.
[b]OR adjusted for factors listed above and for sex, race, ethnicity, nine summary comorbid conditions, living status, marital status, depression, prior kidney transplant, height, geographical region, and DOPPS I vs DOPPS II. Accounts for facility clustering.

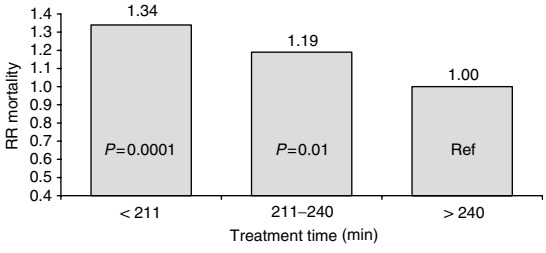

Figure 2 | RR of all-cause mortality, by TT category. The incremental RR of mortality with decreasing TT categories in all DOPPS regions combined. The referent category is TT>4 h (240 min).

the RR of mortality was 7% lower (RR=0.93; $P<0.0001$). Figure 3 displays the effect of TT in the three DOPPS regions. For every 30 min longer, the RR of mortality was 4% lower in the US (RR=0.96; $P=0.04$), 6% lower in Europe (RR was 0.94; $P=0.01$), and 16% lower in Japan (RR=0.84; $P<0.0001$).

Mortality risk and *Kt/V*

A significant relationship between *Kt/V* and RR of mortality was observed, independent of TT. For every 0.1 higher *Kt/V*, the RR of mortality was 2% lower, with ($P=0.012$) and without ($P=0.001$) adjustment for TT.

Table 3 | Associations between ultrafiltration rate (UFR) and treatment time (TT) and mortality

	UFR > 10 ml/h/kg		TT > 240 min	
Outcome	RR	*P*-value	RR	*P*-value
All-cause mortality				
Unadjusted	1.01	0.75	0.68	<0.0001
Adjusted[a]	1.09	0.02	0.81	0.0005
Cardiopulmonary mortality				
Unadjusted	1.00	0.97	0.73	<0.0001
Adjusted[a]	1.04	0.41	0.84	0.03

[a]Based on Cox regression, adjusted for: age, sex, race, ethnicity, time on dialysis, 14 summary comorbid conditions, living status, height, weight, *Kt/V*, blood flow, residual renal function, and catheter use as vascular access, TT (in UFR model), and UFR (in TT model). Stratified by geographical region and phase of study. Accounts for facility clustering.

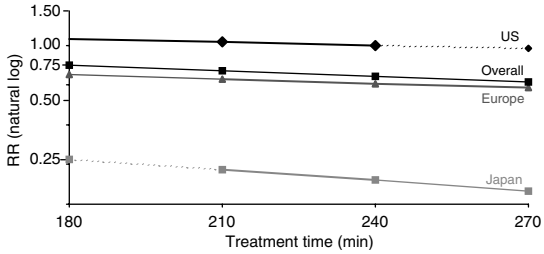

Figure 3 | RR of mortality and TT, by region. The RR of mortality (on a log scale) and TT by region (overall RR = 0.93 per 30 min ($P < 0.0001$). Although the association was statistically significant in each region, it was strongest in Japan (RR = 0.84 per 30 min; $P < 0.0001$), followed by Europe (RR = 0.94 per 30 min; $P = 0.01$) and the United States (RR = 0.96 per 30 min; $P = 0.04$). The thick solid lines represent the highest concentration of patients in each distribution (50% or more); the thin solid lines represent 10–25% of patients; the dotted lines represent the lowest concentration of patients (< 10%).

Interaction between TT and *Kt/V*

A significant interaction between *Kt/V* and TT was found in the multivariable survival models ($P = 0.007$; Figure 4). At any level of *Kt/V*, a longer TT was associated with lower RR of mortality. Furthermore, at higher levels of *Kt/V*, a longer TT was even more beneficial than the same TT for a lower level of *Kt/V*, suggesting a synergistic relationship between TT and *Kt/V* with respect to mortality risk reduction. This interaction occurred in the same direction in all regions and was not significantly different by region.

UFR, mortality risk, and intradialytic hypotension

UFR > 10 ml/h/kg was associated with an elevated risk of mortality (RR = 1.09; $P = 0.02$, with TT in the Cox model) (Table 3). However, there was no significant trend in mortality risk with lower categories of UFR. UFR > 10 ml/h/kg was significantly associated with 30% higher odds of IDH ($P = 0.045$). TT, however, was not associated with increased risk of IDH, with UFR in the model.

DISCUSSION

The main findings from this study are that, in the setting of conventional thrice-weekly HD: (1) longer HD session duration is independently associated with lower mortality, (2) a synergistic mortality-reducing interaction exists between *Kt/V* and TT (i.e., more pronounced RR reduction at higher *Kt/V* combined with longer TT), and (3) a faster rate of fluid removal at dialysis as measured by UFR > 10 ml/h/kg body weight is associated with both higher risk of mortality and increased odds of intradialytic hypotension. We also confirm prior reports from observational studies[21] that higher *Kt/V* is a significant and independent predictor of lower mortality, both with and without adjustment for TT.

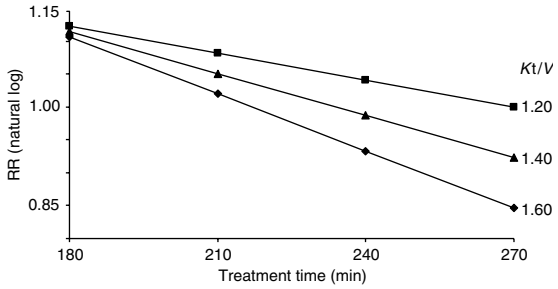

Figure 4 | Interaction between *Kt/V* and TT. The incremental RR of mortality (on a log scale) by TT (*x*-axis) for patients in three different categories of *Kt/V* (interaction $P = 0.007$), illustrating that the effect of TT is greater at higher *Kt/V*.

Many investigators have stressed the importance of prolonging TT in HD.[2,22–27] Prior observational studies have pointed to the possible significance of dialysis session length. Held *et al*[5] investigated the relationship of 3-year mortality and TT in a random sample of 600 HD patients from 36 dialysis units using low flux dialyzers only and found that TT < 3.5 h was associated with significantly higher mortality. However, that study was conducted at a time (1984–1985) when urea kinetic modeling was not widely practiced in the US. Although it adjusted for a variety of patient, provider, and geographic covariates, it did not adjust for *Kt/V* and the authors could not rule out reduced delivered *Kt/V* in the group dialyzing for shorter durations. Recent data from the Australia and New Zealand Dialysis and Transplant Registry indicate that dialysis duration of > 4.5 h may be associated with a lower RR of mortality, and duration < 3.5 h associated with a higher mortality risk.[28] Similar results have been reported from the Japanese HD registry.[6] A recent large US study was unable to demonstrate the effect of TT independent of measures of body size and small solute clearance.[7] The authors reasoned that the narrow range of TT in their cohort, reflecting the practice norm in the US, might help to explain why the independent effect of TT did not emerge in their analysis. The NIH-sponsored National Cooperative Dialysis Study that investigated urea clearance and dialysis duration in a 2 × 2 factorial design found that patients with high blood urea nitrogen and short dialysis time were hospitalized more often than the group with high blood urea nitrogen but longer dialysis.[10,11] Although this result was statistically nonsignificant ($P = 0.06$), and may have been the result of higher delivered *Kt/V* in the longer

dialysis arm, its potential clinical importance was not emphasized. The rather small sample ($n = 151$) and the premature stopping of the National Cooperative Dialysis Study may have led to the study being underpowered to demonstrate a clinically significant difference between the long and short treatment arms. A small, randomized trial of 4 vs 5 h of dialysis demonstrated better tolerability of the longer dialysis sessions but did not study long-term outcomes.[24] The experience from Tassin, France,[2] and the centers performing slow nocturnal dialysis[25] have repeatedly emphasized the importance of HD session length, reporting consistently excellent results, especially with respect to blood pressure control, reduced erythropoietin requirements, fluid management, reduced frequency of IDH, and improved quality of life. However, these times are substantially longer than those reported in our study and therefore not strictly comparable.

Longer dialysis duration may be beneficial in several ways: improved tolerability of the treatment (primarily the result of slower UFR), greater removal of uremic toxins, particularly middle molecules, better control of blood pressure, and better volume management. These mechanisms may in turn reduce cardiovascular morbidity and mortality. Longer TT is utilized in clinical practice as one of the methods to increase delivered Kt/V. This was most apparent in Japan where Kt/V was 1.16 ± 0.22 when TT was 180 min (3 h) and 1.43 ± 0.26 when TT was 270 min (4.5 h). Although there were statistically significant correlations between TT and Kt/V (strongest in Japan, but also statistically significant in Europe and the US, owing to the large sample sizes), they were not of sufficient magnitude ($r^2 = 0.14$ in Japan, and much lower in Europe and the US) to preclude examining the effect of TT on mortality independent of Kt/V. If TT and Kt/V had been highly correlated, we would not have been able to separate their independent effects in a model that adjusted for both variables. Instead, we have found both variables to be significant in the same model; furthermore, their interaction was significant. Although this does not negate the fact that longer TT increases Kt/V and could in part reduce mortality by that mechanism, it points even more importantly to the effect of TT over and above that obtained by a higher delivered Kt/V alone. Not only does it highlight the significance of TT independent of Kt/V, but it also suggests that increasing TT could further enhance the beneficial effect of a given Kt/V. Our results with respect to the association of Kt/V and survival are consistent with the direction of the effect seen in the intention to treat analysis of the HEMO Study,[12] which showed a nonsignificant risk reduction with higher dose of dialysis. Our results are consistent with results from other large observational studies (reviewed in Saran *et al.*[21]).

In our study, the association of longer TTs and lower mortality was strongest in Japan, followed by Europe and the US (Figure 3). Although the explanation for this somewhat differential gradient in the relationship by region is not entirely clear, it may be due in part to the fact that in Japan, Kt/V targets are more often achieved by prolonging TT, whereas in Europe or the US, reliance on blood flow rates and dialyzer size to achieve Kt/V targets may be more common. These pertinent issues should be examined in future analyses. Other possible explanations include: (a) the US having the fewest patients treated in dialysis sessions >4 h (8.2%); (b) the effect of longer dialysis on mortality being confounded by its selective prescription in younger men with larger body size, beyond what is captured by adjustment for height, weight, and age; and (c) non-adherence with HD as manifested by shortening and skipping treatments (both statistically significant predictors of mortality in the Cox models) being more prevalent in the US[13] than in Europe and Japan, which may result in a larger gap between prescribed and delivered dialysis dose in the US, thereby confounding the relationship between TT and mortality. Although the source of regional differences is not completely clear, the Cox model that combines data from all DOPPS stratified by region essentially pools the stratum-specific estimates. The fact that a benefit of longer TT was observed in each of three widely dispersed geographic regions, albeit with some variation in magnitude, lends credence to the demonstrated significant relationship between TT and mortality in all regions combined.

It is a common clinical observation that rapid ultrafiltration often results in IDH. A considerable body of literature deals with management of IDH, with significant advances in dialysis technology pertaining to sodium as well as online hematocrit modeling.[26,27,29–31] However, the fundamental relationship between UFR and patient outcomes has not received the attention it deserves in the HD literature. Few studies have examined the direct association of UFR on long-term outcomes in HD patients. The Netherlands Cooperative Study on the Adequacy of Dialysis recently reported the association between excessive ultrafiltration (measured as total weekly ultrafiltration) and mortality, independent of delivered Kt/V_{urea}.[32] High interdialytic weight gain, volume expansion, the economic barriers to long-duration HD, and the inherent 'unphysiology' of thrice-weekly HD all predispose patients to the necessity for higher UFR with increased frequency of IDH. The finding of significant association of UFR with both mortality and IDH provides one possible mechanism for the protective effect of longer TT, which was significantly associated with lower odds of high UFR in the logistic models (Table 2a and b).

The strengths of the present analysis are the large number of randomly selected HD patients in an international, representative sample of dialysis facilities and the ability to adjust for a variety of case-mix factors, including measures of body size and dialysis dose as measured by Kt/V, and to take into account the presence or absence of residual renal function. Stratification by geography and accounting for facility clustering are also important elements of these analyses demonstrating the differential effects of TT on mortality by region.

We recognize certain limitations of this work. It is an observational study that can only infer association and not causality. Although we have adjusted for a variety of case-mix-related factors, the possibility of residual confounding remains, especially considering the regional variation in results. The precise mechanisms for the apparent greater benefit of longer TT in Japan vs Europe and the US are not clarified by this study and warrant further investigation. TT and UFR are measured at baseline and could potentially change over time. This report does not include time-dependent analyses due to non-availability of serial TT data in the DOPPS. There are no serial measurements of dry weight in the DOPPS, and we cannot accurately determine whether longer TT was associated with better achievement of dry weight. Last but not least, there were not many patients with dialysis sessions longer than five hours.

SUMMARY AND CONCLUSIONS

This study demonstrates that the duration of HD session is independently associated with a lower mortality risk after extensive adjustment for case mix, dialysis dose (Kt/V), body size measures, and indicators of non-adherence. The observed synergistic interaction between Kt/V and TT toward mortality risk reduction implies that delivering a high Kt/V over longer TT may be of greater value than delivering the same Kt/V over shorter TT (with implications for practice modification). Furthermore, this study finds that UFR $>$ 10 ml/h/kg body weight is independently associated with higher risk of both intradialytic hypotension and mortality. However, since this is an observational study and causality is not proven, the issues of TT and UFR merit further examination by a prospective randomized clinical trial in the setting of thrice-weekly HD, as this is likely to remain the paradigm for the majority of HD patients for the foreseeable future. Until results from such a trial are available, we believe this large international prospective cohort study provides support for the view that longer HD sessions could improve outcomes for HD patients receiving thrice-weekly HD.

MATERIALS AND METHODS

Data source

The patient sample was drawn from the combined database for DOPPS I (1997–2002) and DOPPS II (2002–2004), but included information about HD patients in only those countries that participated in both phases (France, Germany, Italy, Japan, Spain, the UK, and the US). A nationally representative sample of dialysis facilities was enrolled in each country, and a random sample of HD patients was selected from each participating facility. Details of study design, facility sampling, patient sampling, and data collection for DOPPS have been published previously.[33] The current study reflects data obtained from the United States (DOPPS I: 145 facilities, $n = 9500$; DOPPS II: 79 facilities, $n = 3500$), Euro-DOPPS countries (DOPPS I: 101 facilities, $n = 4500$; DOPPS II: 101 facilities, $n = 4000$), and Japan (DOPPS I: 65 facilities, $n = 2700$; DOPPS II: 60 facilities, $n = 2800$).

An average of 30 adult chronic HD patients (18 years old or older) participated from each facility. Data collection began in the US in June 1996, in Europe in May 1998, and in Japan in February 1999. Patients were followed until January 2002 in the US, November 2000 in Europe, and October 2001 in Japan. DOPPS II data collection began in 2002 and concluded in 2004 in all seven countries. A study coordinator at each dialysis center collected data using standardized chart abstraction. For this analysis, only prevalent patients from each facility were included. Follow-up information was obtained approximately every 4 months and included dates, diagnoses, and procedures associated with each hospitalization.

Definitions used in this study

Treatment time. The duration of dialysis session used in this analysis came from the dialysis prescription information.

Dialysis dose (Kt/V). The dialysis dose was expressed as single pool Kt/V that was calculated using the second-generation Daugirdas formula.[34]

Ultrafiltration rate. The rate of volume removal at dialysis, expressed in ml/h/kg bodyweight, was based on the weight change per TT, using the post-dialysis weight in the denominator.

Intradialytic hypotension. Any systolic blood pressure drop of $\geqslant$30 mmHg combined with a post-dialysis systolic pressure of $\leqslant$100 mmHg was considered evidence of IDH.

Statistical analysis

Average UFRs and TTs were compared across geographical regions using the initial prevalent cross-sections, which included 8615 patients from DOPPS I and 6921 patients from DOPPS II. All other analyses used the complete sample of more than 22 000 patients. Logistic regression was used to investigate the odds of TT $>$ 240 min vs TT $\leqslant$ 240 min (240 min is usually considered the clinical threshold for longer dialysis) and of UFR $>$ 10 ml/h/kg vs UFR $\leqslant$ 10 ml/h/kg. These models investigated patient characteristics, including age, sex, race, 15 summary comorbid conditions, time since initiation of dialysis (i.e., vintage), post-dialysis weight, height, Kt/V, intradialytic weight loss, living status (e.g., alone, nursing home), marital status, prior kidney transplant, geographical region, TT (in UFR model), and UFR (in TT model). The intermediate outcome of intradialytic hypotension was examined using logistic regression, and the odds ratio for patients with UFR $>$ 10 ml/h/kg vs UFR $\leqslant$ 10 ml/h/kg was estimated. This model was also adjusted for all variables listed above.

Patient risk of mortality was assessed using Cox proportional hazards regression, stratified by the three geographical regions (US, Europe, and Japan) and by the two phases of DOPPS. Both all-cause mortality and cardiopulmonary mortality (including deaths attributed to myocardial infarction, pericarditis, atherosclerotic heart disease, cardiac arrest, valvular heart disease, pulmonary embolism, cardiomyopathy, cardiac arrhythmia, pulmonary edema, hyperkalemia, and congestive heart failure) were investigated. Models included significant predictors of mortality: age, sex, race/ethnicity, time on dialysis, height, weight, Kt/V, employment status, TT, residual renal function, measures of non-adherence (shortening of HD by at least 10 min/month and skipping at least one HD session/month as defined in our previous publication[13]), and 14 summary comorbid conditions. A separate Cox model was run to examine TT trends by region using interaction terms. Interactions were used to allow different associations between mortality and the following adjustment variables by region: age, male, history of transplant, catheter as access type, and weight (in Japan only). These models included both TT and UFR as predictors of mortality. The

association between UFR and mortality was consistent by region. The linear assumption for TT was verified using model fit statistics and plots of Martingale residuals from the Cox models vs TT. An interaction between *Kt/V* and TT was also tested. All models accounted for clustering at the facility level. For the logistic regression models, facility clustering was accommodated using generalized estimating equations, assuming an exchangeable working covariance structure.[35] For the Cox regression models, the robust sandwich estimator, assuming an independence working covariance structure, was used to account for clustering at the facility level.[36] All statistical analyses were carried out using SAS software (version 9.1).

ACKNOWLEDGMENTS

The DOPPS is supported by research grants from Amgen and Kirin without restrictions on publications.

REFERENCES

1. US Renal Data System. *USRDS 2003 Annual Data Report: Atlas of End-Stage Renal Disease in the United States*. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, 2003.
2. Innes A, Charra B, Burden RP *et al.* The effect of long, slow hemodialysis on patient survival. *Nephrol Dial Transplant* 1999; **14**: 919–922.
3. Valderrábano F. Weekly duration of dialysis treatment – does it matter for survival? *Nephrol Dial Transplant* 1996; **11**: 569–572.
4. Shinzato T, Nakai S, Akiba T *et al.* Survival in long-term hemodialysis patients: results from the annual survey of the Japanese Society of Dialysis Therapy. *Nephrol Dial Transplant* 1997; **12**: 884–888.
5. Held PJ, Levin NW, Bovbjerg RR *et al.* Mortality and duration of hemodialysis treatment. *JAMA* 1991; **265**: 871–875.
6. Nakai S, Shinzato T, Sanaka T *et al.* An overview of dialysis treatment in Japan. *J Jpn Soc Dial Ther* 2001; **34**: 1121–1147.
7. Lowrie EG, Li Z, Ofsthun N, Lazarus MJ. Measurement of dialyzer clearance, dialysis time, and body size: death risk relationships among patients. *Kidney Int* 2004; **66**: 2077–2084.
8. Charra B, Scribner BH, Twardowski ZJ, Bergstrom J. The middle molecule hypothesis revisited. Should short, three times weekly hemodialysis be abandoned? *Hemodial Int* 2002; **6**: 9–14.
9. Charra B, Chazot C, Hurot JM *et al.* Volume control in hemodialysis patients. *Hemodial Int* 2000; **4**: 68–74.
10. Parker TF, Laird NM, Lowrie EG. Comparison of the study groups in the National Cooperative Dialysis Study and a description of morbidity, mortality and patient withdrawal. *Kidney Int* 1983; **13**(Suppl): S42–S49.
11. Harter HR. Review of significant findings from the National Cooperative Dialysis Study and recommendations. *Kidney Int* 1983; **13**(Suppl): S107–S112.
12. Eknoyan G, Beck GJ, Cheung AK *et al.* Effect of dialysis dose and membrane flux in maintenance HD. *N Engl J Med* 2002; **347**: 2010–2019.
13. Saran R, Bragg-Gresham JL, Rayner HC *et al.* Nonadherence in hemodialysis: associations with mortality, hospitalization, and practice patterns in the DOPPS. *Kidney Int* 2003; **64**: 254–262.
14. Leggat Jr JE, Orzol SM, Hulbert-Shearon TE *et al.* Noncompliance in hemodialysis: predictors and survival analysis. *Am J Kidney Dis* 1998; **32**: 139–145.
15. Ifudu O, Uribarri J, Rajwani I *et al.* Relation between interdialytic weight gain, body weight and nutrition in hemodialysis patients. *Am J Nephrol* 2002; **22**: 363–368.
16. Testa A, Beaud JM. The other side of the coin: Interdialytic weight gain as an index of good nutrition. *Am J Kidney Dis* 1998; **31**: 830–834.
17. Sharpe N. Left ventricular remodeling: pathophysiology and treatment. *Heart Fail Monit* 2003; **4**: 55–61.
18. Wells M, Foroozan R. Transient visual loss may anticipate occipital infarction from hemodialysis. *Am J Kidney Dis* 2004; **43**: e29–e33.
19. Raja RM. Sodium profiling in elderly haemodialysis patients. *Nephrol Dial Transplant* 1996; **11**(Suppl 8): S42–S45.
20. Tisler A, Akocsi K, Borbas B *et al.* The effect of frequent or occasional dialysis-associated hypotension on survival of patients on maintenance haemodialysis. *Nephrol Dial Transplant* 2003; **18**: 2601–2605.
21. Saran R, Canaud BJ, Depner TA *et al.* Dose of dialysis: key lessons from major observational studies and clinical trials. *Am J Kidney Dis* 2004; **44**(Suppl 3): S47–S53.
22. Twardowski ZJ. Short, thrice-weekly hemodialysis is inadequate regardless of small molecule clearance. *Int J Artif Organs* 2004; **27**: 452–466.
23. Katzarski KS, Charra B, Luik AJ *et al.* Fluid state and blood pressure control in patients treated with long and short haemodialysis. *Nephrol Dial Transplant* 1999; **14**: 369–375.
24. Brunet P, Saingra Y, Leonetti F *et al.* Tolerance of haemodialysis: A randomized cross-over trial of 5-h versus 4-h treatment time. *Nephrol Dial Transplant* 1996; **11**(Suppl 8): 46–51.
25. Raj DS, Charra B, Pierratos A, Work J. In search of ideal hemodialysis: is prolonged frequent dialysis the answer? *Am J Kidney Dis* 1999; **34**: 597–610.
26. Daugirdas JT. Pathophysiology of dialysis hypotension: an update. *Am J Kidney Dis* 2001; **38**(Suppl 4): S11–S17.
27. Sherman RA. Modifying the dialysis prescription to reduce intradialytic hypotension. *Am J Kidney Dis* 2001; **38**(Suppl 4): S18–S25.
28. Marshall MR, Leonardi B, McDonald SP *et al.* Both low hemodialysis dose and shorter length are associated with worse outcomes in Australian and New Zealand patient populations. *J Am Soc Nephrol* 2004; **15**(Suppl): 387A.
29. Donauer J. HD-induced hypotension: impact of technologic advances. *Semin Dial* 2004; **17**: 333–335.
30. Schneditz D, Zaluska WT, Morris AT, Levin NW. Effect of ultrafiltration on peripheral urea sequestration in haemodialysis patients. *Nephrol Dial Transplant* 2001; **16**: 994–998.
31. Donauer J, Kolblin D, Bek M *et al.* Ultrafiltration profiling and measurement of relative blood volume as strategies to reduce hemodialysis-related side effects. *Am J Kidney Dis* 2000; **36**: 115–123.
32. Termorshuizen F, Dekker FW, Van Manen JG *et al.* 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. *J Am Soc Nephrol* 2004; **15**: 1061–1070.
33. Pisoni RL, Gillespie BW, Dickinson DM *et al.* The Dialysis Outcomes and Practice Patterns Study (DOPPS): design, data elements, and methodology. *Am J Kidney Dis* 2004; **44**(Suppl 2): S7–S15.
34. Daugirdas JT. Second generation logarithmic estimates of single-pool variable volume Kt/V: an analysis of error. *J Am Soc Nephrol* 1993; **4**: 1205–1213.
35. SAS Institute. *SAS/STAT User's Guide*, Version 8, vol. 2. SAS Institute: Cary, NC, 2000 452pp.
36. Klein J, Moeschberger M. *Survival Analysis Techniques for Censored and Truncated Data*. Springer: New York, 1997, pp 416–418.