Hemodialysis International 2014; **18**:596–606

Original Articles

Gender, low Kt/V, and mortality in Japanese hemodialysis patients: Opportunities for improvement through modifiable practices

Naoki KIMATA,[1] Angelo KARABOYAS,[2] Brian A. BIEBER,[2] Ronald L. PISONI,[2] Hal MORGENSTERN,[2,3] Brenda W. GILLESPIE,[2,4] Akira SAITO,[5] Tadao AKIZAWA,[6] Shunichi FUKUHARA,[7] Bruce M. ROBINSON,[2,8] Friedrich K. PORT,[2,8] Takashi AKIBA[1]

[1]Tokyo Women's Medical University, Tokyo, Japan; [2]Arbor Research Collaborative for Health, Ann Arbor, Michigan, USA; [3]Departments of Epidemiology and Environmental Health Sciences, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA; [4]Department of Biostatistics, School of Public Health, University of Michigan, Ann Arbor, Michigan, USA; [5]Yokohama Daiichi Hospital, Kanagawa, Japan; [6]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan; [7]Department of Epidemiology and Healthcare Research, Kyoto University Graduate School of Medicine and Public Health, Kyoto, Japan; [8]Department of Internal Medicine-Nephrology, University of Michigan, Ann Arbor, Michigan, USA

Abstract

Guidelines have recommended single pool Kt/V > 1.2 as the minimum dose for chronic hemodialysis (HD) patients on thrice weekly HD. The Dialysis Outcomes and Practice Patterns Study (DOPPS) has shown that "low Kt/V" (<1.2) is more prevalent in Japan than many other countries, though survival is longer in Japan. We examined trends in low Kt/V, dialysis practices associated with low Kt/V, and associations between Kt/V and mortality overall and by gender in Japanese dialysis patients. We analyzed 5784 HD patients from Japan DOPPS (1999–2011), restricted to patients dialyzing for >1 year and receiving thrice weekly dialysis. Logistic regression models estimated the relationships of patient characteristics with Kt/V. Logistic models also were used to estimate the proportion of low Kt/V cases attributable to various treatment practices. Multivariable Cox regression was used to estimate the associations of low Kt/V, blood flow rate (BFR), and treatment time (TT), with all-cause mortality. From 1999 to 2009, the prevalence of low Kt/V declined in men (37–27%) and women (15–10%). BFR <200 mL/min, TT <240 minutes, and dialyzate flow rate (DFR) < 500 mL/min were common (35, 13, and 19% of patients, respectively) and strongly associated with low Kt/V. Fifteen percent of low Kt/V cases were attributable to BFR <200 and 13% to TT <240, compared to only 3% for DFR <500. Lower Kt/V was associated with elevated mortality, more so among women (hazard ratio [HR] = 1.13 per 0.1 lower Kt/V, 95% CI: 1.07–1.20) than among men (HR = 1.06 per 0.1 lower Kt/V, 95% CI: 1.00–1.12). The relatively large proportion of low Kt/V cases in Japanese facilities may potentially be reduced 30% by increasing BFR to 200 mL/min and TT to 4 hours thrice weekly in HD patients. Associations of low Kt/V with elevated mortality suggest that modification of these practices may further improve survival for Japanese HD patients.

Key words: Hemodialysis, survival, treatment time, Kt/V, mortality, adequacy

Correspondence to: R. L. Pisoni, PhD, MS, Arbor Research Collaborative for Health, 340 East Huron Street, Suite 300, Ann Arbor, MI 48104, USA. E-mail: ronald.pisoni@arborresearch.org

DOI:10.1111/hdi.12142

INTRODUCTION

The Japanese hemodialysis (HD) patient population has displayed considerably longer survival overall than that seen in most other countries, with annual mortality risks of 9% to 10% consistently for HD patients in Japan, compared with annual risks of 12% to 24% in other countries.[1–5] The longer survival on HD for patients in Japan compared with those in Europe and North America has also been shown in prior Dialysis Outcomes and Practice Patterns Study (DOPPS) analyses by Goodkin et al. adjusting for differences in patient casemix between regions.[6–8]

The reasons for the longer survival of HD patients in Japan vs. other countries are not clearly understood and likely are due to numerous factors. However, one of the intriguing aspects of care in Japan is the use of lower blood flow rates (BFRs), usually 200 mL/min for a typical HD treatment, compared with BFRs of 300–500 mL/min in many other countries.[1,9,10] This lower BFR may help facilitate the attainment and maintenance of the high rate of ~92% native arteriovenous fistula (AVF) use that has been described in Japanese HD patients for at least the past 12 years.[1,8–10] From the perspective of dialysis session total solute clearance, the lower mean body size of HD patients in Japan compared with patients in many other regions makes it feasible to use a lower BFR, yet provide good dialysis adequacy. However, dialysis adequacy, as measured by single pool (sp) Kt/V, varies considerably among patients in Japan with a substantial fraction of patients having an spKt/V < 1.2.

In view of these marked differences in dialysis prescription and mortality in Japan vs. other countries, we focus here in Japan to describe to what extent having a low spKt/V of <1.2 in Japanese HD patients is attributable to treatment factors such as BFR, HD session length (treatment time [TT]), and other factors. In addition, we describe the relation of facility-level practices of Kt/V achievement, BFR and TT with survival as a means to help understand which levels of these practices are associated with the best outcomes for HD patients in Japan. The understandings from Japan may be applicable to other countries where low Kt/V is still common.

METHODS

Data source

In the present analysis, 5784 patients were included from Japan DOPPS phases 1–4: 1756 from 61 facilities in phase 1 (1999–2001), 1284 from 56 facilities in phase 2 (2002–2004), 1431 from 59 facilities in phase 3 (2005–2007), and 1313 from 58 facilities in phase 4 (2009–2011). The DOPPS sampling plan and study methods have been described elsewhere.[11,12] Starting with 7779 patients with measured Kt/V, patients were excluded from this analysis if they had been on dialysis less than 1 year (n = 1714) to minimize the effects of residual renal function on the results. Moreover, patients were excluded if not dialyzing three times per week (n = 20), had a TT >5 hours (n = 93), had a BFR >550 mL/min (n = 0), were receiving hemodiafiltration (n = 162), or had missing data on age or censoring date (n = 6). Facility-level analyses were limited to facilities with at least eight patients (n = 5752) meeting the inclusion criteria.

Kt/V at baseline was calculated according to the second-generation formula of Daugirdas.[13] BFR and dialyzate flow rate (DFR) at baseline were based on prescribed values. DFR prescription was unavailable in phase 4. Treatment time at baseline was based on actual TT in phases 2–4. In phase 1, actual TT was not available, so prescribed TT was used.

Statistical analysis

Baseline values were reported as percentiles, means, or percentages. Mean Kt/V was reported by gender and weight for patients with TT = 240 minutes and BFR = 200 mL/min. The association of patient characteristics with low Kt/V (<1.2) was assessed using a generalized estimating equation (GEE) model with logit link function. The model included all variables listed in Table 1, adjusted for study phase, and accounted for facility clustering effects. The proportion of cases of low Kt/V attributable to insufficient treatment (i.e., below a certain threshold of BFR, DFR, or TT) was obtained by estimating the population attributable fraction (AF), i.e., the proportion of cases of low Kt/V that would not have occurred if everyone in the study population had sufficient levels (at or above the threshold level) of these treatment parameters. The AF is a function of both the prevalence and effect size of each parameter. For example, to assess the AF of insufficient TT (TT <240 minutes), a fitted GEE model was used, treating BFR, DFR, and TT as continuous variables, to estimate the percentage of patients with low Kt/V attributable to having TT <240 minutes after counterfactually assigning all observed values under 240 minutes to exactly 240 minutes. The AF value can thus be interpreted as the proportion of cases of low Kt/V that could potentially be prevented by improving the treatment to the threshold levels as defined in these analyses. Attributable fraction models were adjusted for DOPPS

Table 1 Patient characteristics by gender and Kt/V category

		Male				Female			
Mean ± SD, or %	All	<1.2	1.2–1.4	1.4–1.6	≥ 1.6	<1.2	1.2–1.4	1.4–1.6	≥ 1.6
N patients (%)	5784	1212 (34)	1323 (37)	730 (21)	265 (8)	287 (13)	473 (21)	689 (31)	805 (36)
N deaths (%)	586 (10)	132 (11)	125 (9)	83 (11)	29 (11)	55 (19)	43 (9)	68 (10)	51 (6)
Age (y)	61.1 ± 12.5	60.1 ± 12.7	60.5 ± 12.0	61.3 ± 12.5	61.3 ± 11.9	64.4 ± 13.0	61.4 ± 13.3	61.7 ± 12.7	61.3 ± 11.9
Vintage (y)	8.6 ± 6.8	6.1 ± 5.6	8.9 ± 6.8	10.0 ± 7.2	11.2 ± 7.4	5.8 ± 5.1	7.6 ± 6.3	9.0 ± 6.3	10.8 ± 7.1
Weight (k)	53.1 ± 10.6	61.5 ± 10.3	57.1 ± 8.5	53.4 ± 7.9	51.4 ± 7.8	49.5 ± 9.9	48.9 ± 8.5	46.5 ± 7.2	43.3 ± 6.9
Height (m)	1.60 ± 0.09	1.66 ± 0.07	1.64 ± 0.07	1.63 ± 0.07	1.62 ± 0.07	1.52 ± 0.07	1.53 ± 0.06	1.52 ± 0.06	1.51 ± 0.06
Albumin (g/dL)	3.79 ± 0.39	3.82 ± 0.43	3.81 ± 0.39	3.80 ± 0.37	3.78 ± 0.38	3.68 ± 0.46	3.78 ± 0.38	3.77 ± 0.37	3.78 ± 0.35
Creatinine (mg/dL)	11.4 ± 2.7	12.3 ± 3.0	12.4 ± 2.6	11.9 ± 2.5	11.3 ± 2.5	9.6 ± 2.7	10.3 ± 2.4	10.3 ± 2.0	10.0 ± 1.9
BFR (mL/min)	200 ± 33	198 ± 29	207 ± 28	213 ± 36	216 ± 34	177 ± 42	186 ± 30	192 ± 33	199 ± 28
TT (min)	241 ± 26	232 ± 27	244 ± 20	252 ± 24	264 ± 26	220 ± 30	230 ± 24	238 ± 20	248 ± 25
Comorbidities									
CAD (%)	29	31	31	30	34	31	26	26	22
Cancer (%)	8	8	9	8	11	7	4	6	7
CV—other (%)	31	29	30	34	40	32	29	29	30
Cerebrovascular (%)	14	14	15	14	16	18	11	13	10
CHF (%)	15	17	15	15	16	20	15	15	13
Diabetes (%)	29	42	30	24	21	38	27	23	15
GI bleed (%)	4	5	5	4	5	8	3	3	4
Hypertension (%)	69	74	69	71	66	66	65	67	64
Lung disease (%)	2	2	2	4	3	3	2	2	2
Neurologic disease (%)	7	7	5	5	7	14	6	8	7
Psychiatric disorder (%)	4	4	3	4	3	6	5	3	3
PVD (%)	15	17	17	16	20	14	12	14	10
Recurrent cellulitis (%)	4	5	5	4	3	5	3	3	2

BFR = blood flow rate; CAD = coronary artery disease; CHF = congestive heart failure; CV = cardiovascular; GI = gastrointestinal; PVD = peripheral vascular disease; TT = treatment time.

phase and the following baseline covariates: age, gender, vintage, weight, height, 13 summary comorbid conditions (listed in Table 1), serum albumin, and creatinine.

For mortality analyses, patients were followed from DOPPS entry until death or the earliest of the following censoring events: 7 days after departure from the facility for change of treatment modality, withdrawal from dialysis, return of renal function, kidney transplantation, transfer to another facility, or the end of follow up. Cox regression was used to estimate the effect of low Kt/V on all-cause mortality, adjusting for the same potential confounders noted above for the logistic models and stratified by DOPPS phase. Kt/V was treated in these models as a continuous variable and categorically as a set of indicator variables. Interaction between Kt/V and weight and body mass index (BMI) was assessed among both men and women. In addition, Kt/V was also measured at the facility level as the proportion of patients in each facility with low Kt/V. The associations of both BFR and TT with all-cause mortality were similarly analyzed at both the patient and facility level. In all analyses of these facility-level predictors, adjustment was also made for two other facility-level variables in order to further account for facility-level variation in patient casemix and in practices that may not have been captured by the patient-level adjustments: mean baseline hemoglobin level and the proportion of patients with baseline serum phosphorus >5.5 mg/dL. The missing indicator method was used in model-based analyses to include the following variables with at least 1% missingness in models: albumin (11%), height (5%), and creatinine (1%). All statistical analyses were performed using the SAS statistical package, version 9.2 (SAS Institute, Cary, NC, USA).

RESULTS

Trends in Kt/V and other characteristics across DOPPS phases

Among the 5784 patients included in the analysis, 586 patients died (10%) during a median follow up of 25.2 months (IQR: 20.9–32.0). Low Kt/V (<1.2) was observed in 26% of patients overall. However, the median facility percentage of patients with low Kt/V declined from 33% in DOPPS 1 to 18% in DOPPS 4 (Figure 1). In each study phase, large variability was seen across Japanese dialysis facilities in the percentage of HD patients with low Kt/V (<1.2), ranging from close to 0% to >50% of patients.

Mean (SD) Kt/V was 1.28 (0.22) in men and 1.51 (0.27) in women, with the highest values observed in DOPPS 4 (Figure 2). The prevalence of low Kt/V declined in men from 37% in DOPPS 1 to 27% in DOPPS 4, and it declined in women from 15% in DOPPS 1 to 10% in DOPPS 4. Both BFR and TT were somewhat higher on average in men than women (Figure 3A and B). Trends in practice across the study phases indicate higher BFRs and shorter TTs in recent years in Japan. Dialyzate flow rate is largely a facility-based practice and did not appear to be customized according to patient gender; thus, the distribution was similar for men and women (Figure 3C). Over 90% of facilities in each phase did not individualize DFRs, defined as having at least 90% of patients within 50 mL/min of the facility median DFR.

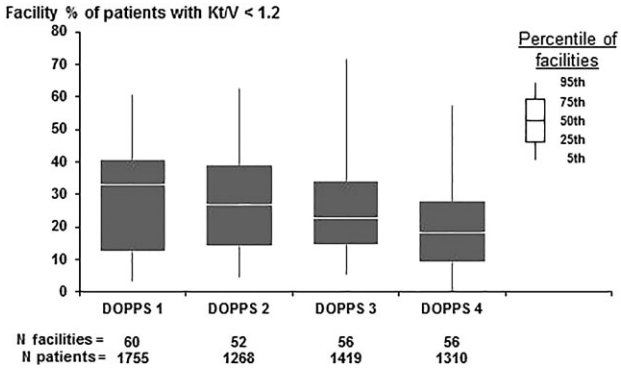

Figure 1 Distribution of facilities according to the proportion of their patients with low Kt/V (<1.2) by DOPPS phase.

Associations with low Kt/V

Table 1 shows the means and percentages of baseline patient characteristics among all study patients by gender and Kt/V level. In a logistic model using GEE with all predictors listed in Table 1, the following variables were positively associated with low baseline Kt/V (<1.2): male gender, diabetes, greater body weight, greater height, shorter vintage on dialysis, neurologic disease, lower albumin, shorter dialysis TT, lower BFRs or DFRs (Table S1). Testing effect modification by gender for each of these associations revealed that the associations between weight and height with low Kt/V were stronger among men than women (P for each interaction < 0.05). A descriptive analysis revealed a consistent pattern of higher observed mean Kt/V levels for female vs. male patients across the entire range of observed patient body weights among 1735 patients with a TT of 240 minutes and a BFR of 200 mL/min (Figure 4). Despite variation in Kt/V by gender at the same weight, we did not find evidence that the relationship between Kt/V and mortality differed by weight or BMI in either men or women (P for interactions > 0.05).

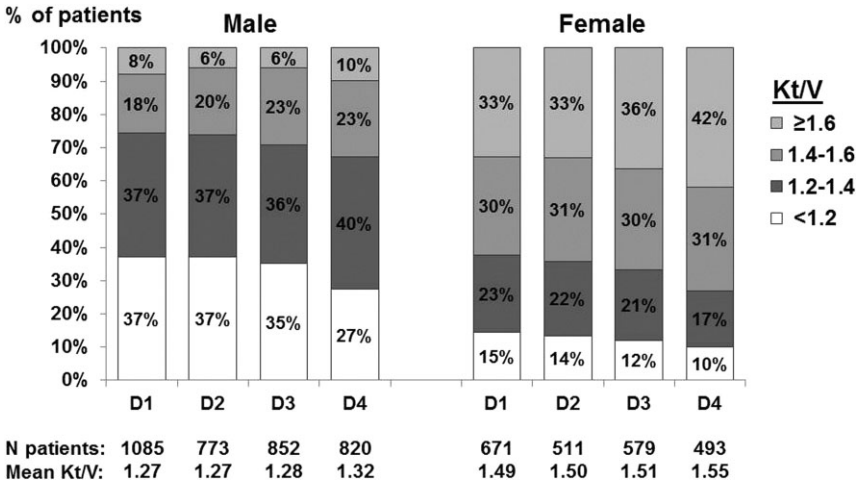

Figure 2 Patient single pool Kt/V categories by gender and DOPPS phase.

The results in Table 2 indicate that the odds of a patient having Kt/V < 1.2 was 8.1 times greater (95% CI: 6.1–10.7) when dialyzing <240 minutes. The odds ratios (ORs) of having low Kt/V for patients with a BFR of <200 mL/min and DFR of <500 mL/min were 2.9 (95% CI: 2.3–3.6) and 1.8 (95% CI: 1.3–2.4), respectively. We then estimated the proportion of low Kt/V cases attributable to a TT <240 minutes, BFR <200 mL/min, and DFR <500 mL/min. While shorter TT was a stronger predictor of low Kt/V than low BFR, the higher prevalence of low BFR in the study sample (35% vs. 13% with TT <240 minutes) resulted in a higher proportion of cases of low

Table 2 Proportion of Kt/V cases <1.2 attributable to treatment practices below a specified cut point in Japan for: (a) all study patients, (b) male patients, and (c) female patients

Subgroup (N Kt/V < 1.2/N patients)	Prevalence of parameter (%)	OR (95% CI) of Kt/V < 1.2	Attributable fraction (%)
(a) All patients (n = 1189/4376)			
TT < 240 min	13	8.1 (6.1,10.7)	13
BFR < 200 mL/min	35	2.9 (2.3,3.6)	15
DFR < 500 mL/min	19	1.8 (1.3,2.4)	3
Any combination[a]	54 (any)	—	30
(b) Male (n = 964/2657)			
TT < 240 min	11	9.8 (6.9,13.9)	10
BFR < 200 mL/min	26	2.9 (2.3,3.7)	10
DFR < 500 mL/min	19	2.3 (1.6,3.2)	3
Any combination[a]	47 (any)	—	24
(c) Female (n = 225/1719)			
TT < 240 min	16	7.6 (5.2,11.2)	22
BFR < 200 mL/min	48	3.7 (2.4,5.7)	43
DFR < 500 mL/min	19	1.2 (0.7,2.0)	2
Any combination[a]	65 (any)	—	61

Three separate GEE models, overall and by gender, which simultaneously adjust for all three treatment practices.
All models additionally adjusted for study phase, age, gender (model (a) only), vintage, height, weight, 13 summary comorbidities, serum albumin, and serum creatinine, and accounted for facility clustering effects. Analyses restricted to DOPPS phases 1–3 due to unavailability of DFR data in DOPPS 4.
[a]Prevalence for any combination is the proportion of patients with any one of the three values below the cut point; attributable fraction for this row is calculated if all values (1, 2, or 3) below the cut point were increased to the cut point.
BFR = blood flow rate; DFR = dialyzate flow rate; TT = treatment time; — = not applicable.

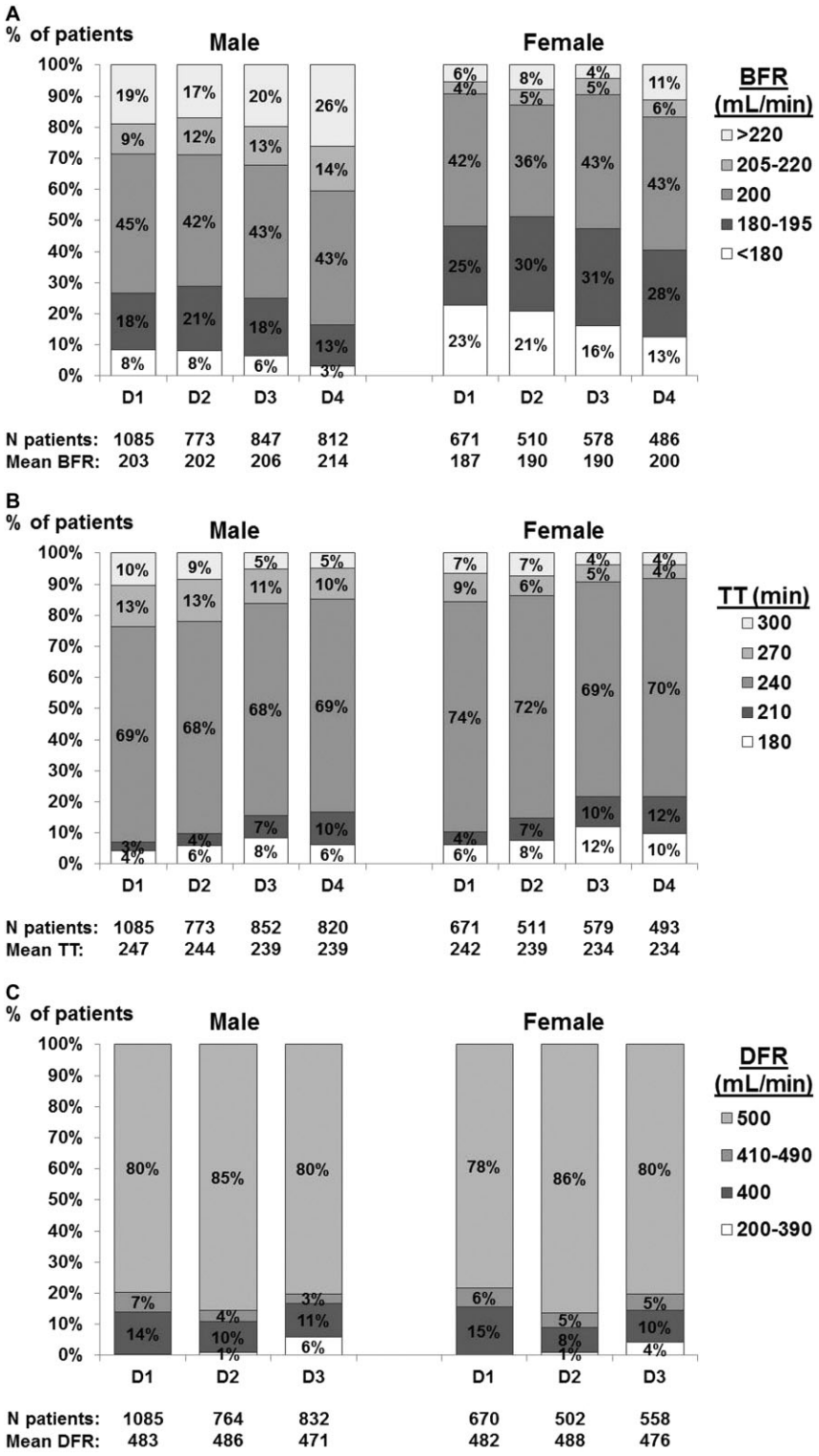

Figure 3 (A) Patient blood flow rate (BFR) categories by gender and DOPPS phase. (B) Patient treatment time (TT) categories by gender and DOPPS phase. Over 90% of patients had TT at exactly 180, 210, 240, 270, or 300 min. All remaining values were rounded to the nearest 30-min interval. (C) Patient dialyzate flow rate (DFR) categories by gender and DOPPS phase. Dialyzate flow rate data unavailable in DOPPS 4.

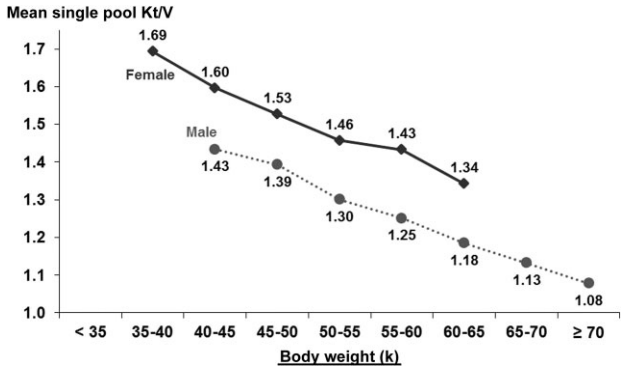

Figure 4 Mean Kt/V, by gender and weight, for n = 1735 patients with treatment time (TT) of 240 min and prescribed blood flow rate of 200 mL/min. Mean values hidden for subgroups with less than 30 patients.

Kt/V being attributed to BFR <200 mL/min (15%) than a short TT (13%). Low DFR had a weaker association with low Kt/V, but still provided additional predictive power even after accounting for TT and BFR. The AF calculated for all three practices combined was 30%. The analysis was repeated for each gender and results are shown in Table 2. A Kt/V cut point of 1.6 was also analyzed for women and showed an AF of 21% for all three practices combined. In a sensitivity analysis using a different cut point for BFR, 72% of men and 91% of women had BFR <220 mL/min (79% overall). The proportion of cases of low Kt/V attributable to BFR <220 mL/min was 29% in men and 69% in women (37% overall).

Kt/V and mortality

The relation between patient-level Kt/V and all-cause mortality was analyzed in the total sample and by gender (Table 3). In a fully adjusted model treating Kt/V as a continuous variable, lower Kt/V was associated with mortality (hazard ratio [HR] per 0.1 lower Kt/V = 1.10; 95% CI: 1.05–1.14). This association was stronger among women (HR = 1.13; 95% CI: 1.07–1.20) than men (HR = 1.06; 95% CI: 1.00–1.12) (P for the interaction between Kt/V and gender = 0.05). The results are qualitatively similar when Kt/V was treated as three binary predictors in the models (Table 3). The HR, comparing Kt/V ≥ 1.6 to Kt/V < 1.2, was 0.36 for women (95% CI: 0.23–0.56) and 0.68 for men (95% CI: 0.45–1.04).

Facility-level models provided further evidence of greater patient mortality with greater exposure to low Kt/V. In a model including both patient and facility-level adjustments (Table 4, model 5), facilities with a larger percentage of patients with low Kt/V displayed higher mortality (HR per 20% patients with low Kt/V = 1.14; 95% CI: 1.00–1.31). Categorical analyses indicated a positive dose–response association between the proportion of facility patients with low Kt/V and mortality (Table 4).

Mortality: relationship with BFR and TT

Because low Kt/V was strongly associated with mortality and substantial proportions of low Kt/V cases observed in Japan were attributable to having a low BFR (<200 mL/min) or low TT (<240 minutes), we estimated the effects of BFR and TT on all-cause mortality. The results indicate a clear inverse association between prescribed BFR and mortality (Figure S1). This inverse relation was also observed as a facility practice, with HR = 1.46 (95% CI: 1.04–2.03) for patients treated in facilities with a mean prescribed BFR <180 mL/min compared with the reference group of 180–210 mL/min. Treatment time at both

Table 3 Patient-level Kt/V and all-cause mortality, overall and by gender

	All patients	Male	Female
N patients	5784	3530	2254
N deaths (%)	586 (10)	369 (10)	217 (10)
Continuous Kt/V			
Per 0.1 lower Kt/V	1.10 (1.05–1.14)	1.06 (1.00–1.12)	1.13 (1.07–1.20)
Categorical Kt/V			
<1.2	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
1.2–1.4	0.73 (0.60–0.89)	0.79 (0.61–1.03)	0.58 (0.38–0.88)
1.4–1.6	0.75 (0.59–0.96)	0.85 (0.62–1.16)	0.64 (0.45–0.91)
≥1.6	0.48 (0.34–0.67)	0.68 (0.45–1.04)	0.36 (0.23–0.56)

Note: Hazard ratios (95% CI) shown; P values for interaction between gender and Kt/V were 0.05 (continuous) and 0.15 (categorical). Separate Cox models adjusted for age, sex, vintage, weight, height, 13 summary comorbidities, serum albumin, and creatinine, stratified by DOPPS phase, and accounting for facility clustering. Results of an additional analysis of patients with Kt/V < 1.2 vs. Kt/V ≥ 1.2 were HR = 1.44 (1.19–1.75) for all patients, HR = 1.26 (0.98–1.61) for men, and HR = 1.92 (1.39–2.64) for women.

Table 4 Facility-level Kt/V and all-cause mortality by level of adjustment

	Model 1 Unadjusted	Model 2 + Demographics[a]	Model 3 +13 Comorbidities	Model 4 + Albumin and creatinine	Model 5 + Facility-level adjustments[b]
Continuous Kt/V: % of patients with low Kt/V (<1.2)					
Per 20% more patients	1.10 (0.98–1.23)	1.15 (1.02–1.28)	1.12 (0.99–1.26)	1.15 (1.02–1.30)	1.14 (1.00–1.31)
Categorical Kt/V: % of patients with low Kt/V (<1.2)					
0% to 12%	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
12% to 23%	1.13 (0.85–1.52)	1.14 (0.88–1.46)	1.19 (0.91–1.54)	1.20 (0.93–1.56)	1.18 (0.91–1.53)
23% to 36%	1.16 (0.86–1.56)	1.22 (0.93–1.61)	1.26 (0.94–1.68)	1.28 (0.96–1.71)	1.22 (0.92–1.62)
≥36%	1.27 (0.91–1.76)	1.37 (1.00–1.87)	1.29 (0.94–1.76)	1.34 (0.98–1.84)	1.37 (1.00–1.88)

Note: Hazard ratios (95% CI) shown; n = 5784 patients from DOPPS phases 1–4. All Cox models stratified by DOPPS phase and accounting for facility clustering.

[a]Demographics: gender, age, vintage, weight, height.

[b]Facility-level adjustments: facility mean hemoglobin and facility % of patients with serum phosphorus > 5.5 mg/dL.

the patient and facility level was also inversely associated with mortality (Figure S2). Mortality rates were higher for patients with TT of 180 minutes (HR = 1.54, 95% CI: 1.16–2.04) than for patients in the reference group (TT = 240 minutes), and in patients treated in facilities with the lowest mean TT (HR = 1.17 for facility mean TT <230 minutes compared to reference group of 230–250 minutes, 95% CI: 0.90–1.50).

DISCUSSION

Hemodialysis in Japan is distinguished from that of most non-Asian countries in a multitude of ways including much lower mortality rates, smaller patient body size, lower BFRs used for HD, and much lower use of catheters for vascular access. In view of these many differences and others, we undertook the current investigation to understand which factors are related to Kt/V achievement in Japan, as well as to understand the relationship of Kt/V to survival. The DOPPS shows that the percentage of patients with "low Kt/V" (<1.2) is still substantial in some countries, including Japan at 18% which is among the highest in the DOPPS countries.[10] In 1997, Shinzato et al.[14] published compelling findings from the Japanese Society for Dialysis Therapy (JSDT), showing that the odds of a patient dying in the year of study (1994) was sharply higher for patients having a Kt/V < 1.2 in the prior year among a large cohort (n = 53,867) of HD patients in Japan. These findings along with those from numerous other studies have led various HD practice guideline committees in many countries to recommend that HD patients receive sufficient dialysis to achieve, at minimum, an spKt/V of 1.2 or higher for thrice weekly HD.[15] In this study, we expand on the findings of Shinzato et al. by showing higher mortality risk in Japan for HD patients with an spKt/V < 1.2. Despite practice guidelines and extensive ongoing evidence of poorer survival for patients with Kt/V < 1.2, a substantial fraction of Japanese HD patients still receive dialysis doses below the guideline recommendation. Across Japanese dialysis units in DOPPS 4 (2009–2011), half of all facilities had >18% of their patients with low Kt/V (<1.2) and one-fourth of all facilities had >28% of their patients with low Kt/V. These results represent a large improvement in dialysis dose achievement in Japan since DOPPS 1 (1999–2001), but these percentages have been higher than reported for other DOPPS countries.[10,16,17] Thus, even though Japan exhibits one of the lowest mortality rates in the world for HD patients, opportunities remain for further improvements, such as a higher dialysis dose for HD patients currently receiving doses below the current JSDT and KDOQI guideline recommendations of spKt/V 1.2 or higher.

In examining patient characteristics associated with low Kt/V, a strong relationship was seen between low Kt/V and male gender and larger body size, as has been shown in prior studies.[18,19] Among the large fraction of male HD patients in Japan having a low Kt/V, mortality rates were 26% higher compared with patients having a Kt/V ≥ 1.2. Higher body weight had a stronger association with low Kt/V among male than female patients which may indicate the need for greater attention to providing a higher Kt/V for patients of larger body size, especially among male HD patients in Japan. Previously, the HEMO trial investigators[18,20,21] showed longer survival (HR = 0.81, P = 0.02) for female HD patients randomized to the higher (spKt/V 1.7 ± 0.1) vs. standard (spKt/V 1.3 ± 0.1) dose group in a subgroup analysis of the HEMO trial. In contrast, little

difference was seen in mortality rates between male HD patients randomized to the higher vs. standard dose group arms of the HEMO trial. Subsequently, Port et al.[22] confirmed these findings in the non-trial setting in describing a strong association between higher dose and lower mortality rates in women but not in men, using the average urea reduction ratio (URR) of incident HD patients in the United States and eKt/V of HD patients on HD for at least 1 year across seven DOPPS countries. In the present study, we have seen low Kt/V among 15% of female HD patients in Japan in DOPPS 1, which had declined to 10% in DOPPS 4. Similar to the prior non-Japanese findings of the HEMO trial and Port et al., in Japan we now describe a stronger association between spKt/V and mortality among female than male HD patients. Our findings suggest a mortality benefit for women on HD in Japan extending to spKt/V levels at least as high as spKt/V 1.6. In addition, we demonstrate that spKt/V achievement for female HD patients is higher than for male HD patients of the same body weight, TT, and BFR, which suggests that the dialyzable fluid volume differs between female and male HD patients at any given body weight. A possible explanation for this surprising mortality risk finding by gender was suggested based on a national US study by Ramirez et al.[23] This study confirmed these differences by gender; however, it showed that when dialysis dose was normalized to body surface area (SAN-stdKt/V) rather than to body fluid volume (in Kt/V), the functional form of the association was similar in shape for men and women, and survival continued to improve as surface area normalized dialysis dose (SAN-stdKt/V) increased in both men and women. Thus, they suggest that SAN-stdKt/V may be a better indicator for HD adequacy than when dose was normalized to body fluid volume as eKt/V or stdKt/V.[23] From our results, in combination with those from prior studies, a consistent pattern of evidence has been observed for longer survival of female HD patients at higher Kt/V levels. Guideline committees and quality improvement initiatives should take advantage of this knowledge to improve outcomes of HD patients, especially women. The association of higher Kt/V with longer survival in female HD patients is one consideration incorporated within the United Kingdom Renal Association's recommendation for dialysis dose achievement in HD patients.[24]

Since Kt/V is still used as the standard indicator of dialysis dose, the current study is useful in revealing several readily modifiable HD practices that were strongly and independently related to low delivered Kt/V in Japan. These practices included having a BFR <200 mL/min, a TT <240 minutes, and a DFR <500 mL/min. We estimated that 30% of patients with low Kt/V were attributable to combinations of these three practices—61% for women and 24% for men. Among these three practices, low Kt/V was more strongly associated with TT <240 minutes (OR = 8.1) than either BFR <200 mL/min (OR = 2.9) or DFR <500 mL/min (OR = 1.8). However, slightly more cases of low Kt/V could be prevented by improving BFR rather than TT to the threshold levels assumed in these analyses, because a greater proportion of the HD population has a "low" value for BFR. Providing patients with a DFR <500 mL/min contributed less (3% of low Kt/V cases). Among women, an estimated 43% of low Kt/V cases were attributable to BFR <200 mL/min (10% for men). An even higher fraction of low Kt/V cases were attributed to a low BFR when a higher contrast level of 220 mL/min was used: 69% of female cases and 29% of male cases. In addition to BFR, the practice of providing patients with a TT <240 minutes also contributed substantially to low Kt/V in this patient population (13% of low Kt/V cases). Thus, these results indicate three easily modifiable approaches for improving Kt/V achievement in Japanese HD patients. Blood flow rates in Japan are substantially lower than those in the 11 other countries in DOPPS 4 with a BFR ≤220 mL/min prescribed for 80% of patients. A lower BFR may allow more frequent use of AVF with longer AVF patency in Japan compared with other countries.[25] However, despite this possibility, our mortality analyses indicate that, overall, a slightly higher BFR either at the patient level or as a facility practice in Japan is associated with a substantially lower mortality rate. In addition, similar to prior international DOPPS findings and prior JSDT findings of longer HD patient survival with longer patient dialysis TT,[9,14,16] the current study provides additional evidence of longer patient survival in facilities with longer average TT.

The findings from the present work are subject to methodological limitations. Because the study is observational, we cannot rule out confounding by unmeasured risk factors for each outcome. To deal with such bias, we adjusted for several potential confounders. We also restricted the analysis to patients receiving HD three times per week who had been on dialysis for more than 1 year to reduce potential influence of residual renal function. Additionally, we tried to minimize unmeasured confounders by examining the practices under consideration as both patient-level and facility-level predictors of mortality, finding qualitatively consistent associations with mortality. In practice-based analyses, we also adjusted for a potential role of other practices related to achieving levels of phosphorus and anemia control. Nevertheless, effect estimates could have been biased due to other

unmeasured or incompletely specified patient-level or facility-level factors.

Lastly, these findings in Japan may be relevant to other countries with a relatively high prevalence of spKt/V of <1.2. In the United States, BFR is typically high and Kt/V values >1.2 are readily achieved in most patients, despite short average TT. Along with the introduction of the Quality Incentive Program payment reducing composite rate payment for URR <65% in 2012, the percentage of patients is now only 5% as of August 2012.[26] Compared to the United States, the prevalence of spKt/V < 1.2 is higher, and average BFR lower, in all other DOPPS countries.[10] In addition to Japan, DOPPS countries with high prevalence of Kt/V < 1.2 include Italy (26%) and China (28%).[27] Prevalence of URR <65% was the second highest in Japan (32%) among DOPPS countries, only lower than Saudi Arabia (48%) (Karkar et al. ASN 2012 abstract, TH-PO802; page 284A).

In conclusion, we have provided a detailed investigation of the trends in low Kt/V, the association of low Kt/V with survival by gender, and its relation with modifiable HD practices in the Japanese DOPPS patient population from 1999 to 2011. The results of this investigation suggest that small changes in modifiable practices, specifically increasing BFRs and dialysis session TTs for some patients, may decrease the percentage of patients with low Kt/V and likely enhance the survival of these patients. These findings from Japan may apply to other countries where large fractions of HD patients have Kt/V levels less than 1.2.

ACKNOWLEDGMENTS

The DOPPS program is supported by Amgen, Kyowa Hakko Kirin, AbbVie Inc., Sanofi Renal, Baxter Healthcare, Vifor Fresenius Medical Care Renal Pharma, Ltd, and Fresenius Medical Care. Additional support for specific projects and countries is also provided in Canada by Amgen, BHC Medical, Janssen, Takeda, Kidney Foundation of Canada (for logistics support); in Germany by Hexal, DGfN, Shire, WiNe Institute; for PDOPPS in Japan by the Japanese Society for Peritoneal Dialysis (JSPD). All support is provided without restrictions on publications.

DISCLOSURE STATEMENT

Dr Robinson has received speaker fees for Kyowa Hakko Kirin. Dr Pisoni has received speaker fees from Amgen, Kyowa Hakko Kirin, and Vifor; has served as a consultant for Pursuit Vascular; and has served on an advisory panel for Merck.

Manuscript received September 2013; revised December 2013.

REFERENCES

1 Nakai S, Iseki K, Itami N, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2010). *Ther Apher Dial*. 2012; **16**:483–521.
2 U.S. Renal Data System. *USRDS 2010 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. Bethesda, MD, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 2010.
3 2012 CORR Report—Treatment of End-Stage Organ Failure in Canada, 2001 to 2010: Canadian Institute for Health Information, 2012. Available from: https://secure.cihi.ca/estore/productFamily.htm?locale=en&pf=PFC1696 (accessed date: December 11, 2012).
4 The Renal Association UK Renal Registry. The Fourteenth Annual Report December 2011, 2011. Available from: http://www.renalreg.com/Reports/2011.html (accessed date: January 13, 2013).
5 ANZDATA Registry. Thirty Fourth Annual Report 2011 Australia and New Zealand Dialysis and Transplant Registry. Adelaide, SA. In: Clayton P, Hurst K, ed, 2011. Available from: http://www.anzdata.org.au/v1/report_2011.html (accessed date: February 1, 2013).
6 Goodkin DA, Bragg-Gresham JL, Koenig KG, et al. Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: The Dialysis Outcomes and Practice Patterns Study (DOPPS). *J Am Soc Nephrol*. 2003; **14**:3270–3277.
7 Goodkin DA, Pisoni RL, Locatelli F, et al. Hemodialysis vascular access training and practices are key to improved access outcomes. *Am J Kidney Dis*. 2010; **56**:1032–1042.
8 Pisoni RL, Arrington CJ, Albert JM, et al. Facility hemodialysis vascular access use and mortality in countries participating in DOPPS: An instrumental variable analysis. *Am J Kidney Dis*. 2009; **53**:475–491.
9 Tentori F, Zhang J, Li Y, et al. Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant*. 2012; **27**:4180–4188.
10 *2010 Annual Report of the Dialysis Outcomes and Practice Patterns Study: Hemodialysis Data 1999–2008*. Ann Arbor, MI, Arbor Research Collaborative for Health. 2010. Available from: http://www.dopps.org/annualreport/ (accessed date: January 29, 2014).
11 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**:7–15.

12 Young EW, Goodkin DA, Mapes DL, et al. The Dialysis Outcomes and Practice Patterns Study (DOPPS): An international hemodialysis study. *Kidney Int*. 2000; **57**:S74–S81.
13 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.
14 Shinzato T, Nakai S, Akiba T, et al. Survival in long-term haemodialysis patients: Results from the annual survey of the Japanese Society for Dialysis Therapy. *Nephrol Dial Transplant*. 1997; **12**:884–888.
15 KDOQI clinical practice guidelines for hemodialysis adequacy, update 2006. 2006. Available from: http://www.kidney.org/Professionals/kdoqi/guideline_upHD_PD_VA/index.htm (accessed date: March 10, 2013).
16 Saran R, Bragg-Gresham JL, Levin NW, et al. Longer treatment time and slower ultrafiltration in hemodialysis: Associations with reduced mortality in the DOPPS. *Kidney Int*. 2006; **69**:1222–1228.
17 Port FK, Pisoni RL, Bommer J, et al. Improving outcomes for dialysis patients in the international Dialysis Outcomes and Practice Patterns Study. *Clin J Am Soc Nephrol*. 2006; **1**:246–255.
18 Eknoyan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med*. 2002; **347**:2010–2019.
19 Wolfe RA, Ashby VB, Daugirdas JT, et al. Body size, dose of hemodialysis, and mortality. *Am J Kidney Dis*. 2000; **35**:80–88.
20 Rocco MV, Dwyer JT, Larive B, et al. The effect of dialysis dose and membrane flux on nutritional parameters in hemodialysis patients: Results of the HEMO Study. *Kidney Int*. 2004; **65**:2321–2334.
21 Depner T, Daugirdas J, Allon M, et al. Dialysis dose and the effect of gender and body size on outcome in the HEMO Study. *Kidney Int*. 2004; **65**:1386–1394.
22 Port FK, Wolfe RA, Hulbert-Shearon TE, et al. High dialysis dose is associated with lower mortality among women but not among men. *Am J Kidney Dis*. 2004; **43**:1014–1023.
23 Ramirez SP, Kapke A, Port FK, et al. Dialysis dose scaled to body surface area and size-adjusted, sex-specific patient mortality. *Clin J Am Soc Nephrol*. 2012; **7**:1977–1987.
24 Mactier R, Hoenich N, Breen C. The renal association clinical guidelines; haemodialysis guidelines 5.1 to 5.10. Final draft. The renal association clinical guidelines, 2009. Available from: http://www.renal.org/Clinical/GuidelinesSection/Haemodialysis.aspx#s5 (accessed date: March 23, 2013).
25 Asano M, Thumma J, Oguchi K, et al.; J-DOPPS Research Group. Vascular access care and treatment practices associated with outcomes of arteriovenous fistula: International comparisons from the Dialysis Outcomes and Practice Patterns Study. *Nephron Clin Pract*. 2013; **124**:23–30.
26 Dialysis Outcomes and Practice Patterns Study Practice Monitor website. Available from: http://www.DOPPS.org/DPM (accessed date: March 10, 2013).
27 Wang M, Bieber BA, Guidinger M, et al. Dialysis treatment time, dialysis frequency, and delivered single pool Kt/V among hemodialysis patients in the China Dialysis Outcomes and Practice Patterns Study (DOPPS). FP624. *Nephrol Dial Transplant Plus*. 2012; **27**(Suppl 2):ii280.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 Patient-level and facility-level blood flow rate and all-cause mortality; Cox models stratified by DOPPS phase and adjusted for age, gender, vintage, weight, height, 13 summary comorbid conditions, serum albumin, and creatinine, and accounting for facility clustering effects. Results were consistent after additional adjustment for treatment time (TT). Facility-level model additionally adjusted for two facility-level parameters: facility mean hemoglobin and facility % of patients with serum phosphorus > 5.5 mg/dL. P value when treating blood flow rate as a continuous variable was 0.28 for patient level and 0.58 for facility mean blood flow rate.
Figure S2 Patient and facility-level treatment time (TT) and all-cause mortality; Cox models stratified by DOPPS phase and adjusted for age, gender, vintage, weight, height, 13 summary comorbid conditions, serum albumin, and creatinine, and accounting for facility clustering effects. Results were consistent after additional adjustment for blood flow rate. Facility-level model additionally adjusted for two facility-level parameters: facility mean hemoglobin and facility % of patients with serum phosphorus > 5.5 mg/dL. Over 90% of patients had treatment time at exactly 180, 210, 240, 270, or 300 min. All remaining values were rounded to the nearest 30-min interval for the patient-level analysis. P value when treating TT as a continuous variable was 0.005 for patient level and 0.02 for facility mean TT.
Table S1 Adjusted odds ratio (95% CI) of Kt/V < 1.2 for patient characteristics, overall and by gender.