Explaining International Trends in Mortality on Hemodialysis Through Changes in Hemodialysis Practices in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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Rationale & Objective: Case-mix adjusted hemodialysis mortality has decreased since 1998. Many factors that influence mortality may have contributed to this trend, and these associations may differ by continental region. We studied changes in hemodialysis facility practices over time and their potential role in mediating changes in patient survival.

Study Design: Observational prospective cohort study.

Setting & Participants: Adult hemodialysis patients treated in 500 hemodialysis facilities participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS) between 1999 and 2015 in the United States, Japan, and 4 European countries: Germany, Italy, Spain, and the United Kingdom.

Predictors: Four practice measures at each facility: the percentages of patients with Kt/V ≥ 1.2, interdialytic weight gain [IDWG] < 5.7%, phosphorus < 6 mg/dL, and using arteriovenous fistulas (AVFs).

Outcome: Patient survival.

Analytical Approach: Mediation analyses, adjusted for case mix, were conducted using 3-year study phase as the exposure and facility practice measures as potential mediators.

Results: In Europe, we observed a 13% improvement in overall case-mix adjusted survival per decade. Trends in facility practice measures, especially Kt/V and phosphorus, explained 10% improvement in case-mix survival per decade, representing 77% (10% explained of 13% improvement) of the observed improvement. In Japan, 73% of the observed 12%/decade improvement in case-mix adjusted survival could be attributed to facility practices, especially Kt/V and IDWG. In the United States, 56% of the observed 47%/decade improvement in case-mix adjusted survival could be attributed to facility practices, especially AVF use and phosphorus control.

Limitations: Unmeasured changes in the characteristics of the patient population over this period may confound the observed associations.

Conclusions: The improvements in adjusted hemodialysis patient survival in Europe, Japan, and the United States from 1999 to 2015 can be largely explained by improvements in specific facility practices. Future changes in patient survival may be responsive to further evolution in the implementation of common clinical practices.

Visual Abstract online

Complete author and article information (including a list of the members of the DOPPS 7 (2018-2021) Country Investigators) provided before references.

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Patient survival on hemodialysis is much lower than survival among the general population and among many populations with chronic diseases, but survival among dialysis patients has been generally improving.[1,2] Between 1999 and 2015, the case-mix adjusted improvement in survival has been substantial, and it has been especially dramatic in the United States, which has historically had higher mortality rates than elsewhere.[2-5] Mortality rates among US dialysis patients, adjusted for demographic factors, experienced a greater percentage decline than among Medicare beneficiaries with other major medical conditions.[3] To our knowledge, the reasons for these improvements have not been well-explained in the literature.

The Dialysis Outcomes and Practice Patterns Study (DOPPS) was launched in 1996 on the premise that survival on hemodialysis could be improved by identification of better clinical practices.[6,7] Clinical practice recommendations, based on varying strengths of evidence, are published and updated by nephrology organizations such as the Kidney Disease Outcomes Quality Initiative (KDOQI), the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA), the Japanese Society for Dialysis Therapy (JSDT), and, since 2013, Kidney Disease Improving Global Outcomes (KDIGO). Attention to some of these recommendations may have materially improved survival through improvements in care provided by dialysis facilities.

The goal of this study was to identify whether and how changes in specific hemodialysis practices explain improved survival within 3 regions between 1999-2015: the United States, Japan, and 4 large western European countries (Germany, Italy, Spain, and the United Kingdom).

PLAIN-LANGUAGE SUMMARY

Case-mix adjusted survival of patients treated with hemodialysis has improved over the last 2 decades in the United States, Japan, and Europe. Some of this improvement can be explained by region-specific changes in 4 dialysis practices, namely increases in the proportions of patients achieving (1) Kt/V ≥ 1.2, (2) serum phosphorus levels < 6 mg/dL, (3) interdialytic weight gain < 5.7% of body weight, and/or (4) use of arteriovenous fistulas as vascular access, with the magnitude varying according to region-specific trends in these practices. These findings suggest that further improvement in these practice measures may be attended by further reductions in mortality among patients treated with maintenance hemodialysis.

Methods

Data

DOPPS is a multiphase, prospective cohort study of adult (≥18 years of age) patients treated with in-center hemodialysis.[7] Study approval and patient consent were obtained as required by national and local ethics committee regulations. The DOPPS was approved by an independent institutional review board (E&I Study Number 98004-2, latest). Mortality data were collected on all patients at each study site, and detailed practice and laboratory data were collected from a random sample of patients (typically 20-30) within each participating study site. We used 1999-2015 DOPPS data from 5 study phases: phase 1 (1999-2001), phase 2 (2002-2004), phase 3 (2005-2008), phase 4 (2009-2011), and phase 5 (2012-2015). We limited analyses to 500 hemodialysis facilities in the countries that participated in all 5 DOPPS phases: Germany, Italy, Spain, and the United Kingdom (which together we have labeled "Europe"), Japan, and the United States. Cross-sections of prevalent patients at these facilities were selected at the start of each 3-year study phase.

Figure 1 lists the inclusion/exclusion criteria and resulting sample sizes including both the "DOPPS census" of 88,157 patients at participating facilities with mortality ascertainment and limited case-mix data and the DOPPS sample of 31,050 DOPPS patients randomly selected for more extensive data collection within each facility. Practices for each facility were determined using facility-level prevalences derived from DOPPS sample patients within each facility.

Patient characteristics were obtained at patient entry (baseline) into a DOPPS phase. Time at risk started at patient entry within each phase and continued until the earliest of any of the following: death, kidney transplantation, up to 7 days after departure from the facility for change of dialysis modality, withdrawal from dialysis (if

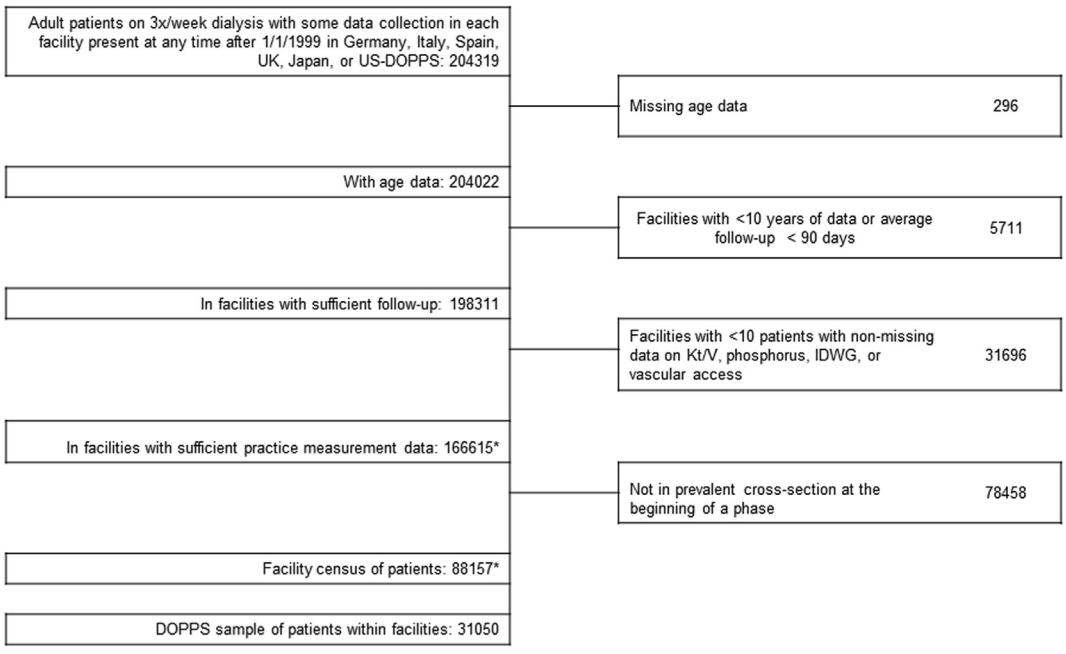

Figure 1. Flow diagram showing eligibility, inclusion/exclusion criteria, and the final sample size. *The 88,157 observations in the census include observations from 45,067 unique patients, with baseline data re-collected for patients at the beginning of each phase if they continued, and with follow-up restarted. The 31,050 observations in the DOPPS sample are based on 25,536 unique patients, with some patients again included in more than 1 phase. Abbreviations: DOPPS, Dialysis Outcomes and Practice Patterns Study; IDWG, interdialytic weight gain.

no indication of death provided), return of kidney function, or transfer to another facility. Follow-up time was censored at the end of each study phase, with follow-up from phase 5 ending in June 2015.

Facility-level practice measures considered as potential explanatory factors (mediators) of mortality trends were of 2 types: (1) those based on the proportion of sampled patients in each facility meeting a treatment threshold and (2) those based on average levels of clinical measures among the sampled patients within each facility. Focusing on facility-level practice measures instead of their corresponding patient-level measures helped reduce confounding by indication.[8]

The following 18 practice measures, grouped into treatment and nutrition, were considered and evaluated for inclusion. The 4 practice measures that were included based on the results of the evaluation (numbered here) are described in the results section later.

- Vascular access: (1) type of vascular access (% arteriovenous fistula, % central venous catheter)
- HD Adequacy: (2) single-pool Kt/V (% ≥1.2), dialysis session length (minutes), (3) interdialytic weight gain (IDWG < 5.7% of patient postdialysis weight), predialysis systolic blood pressure (% weekly average within 140-160 mm Hg), postdialysis systolic blood pressure (% weekly average within 140-160 mm Hg), prescribed dialysate sodium concentration
- Nutrition: Serum albumin (% ≥4 g/dL), average postdialysis weight (kg)
- Anemia: Hemoglobin (% within 10-12 g/dL); ferritin (% 200-500 ng/mL)
- Chronic kidney disease (CKD) mineral bone disease (MBD): (4) serum phosphorus (% < 6 mg/dL), parathyroid hormone (PTH) level (% < 600 pg/mL)
- Other: Number of patients per nurse, number of patients per non-nurse staff member, prescribed dialysate potassium concentration, and serum sodium concentration

Statistical Analysis

We are assuming that calendar time, represented by DOPPS phases 1-5 during 1999-2015, has no effect on patient survival except through measured and unmeasured mediators. Thus, treating practice measures as potential mediators between calendar time and survival, adjusted for other factors (eg, patient case mix), enables us to assess the degree to which changes in those practice measures explain trends in patient survival. In short, the indirect effect of calendar time in each global region is the average case-mix adjusted improvement in patient survival (per decade) attributable to the facility practices acting as 4 during the 17-year study period.

The main outcome in this study is survival, which is the probability of *not* dying from any cause during up to 3 years of follow-up within each DOPPS phase. Our statistical method is a type of causal mediation analysis. A mediator is a variable that lies in the causal pathway between a given exposure and an outcome of interest.

Exposure: calendar time (using DOPPS phases 1-5, 1999-2015)

↓

Mediators: hemodialysis facility practices during follow-up (focusing on 4 practice measures)

↓

Outcome: patient survival during follow-up

We use the term "causal pathway" to describe the causal effects that must be considered in any attempt to identify possible sources of confounding and bias when investigating potential risk factors.[9] We have attempted to develop estimates that are as unbiased and unconfounded as possible, but estimates based on observational data should always be interpreted cautiously.

We are decomposing the estimated total effect of the exposure on the outcome into 2 parts: an indirect (mediated) effect and a direct effect, as illustrated in Figure S1. Because the "exposure" is calendar time—not an observed exposure or intervention in the usual sense—our mediation analysis is somewhat unusual. The estimated indirect effect of the exposure (calendar time) on the outcome is that portion of the total effect that is "explained by" all measured mediators (practices), and we can express that indirect effect as a proportion of the total effect. The estimated direct effect is that portion of the total effect that is explained by unmeasured and possibly unknown mediators or residual bias. Note that our use of the term "effect" comes from standard statistical terminology in mediation analyses; we are estimating the possible direct and indirect effects using associations found in observational data.

Dialysis practice measures were evaluated separately in each region as potential mediators using the "product method" to estimate indirect effects, as illustrated in Figure S1. Accelerated failure time (AFT) models were used to model relative survival time (time to death) of patients from the baseline start of each phase, so effects are shown as the expected survival time, proportional to a reference category. Adjustment was made in each model of the mediators and each AFT model for the following potential confounders: age, race (Black vs non-Black, except in Japan), sex, years on dialysis at baseline in each DOPPS phase (vintage), 13 comorbid conditions (coronary artery disease, cancer, cardiovascular disease, cerebrovascular disease, congestive heart failure, diabetes, gastrointestinal bleeding, hypertension, lung disease, neurological disorder, psychiatric disorder, peripheral vascular disease, and recurring cellulitis), body mass index (BMI), urine volume (<200 vs 200+ mL/day), and an identifier for US facilities when data collection came from electronic health records.

Table 1. Summary Statistics of Outcomes, Demographics, Comorbid Conditions, and Practice Measures by DOPPS Phase and Global Region

	DOPPS Phase (y)					Region		
	1 (99-01)	2 (02-04)	3 (05-08)	4 (09-11)	5 (12-15)	Europe	Japan	US
Patients, Events, and Follow-up								
DOPPS census count	19,931	15,750	15,700	19,345	17,432	26,264	27,121	34,773
DOPPS sample count	7,115	5,667	5,483	6,829	5,956	10,094	8,523	12,433
Deaths in sample	1,664	1,307	1,253	1,465	1,362	2,513	978	3,560
Deaths in census	4,582	3,369	3,537	3,920	3,846	6,682	3,039	9,533
Follow-up, y	1.6	1.6	2.0	1.7	1.9	1.8	2.1	1.5
Demographics and Comorbid Factors in Sample								
Age, y	60.2	61.8	62.5	64.0	65.0	63.6	62.2	62.1
Age 65+ y	42%	48%	49%	52%	55%	55%	44%	47%
Male	58%	57%	58%	58%	61%	58%	62%	55%
BMI, kg/m^2	23.8	24.2	24.5	26.0	25.8	25.2	20.9	27.4
CAD	35%	44%	54%	38%	30%	38%	28%	49%
Cancer	8%	10%	12%	14%	12%	13%	8%	12%
Cardiovascular, other	30%	34%	35%	29%	22%	34%	28%	27%
Cerebrovascular	15%	16%	16%	14%	12%	16%	13%	15%
CHF	29%	28%	37%	26%	22%	24%	16%	40%
Diabetes	35%	36%	38%	48%	46%	28%	32%	57%
GI bleed	6%	6%	5%	5%	4%	5%	4%	6%
HTN	74%	77%	80%	85%	84%	79%	70%	87%
Lung	9%	10%	11%	13%	10%	13%	3%	14%
Neurologic disease	7%	11%	11%	12%	8%	10%	7%	11%
Psychiatric disorder	18%	18%	12%	20%	13%	18%	4%	24%
PVD	20%	24%	26%	27%	20%	27%	14%	26%
Recurring cellulitis	6%	7%	7%	10%	6%	8%	4%	10%
Vintage	5.1	4.9	5.6	5.3	5.5	5.0	7.9	3.7
Residual urine volume >200 mL/d	25%	26%	30%	26%	26%	33%	22%	24%
Practice Measures[a]								
Kt/V 1.2+, fac avg	75%	77%	82%	86%	87%	79%	74%	88%
Fistula, fac avg	53%	61%	71%	65%	72%	72%	91%	40%
Catheter, fac avg	26%	23%	16%	24%	18%	22%	2%	35%
Albumin 4+g/dL, fac avg	35%	33%	37%	36%	33%	38%	30%	36%
Hb 10-12 g/dL, fac avg	47%	46%	48%	57%	61%	48%	52%	54%
Postdialysis weight, fac avg kg	65.8	66.6	67.3	72.6	71.8	69.6	53.5	78.8
IDWG <5.7%, fac avg	87%	89%	91%	93%	95%	95%	85%	91%
Phosphorus < 6 mg/dL, fac avg	60%	63%	70%	74%	75%	72%	66%	67%
Ferritin 200-500 ng/mL, fac avg	29%	32%	32%	27%	23%	37%	19%	28%
SBP 140-160 mm Hg, fac avg								
Postdialysis	30%	29%	25%	25%	26%	24%	33%	26%
Predialysis	37%	36%	34%	33%	34%	33%	39%	33%
Avg patients/nurse	4.5	6.9	7.9	6.6	6.7	6.2	5.8	7.3
Avg patients/non-nurse staff	6.6	9.1	8.0	7.5	8.2	5.9	14.0	4.0
Prescribed dialysate potassium, mEq/L	2.1	2.0	2.1	2.1	2.2	2.1	2.0	2.1
Prescribed starting dialysate sodium, mmol/L	140.8	140.9	140.2	139.4	139.4	139.4	140.6	140.6
Dialysis session length, min	227.3	229.4	233.6	228.6	231.9	236.4	239.8	218.0
Serum sodium, mEq/L	138.3	138.3	138.4	138.2	138.1	138.2	138.9	137.9
PTH < 600 pg/mL, fac avg	88%	90%	89%	89%	88%	88%	95%	85%

Values are count, mean, or % as indicated. Abbreviations: Avg, average; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; DOPPS, Dialysis Outcomes and Practice Patterns Study; fac avg, facility average; GI, gastrointestinal; Hb, hemoglobin; HTN, hypertension; IDWG, interdialytic weight gain; PTH, parathyroid hormone; PVD, peripheral vascular disease; SBP, systolic blood pressure.

[a]Facility average is calculated from DOPPS sample patient data within the facility if the facility had at least 10 such patients with non-missing data. All demographic, comorbid factors, and practice measures listed have a $P < 0.0001$ for their trend over time within at least 1 region. Comorbid conditions, BMI, and practice measures expressed as percentages are all based on 31,080 sampled patients. All patient factors in the table except age, sex, and vintage and all practice measure data based on a facility average were based on data collected on the sampled patients within each facility.

The indirect effect of time through all potential mediators (our primary interest) was calculated as the sum of the products of 2 estimated parameters: the effect of calendar time on each mediator from the linear models and the effect of each mediator on survival time from the AFT model, as described in the text accompanying Figure S1. The collective indirect effect of the 4 mediators is partitioned into the contribution made by each potential mediator. These estimated effects are expressed as the change expressed as a proportion of the overall trend in patient survival per calendar decade. We computed 95% confidence intervals of the indirect effect estimates using a bootstrap approach (200 iterations per model).[10] Analyses were performed separately for each region.

Covariates had up to 5% missing data. We handled this using the SAS multiple imputation procedure with 20 imputations and the fully conditional specification option, which achieves satisfactory results with fewer iterations than Markov Chain Monte Carlo (MCMC) methods.[11,12] Imputation was carried out within each bootstrapped replicate dataset to produce valid estimates of the confidence intervals.[13]

Sensitivity analyses were conducted using the larger population of census data (with restricted covariate adjustment), different groups of practice measures treated as potential mediators, and subgroups of the total patient population (age <65 vs 65+, male vs female).

Results

Table 1 describes the patient population and the covariates used by phase and by region. The expected time to death (survival time) from DOPPS baseline in each region, by phase, relative to Europe in phase 5, based on AFT models fitted to DOPPS patients, unadjusted and adjusted for age, is shown in Figure 2. The within-sample trends show more variability and are shown in Figure S2. The age-adjusted relative life expectancy was higher in Japan and remained nearly constant. It was lower in Europe and the United States and increased over time.

Table 2 shows unadjusted, age-adjusted, and fully adjusted trends in survival times per decade, overall and stratified by age category (<65, ≥65) and sex, derived from AFT models on survival within each region. Cell values >1 indicate improvements in survival time during follow-up. The fully adjusted trend estimates per decade were lower for Europe (1.13) and Japan (1.12) than for the United States (1.47), indicating life expectancy increased by 13%, 12%, and 47% per decade, respectively. Adjusted estimates are generally higher, probably due to adjustment for the aging trends. Fully adjusted improvements in survival time were slightly greater in patients <65 years of age in Europe and Japan, but not in the United States. Relative improvements in female versus male patient survival were greatest in Japan (females: 1.28; males: 1.02).

The 18 practice measures were narrowed to 4 that satisfied the 2 basic features of a mediator: they were associated with the exposure—that is, they changed consistently over the study period (1999-2015, see Figs S3a-S3p) and they were consistently associated with survival. Measures that were in the causal pathways of each other, such as dialysate sodium concentration and IDWG, were considered duplicative, and 1 primary measure for each such causal pathway was chosen. This process is summarized in Table 3. The 4 potential mediators that met these criteria were used in our main analyses: the proportion of patients with Kt/V > 1.2, the percentage of fistula users, the proportion of patients with

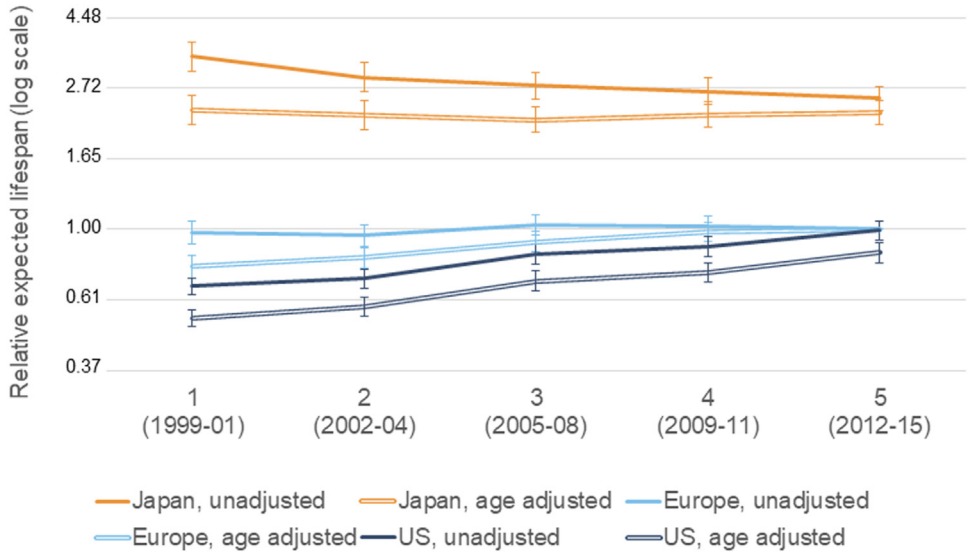

Figure 2. Unadjusted and age-adjusted mean survival time, by DOPPS phase (1-5) and global region, relative to Europe in phase 5 (reference group). Abbreviation: DOPPS, Dialysis Outcomes and Practice Patterns Study.

Table 2. Average Proportional Improvement in Expected Survival Time Per Decade, Unadjusted, Age-adjusted, and Fully Adjusted, by Age Category and Sex Within Each Region

	All	Age <65	Age 65+	Female	Male
Europe					
Unadjusted	0.97 (0.90-1.05)	1.21 (1.04-1.41)	0.98 (0.90-1.08)	0.94 (0.83-1.07)	0.99 (0.90-1.10)
Age adjusted	1.14 (1.05-1.23)	1.25 (1.07-1.45)	1.11 (1.02-1.22)	1.11 (0.98-1.25)	1.16 (1.06-1.28)
Fully adjusted	1.13 (1.04-1.23)	1.24 (1.06-1.47)	1.10 (0.99-1.21)	1.12 (0.98-1.28)	1.13 (1.02-1.26)
Japan					
Unadjusted	0.79 (0.69-0.90)	0.90 (0.71-1.15)	0.97 (0.83-1.14)	0.97 (0.78-1.20)	0.70 (0.59-0.84)
Age adjusted	1.07 (0.94-1.22)	1.05 (0.82-1.34)	1.07 (0.92-1.25)	1.33 (1.08-1.64)	0.95 (0.80-1.12)
Fully adjusted	1.12 (0.98-1.29)	1.20 (0.93-1.55)	1.11 (0.94-1.31)	1.28 (1.02-1.60)	1.02 (0.86-1.22)
United States					
Unadjusted	1.35 (1.25-1.46)	1.34 (1.18-1.53)	1.41 (1.28-1.55)	1.42 (1.26-1.60)	1.30 (1.17-1.44)
Age adjusted	1.42 (1.32-1.53)	1.34 (1.18-1.53)	1.47 (1.34-1.62)	1.44 (1.28-1.62)	1.41 (1.27-1.56)
Fully adjusted	1.47 (1.36-1.60)	1.43 (1.24-1.65)	1.54 (1.39-1.71)	1.51 (1.33-1.72)	1.43 (1.28-1.59)

Estimates from phase as a continuous exposure in accelerated failure time models on 31,051 Dialysis Outcomes and Practice Patterns Study (DOPPS) sample patients within each region, stratified by age and sex. Fully adjusted for age, Black/non-Black race (except in Japan), sex, time on dialysis, residual urine volume >200 mL vs ≤200 mL, body mass index, and 13 comorbid conditions (coronary artery disease, congestive heart failure, other cardiovascular, cancer, cerebrovascular disease, diabetes, gastrointestinal bleed, hypertension, lung disease, neurological disease, psychiatric disorder, peripheral vascular disease, and recurring cellulitis).

phosphorus < 6 mg/dL, and the proportion of patients with IDWG < 5.7%.

Figure 3 shows the trends for each of the 4 practice measures (potential mediators) by region, and Figure S3 show the trends in the other practice measures. Although phosphorus control and IDWG < 5.7% show smooth, continuous improvements across DOPPS phases within regions, the other measures, particularly fistula use, show very different trends across phases. Improvement in fistula use was much greater in the United States, but fistula use in the United States was still lower in phase 5 than in the other regions.

Results of the main mediation analyses for the 4 potential mediators in each region are summarized in Figure 4. The proportions illustrated in the figure reflect the indirect (mediated) effects of the 4 mediators (color coded) and their net combination (dotted) that explain improvement in survival time per decade in each global region. In Europe, the primary mediators were Kt/V and phosphorus, and the net mediation from all 4 practices was 10% (95% CI, ±6%). "Negative mediation" from IDWG in Figure 4 indicates that the observed increase in this measure resulted in *less* improvement in survival than would have occurred with no change in that facility mediator. The total case-mix adjusted survival improvement was 13%, and the percent mediated by the 4 mediators was 10%, or 77% of this 13% figure.

In Japan, the primary mediators were IDWG and Kt/V, and the net mediation from all 4 practices was 9% (95% CI, ±6%). The total case-mix adjusted survival improvement was 12%, so the percent mediated by the 4 mediators was 9%/12% = 73%.

In the United States, all 4 mediators except IDWG had impacts on survival improvement, and the net mediation was 26% (95% CI, ±10%). The total case-mix adjusted survival improvement was 47%, so the percent mediated by the 4 mediators was 26%/47% = 56%.

Results based on census data in DOPPS facilities were similar to those based on DOPPS sample patients in Figure 4 (Fig S4). Variation existed between patient subgroups and adjusting for additional confounders, but the mediation (indirect effects) remained appreciable (Fig S5).

Discussion

Some of the confounder-adjusted changes in survival during the 17-year study period can be explained by improvements in 4 facility practices, measured as the proportions of hemodialysis patients in a facility meeting practice thresholds. The relative importance of those practices differs across the 3 global regions. The indirect effect of Kt/V ≥ 1.2 was observed in all 3 regions; but the indirect effect of IDWG < 5.7% was greater in Japan, the indirect effect of more fistula use was greater in the United States, and the indirect effect of phosphorus < 6 mg/dL was greater in Europe and the United States. The net indirect effect of all facility practices was appreciably larger in the United States (26% per decade) than in Europe (10% per decade) or Japan (9% per decade), primarily because hemodialysis patients in the United States experienced the greatest confounder-adjusted improvement (total effect) in survival time during follow-up (47%/decade in the United States vs 13%/decade in Europe and 12%/decade in Japan).

Facilities in Europe, Japan, and the United States have, on average, experienced improvements in several measures of dialysis practice, such as Kt/V dialysis adequacy, use of fistulas, phosphorus control, and IDWG (Fig 3). For the hemodialysis population in DOPPS facilities, we estimated that improvements in practice explained 77% (10%/13%) of the overall survival improvement in Europe, 73% (9%/12%) in Japan, and 56% (26%/47%) in the United States. The following factors explain substantial amounts of the improved survival in the 3 regions: fistula use and

Table 3. Practice Measures Evaluated and Reasons for Inclusion/Exclusion

Factor	Included or Reason for Exclusion
Vascular Access	
Guidelines: KDOQI 2000,[24] 2015,[25] 2019[26]; JSDT 2005,[27] 2011[28]	
Vascular access type (fistula vs graft/catheter)	Included
Vascular access type (catheter vs fistula/graft)	Mediation analysis results very similar in magnitude to those based on fistula
Hemodialysis Adequacy	
Guidelines: KDOQI 2006,[29] 2015[24]; JSDT 2015[16]	
IDWG < 5.7% of body weight	Included
Predialysis systolic blood pressure, 140-160 mm Hg	No consistent trend, higher values are generally associated with lower risk
Kt/V < 1.2	Included
Dialysis session length, min	Japan, Europe, and the United States have very different ranges, meaning a single threshold would have different effects in each region. Trends are modest or non-directional, and this is in the causal pathway for Kt/V.
Prescribed dialysate sodium concentration (mmol/L) [guideline = avoid sodium profiling]	In causal pathway for IDWG
Nutrition	
Guidelines: KDOQI 2000,[30] 2020[31]	
Albumin levels	Minimal trends
Anemia	
Guidelines: KDOQI 2000,[32] 2002,[33] 2007,[34] KDIGO 2012[35]; JSDT 2004,[36] 2008[37]	
Hemoglobin 10-12 g/dL	Association between hemoglobin within 10-12 range (compared to outside this range) vs mortality varied by time period and region
Ferritin 200-500 ng/mL	Weak and inconsistent association of ferritin level with mortality in DOPPS data
Mineral Bone Disorder	
Guidelines: KDOQI 2003[38]; KDIGO 2009,[17] 2017[18]; JSDT 2008,[39] 2013[40]	
Serum phosphorus < 6 mg/dL	Included
PTH < 600	Weak trends; PTH levels among patients starting dialysis in Japan are substantially lower (these differences are not necessarily due to different treatment on dialysis)
Other	
Serum sodium, mEq/L	In causal pathway for IDWG
Prescribed dialysate potassium, mmol/L	No guideline-based recommended target, ambiguous association with mortality[41]
Patients per nurse, no.	Not particularly associated with patient survival
Patients per non-nurse staff, no.	Not particularly associated with patient survival

Each measure is a specific range either described directly within guidelines or observational evidence, or was chosen to be an undesirable level in any of the guidelines. Abbreviations: IDWG, interdialytic weight gain; JSDT, Japanese Society for Dialysis Therapy; KDIGO, Kidney Disease Improving Global Outcomes; KDOQI, Kidney Disease Outcomes Quality Initiative; PTH, parathyroid hormone.

phosphorus control in the United States; Kt/V and serum phosphorus control in Europe; and Kt/V and IDWG in Japan. Sensitivity analyses tended to show these same factors having the largest effects.

The observed differences in the direct and indirect effects of each practice by region is due largely to differences in baseline practice. Fistula use in Japan was already 91%, giving very little room for improvement, while it was lowest in the United States, thus being an important contributor to improved survival over time. Quality improvement initiatives in the United States extending initially from the Fistula First Initiative, launched by the Centers for Medicare & Medicaid Services in 2003, should be considered widely successful in not only lowering patient exposure to central venous catheters but also very likely in extending lives. After this period, fistula use in the United States dropped, presumably due to COVID-19, from 64% in 2018 to 61% in 2021. We believe there is still substantial room for improvement in fistula use for US patients, particularly during the earliest time periods on dialysis; 85% of the HD patients started with a catheter in 2021.[14]

In 2015, both KDOQI and JSDT indicated that a spKt/V 1.2 is the minimal adequate dose, although higher doses may be desirable for some patients. Adherence to Kt/V ≥ 1.2 has been greatest in the United States from the start, such that the modest improvement over the last 2 decades had little effect on improvement in survival in the

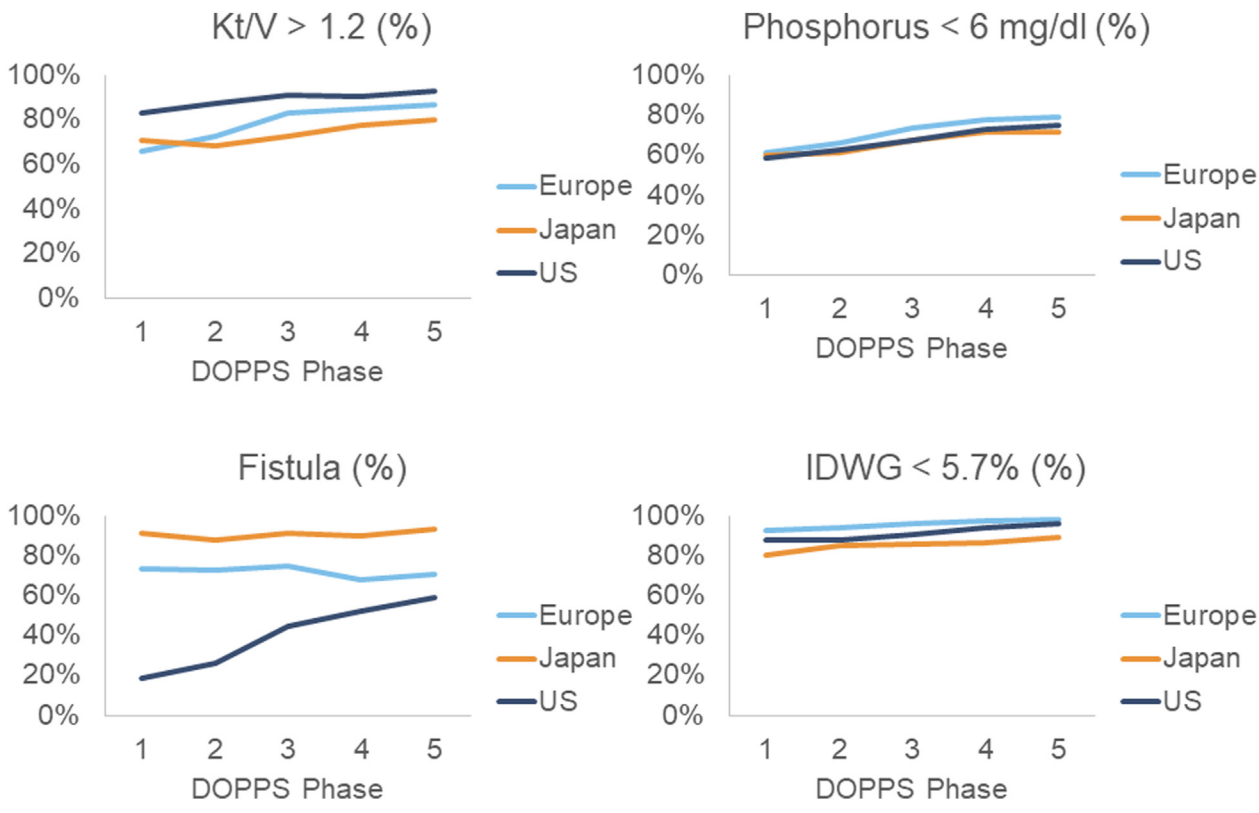

Figure 3. Trends in the unadjusted prevalence of 4 facility practices (A-D), by DOPPS phase (1-5*) and global region. *DOPPS phases: 1 (1999-2001), 2 (2002-2004), 3 (2005-2008), 4 (2009-2011), and 5 (2012-2015). Abbreviations: DOPPS, Dialysis Outcomes and Practice Patterns Study; IDWG, interdialytic weight gain.

United States over time (Table 1). The notable increase in Kt/V ≥ 1.2 over 2 decades in Japan has been attributed to guidance and eventual guidelines recommending minimum blood flow rates of 200 mL/minute.[15,16] Serum phosphorus level was >6.0 mg/dL in ∼40% of patients in the early 2000s in Europe, Japan, and the United States, and substantial decreases over the last 2 decades have helped to explain improved survival in all 3 regions. KDIGO's recommendations in 2009 and 2017 to bring serum phosphorus toward the normal range, supported by clinical insights and observational analyses, appears well justified as we await definitive guidance from clinical trials.[17-20] Lastly, IDWG was >5.7% in 20% or fewer patients in all 3 regions in the early 2000s, with modest further

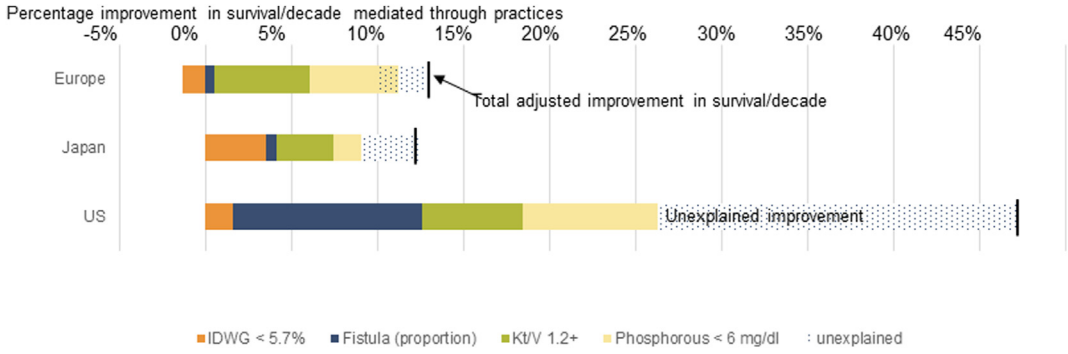

Figure 4. Indirect effects of calendar time (DOPPS phase) on percentage improvement in survival time per decade, as mediated by 4 facility practices among hemodialysis patients in each of 3 global regions. Percentage improvement or decrease in survival attributable to each practice measure is shown, along with the total case mix-adjusted improvement in survival indicated with a vertical bar. Case-mix adjustments include age, sex, Black versus non-Black, vintage, residual urine volume > 200 mL, body mass index, 13 comorbid conditions, and large dialysis organization (versus smaller chain or independent facilities) (US phases 4 and 5). Abbreviations: DOPPS, Dialysis Outcomes and Practice Patterns Study; IDWG, interdialytic weight gain.

reductions over the last 2 decades. That said, dialysis patients in Japan have consistently had greater IDWG, along with higher predialysis blood pressure,[21,22] than in Europe or the United States. In this context, the greater observed reduction that we report in excessive IDWG (>5.7%) and consequent improvement in survival in Japan is as expected.

Although we believe we have identified factors that may help explain regional improvements in mortality during 1999-2015, practices and dialysis mortality have changed after this period. We hope that the methods we have explored may assist in future analyses of mortality and the interference with standard practices associated with COVID-19, among the many other changes and developments since 2015. We believe that the improved practice measures and adjusted patient survival should be commended in all these regions; however, the United States appeared to improve more substantially than the other regions, possibly because the United States started out with much lower survival. The remaining unexplained differences in regional improvement could be due to any number of other factors, including a greater focus on safety and limiting intradialytic complications, more attentive follow-up after hospitalization, and changes in medication usage (eg, erythropoiesis-stimulating agent).

There are several limitations to this work. The association between each facility practice measure and survival may be confounded by unmeasured risk factors; similarly, trends in unmeasured risk factors could confound the associations we found between changes over time in practice and mortality trends. Although each practice measure is aggregated across all DOPPS patients in the facility, reducing the likelihood of confounding by indication, that aggregation (a form of "semi-ecologic analysis") results in bias due to patient-level misclassification.[23] We also acknowledge that our modeling approach ignores the multilevel hierarchy between time, facility-level practice measures, and patient-level outcomes.

Although we treated covariates as fixed at the start of each phase, the patient population in each region may have changed within each DOPPS phase (~3-year duration).

Sampling in the United States in phases 4 and 5 included facilities where primary data collection was through electronic health records (EHR), and earlier phases included only data from medical record abstraction. In case this change in data collection affected the completeness of any of the data collected, we adjusted for an indicator for EHR data collection. This issue would affect only US trends.

The 4 practice measures are not purely reflections of facility practices. Each one may represent more complicated constructs than facility practice alone; each can also be influenced by changes in medication and dialysis treatment, patient choice and adherence, and other factors. For example, although IDWG is associated with facility practices such as dialysate sodium concentration,[23] it is also influenced by patient diet, in conjunction with and independently of facility efforts to influence patient sodium intake. The 4 facility practice measures may represent general indicators of "good" quality of care, available technology and resources, or patient choices and adherence, instead of each being directly responsible for the mortality trend. The 4 measures were not strongly correlated with each other, with correlation coefficients ranging from −0.10 to 0.10; that is, good practices in one area did not necessarily correspond to good overall practice. These analyses were limited to the associations between these specific measures and trends in mortality, not in how changes in these measures were achieved (ie, by clinical practice or by other factors).

In conclusion, to our knowledge, the reasons for the improving trend in case-mix-adjusted hemodialysis patient survival seen in 4 European countries (13% per decade), the United States (47% per decade), and in Japan (12% per decade) since 1999 have not been adequately addressed in the literature. Through mediation analyses, we found that 4 facility practices accounted for a large proportion of overall survival improvement between 1999 and 2015 in each of 3 global regions. Factors associated with the greatest survival improvement include, for the United States, greater fistula use, fewer patients with $Kt/V < 1.2$, and improved phosphorus control; for Europe, improvements in Kt/V and phosphorus control; and for Japan, IDWG. Our findings raise the possibility that further improvement in hemodialysis patient survival may be achieved by continuing to increase facility adherence to evidence-based practice thresholds.

Supplementary Material

Supplementary File (PDF)

Figure S1: Causal diagram illustrating the mediation analysis, with equations described.

Figure S2: Unadjusted and fully adjusted relative expected survival time by DOPPS phase and by region.

Figure S3: Catheter use, ferritin, hemoglobin, parathyroid hormone, predialysis systolic blood pressure, treatment time, dialysate sodium, dialysate potassium, serum sodium, staffing ratios, serum albumin, and postdialysis weight by phase within region.

Figure S4: Indirect effects of calendar time (DOPPS phase) on percentage improvement in survival time per decade, as mediated by 4 facility practices among hemodialysis patients in each of 3 global regions: sampled patients only (not the full census).

Figure S5: Comparison of results of product method estimates of indirect effects mediated through practice measures across sample and census patient populations by age, sex, and dialysis vintage.

Article Information

DOPPS 7 (2018-2021) Country Investigators: A list of the Country Investigators from DOPPS study phases can be found at https://www.dopps.org/OurStudies/HemodialysisDOPPS.aspx.

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Data Sharing: The data that support the findings of this study are available from the corresponding author upon reasonable request. Data may be made available to qualified researchers for approved scientific uses. Some limitations and fees may apply. Arbor Research Collaborative for Health encourages investigators, whether or not previously affiliated with the Dialysis Outcomes and Practice Patterns Study (DOPPS), to submit proposals for data use, collaboration, and ancillary studies.

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International Trends in Mortality on Hemodialysis Through Changes in Hemodialysis Practices

Aim and Population

DOPPS
Dialysis Outcomes and Practice Patterns Study

Observational prospective cohort study

Adult patients treated with hemodialysis:

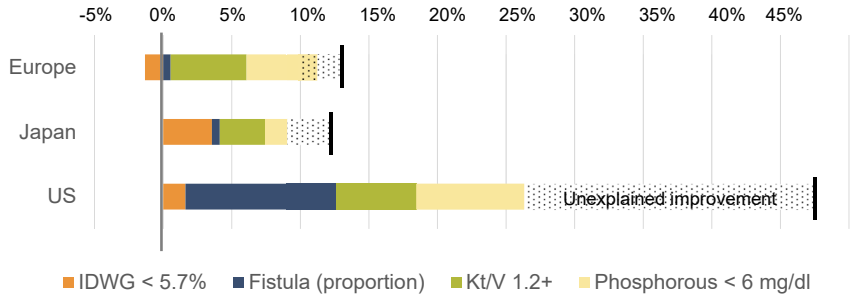
- **Europe*:** 26,264 patients
- **Japan:** 27,121 patients
- **US:** 34,773 patients

**Germany, Italy, Spain, & UK*

Findings

HD practices change over time, but trends differ by region

Proportional improvement in case-mix adjusted survival/decade mediated through practices



CONCLUSION: Improvements in adjusted HD patient survival in Europe, Japan, and the US from 1999-2015 can be largely explained by improvements in specific facility practices.

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