Modifiable Practices Associated with Sudden Death among Hemodialysis Patients in the Dialysis Outcomes and Practice Patterns Study

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Summary

Background and objectives Sudden death is common in hemodialysis patients, but whether modifiable practices affect the risk of sudden death remains unclear.

Design, setting, participants, & measurements This study analyzed 37,765 participants in 12 countries in the Dialysis Outcomes and Practice Patterns Study to explore the association of the following practices with sudden death (due to cardiac arrhythmia, cardiac arrest, and/or hyperkalemia): treatment time [TT] <210 minutes, Kt/V <1.2, ultrafiltration volume >5.7% of postdialysis weight, low dialysate potassium [K_D <3]), and prescription of Q wave/T wave interval–prolonging drugs. Cox regression was used to estimate effects on mortality, adjusting for potential confounders. An instrumental variable approach was used to further control for unmeasured patient-level confounding.

Results There were 9046 deaths, 26% of which were sudden (crude mortality rate, 15.3/100 patient-years; median follow-up, 1.59 years). Associations with sudden death included hazard ratios of 1.13 for short TT, 1.15 for large ultrafiltration volume, and 1.10 for low Kt/V. Compared with $K_D \geq 3$ mEq/L, the sudden death rate was higher for $K_D \leq 1.5$ and $K_D = 2$–2.5 mEq/L. The instrumental variable approach yielded generally consistent findings. The sudden death rate was elevated for patients taking amiodarone, but not other Q wave/T wave interval–prolonging drugs.

Conclusions This study identified modifiable dialysis practices associated with higher risk of sudden death, including short TT, large ultrafiltration volume, and low K_D. Because K_D <3 mEq/L is common and easy to change, K_D tailoring may prevent some sudden deaths. This hypothesis merits testing in clinical trials.

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Introduction

Cardiovascular disease accounts for approximately 50% of the highly premature mortality observed in hemodialysis patients. Close to 50% of cardiovascular deaths in hemodialysis patients are sudden; sudden death thus accounts for 20%–25% of all deaths in hemodialysis patients (1,2). Although sudden death is also common among patients on peritoneal dialysis (1,2), there are reasons to speculate that practices related to the hemodialysis treatment itself may play a specific role. These include the well established risk of arrhythmias associated with electrolyte imbalances, especially potassium shifts (3), as well as the increased risk of sudden death in the 12-hour period that begins with the start of the hemodialysis session or at the end of the long hemodialysis-free interval (4).

Several patient characteristics—such as heart failure, left ventricular hypertrophy, and coronary artery disease—have been associated with a high risk of sudden death in hemodialysis patients (1,5). However, whether readily modifiable practices are associated with the risk of sudden death among hemodialysis patients has received relatively little attention (6). We postulated that selected characteristics of the hemodialysis regimen and/or drug treatment may also affect the risk of sudden death. Specifically, we hypothesized that the rapid changes in extracellular fluid and electrolyte concentrations that occur during shorter dialysis sessions, using low dialysate potassium (K_D) and at a higher ultrafiltration rate, may trigger arrhythmias and other cardiac events that may lead to higher incidence of sudden death. To explore these hypotheses, we analyzed the detailed data from the Dialysis Outcomes and Practice Patterns Study (DOPPS), taking advantage of the substantial variability of practices across the 12 participating countries (7).

Materials and Methods

Study Design and Data Sources

DOPPS is a prospective, observational study of hemodialysis practices and outcomes in 12 countries.

Details on the study design have been described previously (7). We analyzed data from participants in the first three phases (1, 1996–2001; 2, 2002–2004; 3, 2005–2008). Baseline patient characteristics including demographics, detailed comorbidities, laboratory values, and dialysis treatment characteristics are obtained at the time of study entry by medical record abstraction. Clinical variables and medical events, including mortality and cause of death, are updated every 4 months. The study sample comprised 37,765 patients on thrice-weekly hemodialysis from 930 dialysis facilities in 12 countries. Participants were followed until the earliest incidence of death, transplant, change of treatment modality, withdrawal from dialysis, transfer to another facility, or study end. Time at risk was defined as the period from study enrollment until the end of patient follow-up.

Exposure Variables

This study considered the following four modifiable dialysis practices: short duration of dialysis sessions (prescribed treatment time <210 minutes), low dialysis dose (single pool Kt/V <1.2), large ultrafiltration volume (>5.7% of the postdialysis weight), and K_D <3 mEq/L (categorized as ≤1.5 and 2–2.5 mEq/L). Prescription of β blockers and Q wave/T wave interval (QTI)–prolonging drugs (amiodarone, selected antidepressants, antipsychotics, and others) (8,9) was also considered.

Outcomes

The primary outcomes of interest were sudden death and all-cause mortality. Sudden death was defined as primary cause of death reported as death due to cardiac arrhythmia, cardiac arrest, and/or hyperkalemia. Other deaths were classified as "other cardiovascular death" if due to cardiovascular disease (myocardial infarction, pericarditis, atherosclerotic heart disease, cardiomyopathy, valvular heart disease, pulmonary edema due to exogenous fluid, congestive heart failure, and cerebrovascular accident) and "noncardiovascular death" (all deaths not classified as "sudden death" or "other cardiovascular death"). Cause of death was imputed for patients in whom the cause was not reported or available (see Statistical Analyses).

Statistical Analyses

Standard descriptive statistics were used to describe characteristics of study participants by the four modifiable dialysis treatment practices. Cox regression models were used to assess the associations of the four dialysis practices and QTI-prolonging medications with all-cause mortality, sudden death, other cardiovascular death, and noncardiovascular death. Models were adjusted for age, sex, black race, body mass index, years with ESRD, 14 comorbidity classes (coronary artery disease, other cardiac disease, cerebrovascular disease, congestive heart failure, diabetes, gastrointestinal bleeding, hypertension, peripheral vascular disease, lung disease, neurologic disorder, cancer [excluding skin], psychiatric disease, recurrent cellulitis, and HIV infection), catheter use, serum albumin, phosphorus, calcium, parathyroid hormone, hemoglobin, serum creatinine, ferritin, white blood cell count, and single pool Kt/V (except for models with single pool Kt/V and treatment time as exposure variables). To speed computation and allow for different baseline hazard functions, models were stratified by DOPPS phase and country. Models were also adjusted for indicators of facility achievement of clinical guidelines (facility proportion of patients with hemoglobin <11g/dl, albumin <3.2 g/dl, phosphorus >5.5 mg/dl, Kt/V <1.2, and using a catheter as vascular access). Robust variance estimates (sandwich estimator) were used to account for facility-level clustering.

To partially reduce the effect of unmeasured patient-level confounders, we also applied an instrumental variable approach, using the dialysis facilities as the instruments (10–13). For each of the four dialysis practices, we conducted separate instrumental variable analyses, applying a two-stage model method, which is an extension of two-stage least squares. In the first stage, the patient-level predicted treatment was determined using a linear regression model, including all patient covariates and indicators of facility achievement of clinical guidelines, as well as facility indicators as the instruments. In the second stage, Cox regression was used to estimate the hazard of mortality associated with the patient-level predicted treatment with the same covariate adjustments as in the first stage (14–21). Given the low F statistic observed for two of the practices (Kt/V and ultrafiltration volume), we also used limited information maximum likelihood regression, which is considered more robust when instruments are weak (11,22), that is, when the first stage partial F statistic is <10 (23). Limited information maximum likelihood regression uses linear models for both the first and second stage. We used 1-year mortality as the second stage outcome because the censoring rate is low, and modeled it as a dichotomous variable using linear regression as an approximation to logistic regression. IVEware was used to perform multiple imputations of missing data, including cause of death (24). Estimates and their variances from the multiple imputation results were combined according to the Rubin method (25). Sensitivity analyses limited to nonmissing data were performed. The assumption of proportionality of hazards in the Cox regression model was confirmed by an interaction term between each covariate and log-transformed follow-up time. Analyses were performed using SAS software (version 9.2; SAS Institute, Cary, NC). The authors followed the Strengthening the Reporting of Observational studies in Epidemiology guidelines for reporting observational studies (26).

Results

Patient Characteristics

The overall study sample is described in Table 1. As expected, differences were observed between patients with low and adequate Kt/V, as well as between patients treated versus not treated with each of the other three dialysis practices.

Among the 37,765 DOPPS participants included in these analyses, 9046 died (crude mortality rate, 15.3/100 patient-years; median follow-up, 1.59 years; range, 0.003–5.43). The distribution of causes of death in each DOPPS country is shown in Figure 1. Because the number of deaths without a reported cause was relatively high in some countries (Figure 1A), causes of death are also shown

Table 1. Patient characteristics by treatment practice

Mean (SD) or %	Treatment Time <210 min		Kt/V <1.2		Ultrafiltration Volume >5.7%		K_D <3 mEq/L	
	No	Yes	No	Yes	No	Yes	No	Yes
Patients (n)	28,878	8536	18,824	7273	26,880	3970	6606	29,629
Age (yr)	61.0 (14.6)	64.6 (15.3)[a]	62.0 (14.8)	61.2 (14.5)[b]	62.5 (14.6)	57.2 (14.9)[a]	64.4 (14.5)	61.3 (14.8)[a]
Male	60	49[a]	53	72[a]	58	55[a]	54	59[a]
Black	13	15[a]	14	13[a]	13	13[a]	13	14[a]
Vintage	4.2 (5.5)	2.0 (3.8)[a]	4.9 (5.7)	2.6 (4.3)[a]	3.7 (5.2)	6.3 (6.2)[a]	1.8 (3.5)	4.1 (5.5)[a]
Body mass index	24.9 (5.8)	24.1 (5.2)[a]	24.2 (5.6)	25.4 (5.9)[a]	25.0 (5.7)	21.5 (4.0)[a]	25.8 (5.9)	24.5 (5.6)[c]
Catheter	23	35[a]	18	28[a]	23	11[a]	41	22[a]
Comorbid conditions								
coronary artery disease	45	46	46	42	46	40	54	43[a]
other cardiovascular	35	32[c]	36	31[a]	34	35[a]	39	33[a]
cerebrovascular disease	16	18[a]	17	16	17	14[a]	20	16[a]
congestive heart failure	35	37	35	33	34	33[a]	42	34[a]
diabetes	38	40	35	44[a]	38	35[b]	46	37[a]
Laboratory results								
hemoglobin (g/dl)	10.9 (1.7)	10.5 (1.7)[a]	11.1 (1.6)	10.5 (1.8)[a]	10.9 (1.7)	10.6 (1.6)	10.8 (1.7)	10.8 (1.7)[a]
albumin (g/dl)	3.7 (0.5)	3.6 (0.6)[a]	3.7 (0.5)	3.7 (0.6)[a]	3.7 (0.5)	3.8 (0.5)[a]	3.5 (0.6)	3.7 (0.5)[a]
potassium (mEq/L)	5.0 (0.8)	4.8 (0.8)[a]	5.0 (0.8)	4.9 (0.8)[a]	4.9 (0.8)	5.2 (0.8)[a]	4.7 (0.8)	5.0 (0.8)[a]
phosphorous (mg/dl)	5.6 (1.8)	5.6 (1.9)[a]	5.5 (1.7)	5.7 (1.9)[a]	5.5 (1.8)	5.9 (1.9)[a]	5.4 (1.9)	5.6 (1.8)[a]
parathyroid hormone (pg/ml)	177 (275)	187 (282)	172 (272)	184 (269)[b]	178 (271)	175 (297)[a]	190 (269)	178 (280)
creatinine (mg/dl)	9.2 (3.2)	8.0 (3.1)[a]	9.2 (3.0)	9.2 (3.5)[a]	8.9 (3.1)	10.1 (3.2)[a]	7.3 (3.0)	9.2 (3.2)[a]
ferritin (ng/ml)	285 (431)	247 (403)[c]	314 (456)	203 (332)[a]	286 (429)	222 (439)[b]	278 (410)	273 (426)[a]

Serum parathyroid hormone and ferritin values are summarized as median (interquartile range). Significance values obtained from logistic and mixed linear regression models adjusted for the Dialysis Outcomes and Practice Patterns Study phase and accounted for facility clustering effects. K_D, dialysate potassium.
[a] $P<0.001$ for "yes" versus "no" column.
[b] $0.05 \leq P < 0.10$ for "yes" versus "no" column.
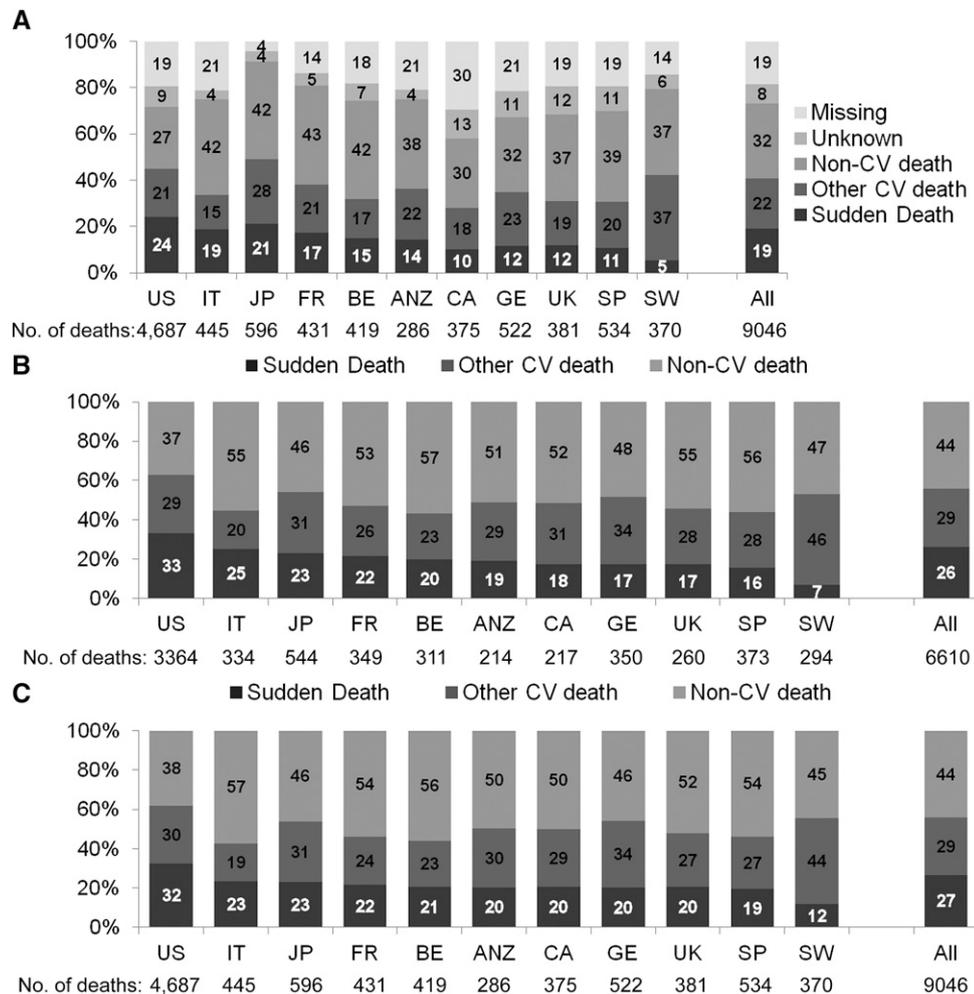[c] $0.001 \leq P < 0.05$ for "yes" versus "no" column.

Figure 1. | Cause of death by country. (A) Observed cause of death by country (*n*=9046 deaths), as reported. (B) Cause of death by country (*n*=6610 deaths), with 2436 deaths excluded due to missing/unknown causes. (C) Cause of death by country (*n*=9046), with imputed causes of death for 2436 with missing/unknown causes. Data from the following phases of the of the Dialysis Outcomes and Practice Patterns Study: phase 1, *n*=15,589 patients from 308 facilities in seven countries, including France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States; phase 2, *n*=11,675 patients from 322 facilities in 12 countries, including the above-mentioned countries as well as Australia, New Zealand, Belgium, Canada, and Sweden; and phase 3, *n*=10,501 patients from 300 facilities in the same 12 countries as in phase 2. US, United States; IT, Italy; JP, Japan; FR, France; BE, Belgium; ANZ, Australia and New Zealand; CA, Canada; GE, Germany; UK, United Kingdom; SP, Spain; SW, Sweden; CV, cardiovascular.

excluding missing causes (Figure 1B) and using imputed causes from one set of the multiple imputation procedure (Figure 1C). When excluding missing/unknown causes, sudden death ranged from 33.4% of deaths in the United States to 6.8% in Sweden. Approximately 6.7% of sudden deaths are reported as due to hyperkalemia.

Variation in Dialysis Practices

Wide variation in the four dialysis practices was observed both across facilities within each DOPPS country and across countries (Figure 2).

Association of Dialysis Practices with Mortality

Higher risk for sudden death and all-cause mortality was seen for patients with treatment time <210 minutes (hazard ratio [HR], 1.13; 95% confidence interval [95% CI], 1.00–1.27; *P*=0.04; and HR, 1.06; 95% CI, 1.00–1.13; *P*=0.04) and ultrafiltration volume >5.7% (HR, 1.15; 95%

CI, 1.00–1.32; *P*=0.04; and HR, 1.09; 95% CI, 1.01–1.19; *P*=0.03). For Kt/V <1.2, the HR for sudden death was 1.06 (95% CI, 1.00–1.12; *P*=0.07) and the HR for all-cause mortality was 1.10 (95% CI, 0.97–1.24; *P*=0.15). For the instrumental variable analyses, the magnitude of the estimates was generally greater than for the standard patient-level analyses, although as expected the estimates were less precise (Table 2).

$K_D \leq 1.5$ and $K_D = 2–2.5$ were associated with increased risk for sudden death (HR, 1.39 for $K_D \leq 1.5$; 95% CI, 1.12–1.74; *P*=0.004; and HR, 1.17 for $K_D = 2–2.5$; 95% CI, 1.01–1.37; *P*=0.04) and all-cause mortality (HR, 1.13 for $K_D \leq 1.5$; 95% CI, 1.03–1.25; *P*=0.01; and HR, 1.08 for $K_D = 2–2.5$; 95% CI, 1.01–1.16; *P*=0.03) compared with $K_D \geq 3$ (Table 3). Similar associations of sudden death with low K_D were observed when models were further adjusted for serum bicarbonate or dialysate bicarbonate (not shown). For $K_D \leq 1.5$, the magnitude of the associations
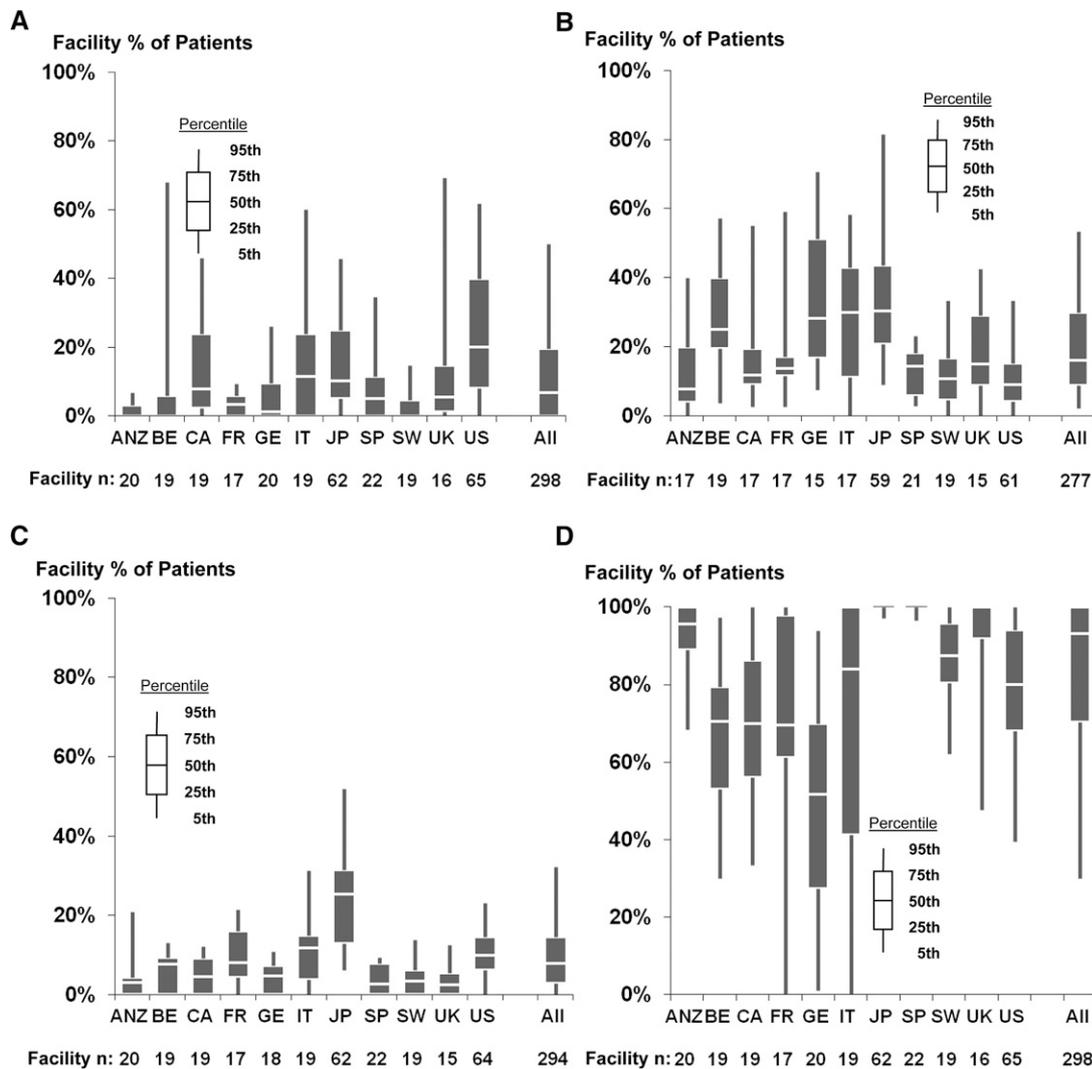
Figure 2. | Facility percentage of patients with short treatment time, low Kt/V, large ultrafiltration volume and low dialysate potassium, by country. Data from phase 3 of the Dialysis Outcomes and Practice Patterns Study, which included 298 facilities with ≥10 patients with each treatment of interest. ANZ, Australia and New Zealand; BE, Belgium; CA, Canada; FR, France; GE, Germany; IT, Italy; JP, Japan; SP, Spain; SW, Sweden; US, United States; UK, United Kingdom; UF, ultrafiltration.

(especially for sudden death) was greater for patients with serum potassium <5 versus ≥5 mEq/L. For K_D=2–2.5, the associations were generally comparable for patients with serum potassium <5 versus ≥5 mEq/L.

Higher risk of all-cause mortality and sudden death was also found when the four dialysis practices were modeled as continuous variables (Figure 3).

Medications

Higher risk of sudden death was evident for amiodarone prescription (HR, 1.44; 95% CI, 1.16–1.81; P=0.001), but not for prescription of other QTI-prolonging drugs (HR, 1.10; 95% CI, 0.94–1.28; P=0.22). β blockers were associated with a lower risk of sudden death (HR, 0.88; 95% CI, 0.78–0.99; P=0.03).

Sensitivity Analyses

Our findings were confirmed in a series of sensitivity analyses. Similar associations between dialysis practices

and mortality were found in the following: in models restricted to prevalent patients (time on dialysis >6 months) and to "healthier" patients (nondiabetic participants aged <65 years); when observed causes of death were used in place of imputed causes of death; when all four practices were included in the same Cox model, indicating that the association of each practice with sudden death was independent of the other three; and when deaths attributed to hyperkalemia were excluded (data not shown).

Discussion

Among 6610 patients with a recorded cause of death in our study, 1734 (26%) deaths were sudden, similar to previous reports on sudden death in US hemodialysis patients (1,2). However, our DOPPS results demonstrate for the first time substantial differences between countries in the proportion of deaths that are reported as

Table 2.   Association of dialysis treatment practices (treatment time, single pool Kt/V, ultrafiltration volume) with mortality

	Patient Level			Instrumental Variable Approach		
	HR	95% CI	*P*	HR	95% CI	*P*
Treatment time <210 min (versus ≥210 min)						
all-cause mortality	1.06	(1.00–1.13)	0.04	1.09	(0.94–1.27)	0.26
sudden death	1.13	(1.00–1.27)	0.04	1.38	(1.04–1.83)	0.03
other cardiovascular death	1.00	(0.89–1.12)	0.96	0.77	(0.58–1.03)	0.08
noncardiovascular death	1.06	(0.97–1.17)	0.20	1.16	(0.93–1.44)	0.18
Kt/V <1.2 (versus ≥1.2)						
all-cause mortality	1.06	(1.00–1.12)	0.07	1.39	(1.07–1.81)	0.01
sudden death	1.10	(0.97–1.24)	0.15	1.71	(1.02–2.87)	0.04
other cardiovascular death	0.96	(0.85–1.08)	0.48	0.95	(0.60–1.50)	0.83
noncardiovascular death	1.10	(1.00–1.21)	0.04	1.59	(1.11–2.29)	0.01
Ultrafiltration volume >5.7% of postweight (versus ≤5.7%)						
all-cause mortality	1.09	(1.01–1.19)	0.03	1.32	(0.84–2.08)	0.23
sudden death	1.15	(1.00–1.32)	0.04	1.56	(0.60–4.03)	0.35
other cardiovascular death	1.17	(1.01–1.36)	0.04	2.36	(1.02–5.46)	0.05
noncardiovascular death	1.00	(0.88–1.14)	0.98	0.78	(0.43–1.43)	0.42

N=37,741. HRs and CIs adjusted for variables listed in Table 1 and in the Materials and Methods, stratified by phase and country, and accounted for facility clustering. IV, instrumental variable; HR, hazard ratio; 95% CI, 95% confidence interval.

sudden: 33.4% in the United States, 17.5% in Canada, 17.8% in Europe, 19.2% in Australia and New Zealand, and 23.2% in Japan. More importantly, our analysis identified several modifiable practices associated with higher sudden death risk. These include short treatment time, excessive ultrafiltration volume, and low Kt/V (most evident in instrumental variable analysis). A low K_D level was also associated with higher sudden death risk, which was most evident in patients with a relatively low (<5) predialysis potassium serum level.

The finding that low K_D may trigger some sudden death in hemodialysis patients was previously suggested by the case series of Karnik *et al.* (27) and Bleyer *et al.* (4). These authors showed that among patients on hemodialysis who eventually suffered sudden death, the proportion of patients on K0 or K1 dialysate was much higher than in controls. In addition, it has long been known that the relative hypokalemia at the end of hemodialysis sessions and/or the electrolyte shifts during hemodialysis may trigger various arrhythmias, including ventricular ones (3). More recently, Genovesi *et al.* demonstrated in a small-sized crossover study in 16 hemodialysis patients that K2 dialysate was associated, compared with K3 dialysate, with a longer duration of QTIs corrected for heart rate (28), a risk factor for sudden death in the general population. A recent study of a series of cardiac arrests at outpatient dialysis centers further showed that cardiac arrests were mostly related to ventricular fibrillation, especially those occurring during or shortly after hemodialysis (29). More recently, Kovesdy *et al.* (30) studied the association between predialysis serum potassium and survival in a cohort of US hemodialysis patients. The best survival was observed in patients with predialysis potassium ranging from 4.6 to 5.3, but these authors were unable to study the effect of either predialysis potassium or K_D on sudden death. Similarly, Al-Ghamdi

et al. (31) did not detect, after adjustment for malnutrition and inflammation, any association between K_D and overall risk of death in 1267 hemodialysis patients from North Alberta. Finally, Pun *et al.* (6) recently reported that K_D <2 was a risk factor for sudden cardiac arrest within hemodialysis clinics in a case-control study. Our results extend those of Pun *et al.* to the international cohort of DOPPS and demonstrate major differences in sudden death risk and typical K_D level between DOPPS countries (Figures 1B and 2D). Most importantly, our findings indicate that the higher mortality risk occurs with K_D <3, rather than only <2. The implications of this finding cannot be overemphasized because the median K_D level in this study was well <3 in all countries. Finally, we analyzed all sudden death, rather than only sudden cardiac arrest within hemodialysis units; our results are relevant for the potential prevention of many more sudden deaths than those of Pun *et al.* (6).

In contrast to the suggestion of the recent editorial (32) discussing strategies toward preventing sudden death in hemodialysis patients, our results do not necessarily imply completely banishing low K_D (≤2) from hemodialysis units. Both patient-level and instrumental variable analyses, however, indicate that the prescription of K_D ≥3 may reduce the risk of sudden death, especially in patients with predialysis potassium level <5. At the same time, the optimal strategy for patients with significant hyperkalemia, especially >6 and recurrent hyperkalemia, remains unclear (in our data, too few patients had both serum potassium >6 and high K_D ≥3 for us to study this treatment approach). The challenge in such patients is to avoid both life-threatening predialysis hyperkalemia and postdialysis relative hypokalemia (or at least very rapid decrease of serum potassium level, and the related risk of lethal arrhythmias). Resins such as kayexalate may be used, but may have their own risks (33). Alternative strategies, such as more frequent hemodialysis sessions, may

Table 3. Association of $K_D{}^a$ with mortality

	Patient Level						Instrumental Variable Approach					
	$K_D \leq 1.5$ (versus ≥ 3)			K_D=2–2.5 (versus ≥ 3)			$K_D \leq 1.5$ (versus ≥ 3)			K_D=2–2.5 (versus ≥ 3)		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
All patients (N=37,741)												
all-cause mortality	1.13	(1.03–1.25)	0.01	1.08	(1.01–1.16)	0.03	1.09	(0.88–1.35)	0.43	1.23	(1.04–1.45)	0.01
sudden death	1.39	(1.12–1.74)	0.004	1.17	(1.01–1.37)	0.04	1.67	(0.99–2.81)	0.05	1.61	(1.12–2.30)	0.01
other cardiovascular death	1.14	(0.95–1.36)	0.16	1.04	(0.91–1.19)	0.54	1.11	(0.75–1.64)	0.62	1.23	(0.90–1.68)	0.19
noncardiovascular death	0.99	(0.84–1.17)	0.93	1.05	(0.94–1.16)	0.38	0.84	(0.61–1.16)	0.29	1.03	(0.83–1.29)	0.76
Among patients with serum $K \geq 5$ (n=17,327)												
all-cause mortality	1.09	(0.95–1.26)	0.23	1.08	(0.97–1.20)	0.17	1.13	(0.87–1.47)	0.37	1.23	(0.99–1.52)	0.06
sudden death	1.21	(0.91–1.61)	0.18	1.11	(0.90–1.38)	0.33	1.27	(0.73–2.22)	0.40	1.30	(0.81–2.08)	0.28
other cardiovascular death	1.16	(0.88–1.52)	0.29	1.00	(0.82–1.21)	0.97	1.18	(0.74–1.88)	0.49	1.17	(0.79–1.72)	0.44
noncardiovascular death	0.97	(0.77–1.22)	0.81	1.10	(0.93–1.31)	0.27	1.02	(0.70–1.47)	0.93	1.21	(0.87–1.69)	0.25
Among patients with serum $K < 5$ (n=20,414)												
all-cause mortality	1.15	(1.00–1.33)	0.04	1.06	(0.98–1.15)	0.15	1.04	(0.80–1.36)	0.76	1.23	(1.03–1.46)	0.02
sudden death	1.53	(1.10–2.13)	0.01	1.18	(0.98–1.42)	0.08	2.01	(0.96–4.24)	0.06	1.86	(1.31–2.63)	<0.001
other cardiovascular death	1.05	(0.85–1.31)	0.64	1.05	(0.88–1.24)	0.58	0.94	(0.56–1.56)	0.80	1.23	(0.86–1.76)	0.26
noncardiovascular death	1.03	(0.77–1.38)	0.83	1.00	(0.88–1.15)	0.95	0.77	(0.51–1.15)	0.20	0.95	(0.75–1.22)	0.71

HRs and confidence intervals CIs adjusted for variables listed in Table 1 and in the Materials and Methods, stratified by phase and country and accounted for facility clustering. IV, instrumental variable; HR, hazard ratio; 95% CI, 95% confidence interval. K_D, dialysate potassium.

$^a K_D \leq 1.5$, n=5493; K_D=2–2.5, n=25,552; $K_D \geq 3$, n=6696.
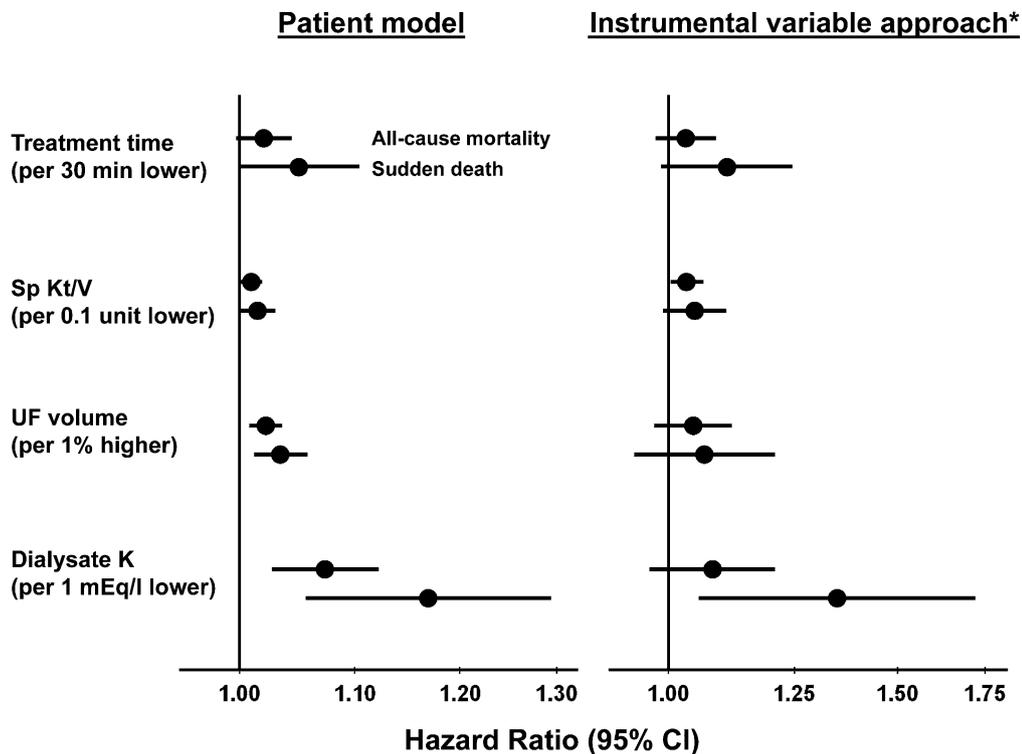
Figure 3. | **Association of treatment practices with sudden death.** Adjusted for variables listed in Table 1 and in the Materials and Methods, stratified by phase and country and accounted for facility clustering. *Used predicted treatment from first stage. IV, instrumental variable; UF, ultrafiltration; 95% CI, 95% confidence interval.

be required in such cases. These possibilities merit additional study.

The mechanisms underlying the risk of sudden death associated with excessively low Kt/V, short treatment time, and large ultrafiltration volume are potentially multiple: they include rapid electrolyte and/or volume shifts, potentially contributing to arrhythmias but also to repeated myocardial stunning and derived injury (34), as well as the persistent accumulation of uremic toxins. Our results on the risk of sudden death associated with short treatment time and low Kt/V are in line with recent DOPPS results on the risk of overall mortality associated with the same characteristics (35). As previously reported in other cohorts (27), the risk of sudden death among DOPPS participants is higher after the long dialysis interval, that is, on Monday for a Monday, Wednesday, and Friday hemodialysis schedule or Tuesday for a Tuesday, Thursday, and Saturday hemodialysis schedule (36). Volume and/or electrolyte abnormalities may contribute to this association, in keeping with the findings presented herein. Interestingly, the authors of the recent Frequent Hemodialysis Network trial reported a significant reduction of left ventricular mass in hemodialysis patients randomized to more frequent (six times per week) hemodialysis versus those remaining on the conventional thrice-weekly schedule (37), a finding again supporting the deleterious effect of large, relatively rapid volume shifts on the heart of hemodialysis patients.

Most previous studies on the risk of sudden death focused on patient characteristics associated with sudden death. These include, not surprisingly, heart failure (4), coronary artery disease, left ventricular hypertrophy (38), inflammation malnutrition complex (2,39), and poor glycemic control (40). We also observed higher risk of sudden death for cardiovascular comorbidities (including congestive heart failure, coronary artery disease, and other cardiovascular and cerebrovascular diseases) and inflammatory markers including ferritin and white blood cell count (data not shown). Except for glycemic control, all of these characteristics are difficult to readily modify in the dialysis unit, in contrast to the dialysis practices predicting sudden death on which our analysis is focused.

This study is the first, to our knowledge, to assess in hemodialysis patients the association between sudden death and the prescription of drugs prolonging the QTI on the electrocardiogram. A potential deleterious effect had been repeatedly proposed by experts in the field (1,41,42) and appeared very plausible in view of the well known polypharmacy of the current hemodialysis population, including many drugs either prolonging the QTI or reducing the metabolism of the former category of drugs. Despite the attractiveness of the hypothesis, we were unable to demonstrate for most of these drugs that their use contributes to the risk of sudden death in hemodialysis patients. This may be due to their low use overall, despite the large size of the database. On the other hand, β blockers were associated with a lower risk of sudden death, in line with their capacity to counteract the increased sympathetic activity common in hemodialysis patients (1,42). This finding is also consistent with previously reported associations of β blockers with lower all-cause and cardiovascular mortality (43). The

association of a higher risk of sudden death with amiodarone likely reflects a prescription by indication bias.

This study has multiple strengths, including the large sample size, nationally representative patient samples, prospective data collection, and extensive adjustment for patient characteristics, comorbidities, and laboratory results. In addition, the detailed DOPPS medication database made it possible for the first time to study the effect of drugs that prolong the QTI on the risk of sudden death. Furthermore, all sensitivity analyses show consistent associations between the modifiable practices and sudden death. These associations, obtained using baseline exposures, were consistent over the duration of study follow-up. Finally, the use of facility-level instrumental variable analyses, with results that were qualitatively consistent with the standard patient-level analyses, tends to lessen the risk of patient-level confounding by indication. Here, we utilize facilities as natural "instruments," mimicking a natural experiment in which patients are "pseudo-randomly" assigned. The idea is that patients at different facilities tend to receive different levels of treatment for reasons not associated with patients' outcome or patient-level unmeasured confounders, after accounting for patients' observed characteristics. Interestingly, although the directions of the estimates obtained from the instrumental variable analyses and the patient-level analyses were consistent, in several scenarios the instrumental variable estimates were appreciably larger (*e.g.*, for low K_D) (Table 3 and Figure 3). Although these differences may be because the IV approach reduced bias due to unmeasured confounders, we also cannot exclude the possibility of bias from violation of instrumental variable assumptions, such as the possibility of facility-level confounding.

Several limitations must be acknowledged. As is true of any observational study, we are not able to claim causality. We also note that the number of patients who had received an implantable cardiac defibrillator was too small to study the effect of their use on the risk of sudden death (44). In addition, as in any large clinical database, some errors may be present in coding (*e.g.*, cause of death) but these should have favored the null hypothesis, whereas we observed in both patient-level and facility-level analysis consistent associations between some modifiable practices and sudden death, as coded. It should also be mentioned that we did not have information on the time interval between the end of the last hemodialysis session and sudden death. Finally, we did not have electrocardiographic data regarding the presence of left ventricular hypertrophy (38) or prolonged QTI (28), nor potentially relevant biomarker data. Adiponectin levels (39), vitamin D levels (45), and antiheparin antibodies (39) have been implicated as potential contributors to sudden death and/or cardiovascular mortality in hemodialysis patients with diabetes in *post hoc* analyses of the Die Deutsche Diabetes Dialyse trial.

We have identified several readily modifiable facility practices associated with an independent risk of sudden death, both in standard patient-level analyses and in instrumental variable analyses based on facility variation in practice. Specifically, short treatment time, low dialysis dose, high ultrafiltration volume, and low K_D are associated with sudden death as well as overall mortality. Because low K_D (<3) is commonly used and it is the easiest

practice to modify, our study suggests that more careful adaptation of K_D level may help minimize the effect of sudden death observed in hemodialysis patients. Clinical trials are needed to test this possibility, and may be feasible for practices such as K_D in which substantial variation in care exists and clinical uncertainty remains significant.

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