Nephrol Dial Transplant (2019) 34: 1577–1584
doi: 10.1093/ndt/gfz007
Advance Access publication 28 February 2019

ORIGINAL ARTICLE

The association between longer haemodialysis treatment times and hospitalization and mortality after the two-day break in individuals receiving three times a week haemodialysis

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ABSTRACT

Background. On the first haemodialysis (HD) day after the 2-day break in three times a week (3×W) in-centre HD, mortality and hospitalization are higher. If longer HD sessions prescribed 3×W is associated with a reduction in these events is unknown.

Methods. HD session length in 19 557 prevalent European in-centre 3×W HD patients participating in the Dialysis Outcomes and Practice Patterns Study (1998–2011) were categorized into <200, 200–225, 226–250 or >250 min. Standardized event rates on the first (HD1) versus the second (HD2) HD day after the 2-day break, with supporting Cox proportional hazards models adjusted for patient and dialysis characteristics, were generated for all-cause mortality, all-cause hospitalization, out-of-hospital death and fluid overload hospitalization.

Results. By comparing HD1 with HD2, increased rates of all endpoints were observed (all $P < 0.002$). As HD session lengthened across the four groups, all-cause mortality per 100 patient-years on the HD1 (23.0, 20.4, 16.4 and 14.6) and HD2 (26.1, 13.3, 13.4 and 12.1) reduced. Similar improvements were observed for out-of-hospital death but were less marked for hospitalization endpoints. However, even patients dialysing >250 min were at significantly greater risk on HD1 when compared with their HD2 for out-of-hospital death [hazard ratio (HR) = 2.1, 95% CI 1.0–4.3], all-cause hospitalization (HR = 1.3, 95% CI 1.2–1.4) and fluid overload hospitalization (HR = 3.2, 95% CI 1.8–6.0).

Conclusions. Despite the association between reduced mortality across all dialysis days in patients performing longer sessions, elevated risk on the first dialysis day relative to the second persists even in patients dialysing 4.5 h 3×W.

Keywords: haemodialysis, hospitalization, interdialytic interval, mortality, treatment time

ADDITIONAL CONTENT

An author video to accompany this article is available at: https://academic.oup.com/ndt/pages/author_videos.

INTRODUCTION

Over 90% of prevalent patients receiving in-centre haemodialysis (HD) for end-stage renal failure receive it three times a week (3×W) [1]. The majority attend HD sessions on Monday, Wednesday and Friday, or Tuesday, Thursday and Saturday. As a result, there are two consecutive days without HD treatment at the end of the dialysis week. Observational data show an association between increased mortality and hospitalization on the first day after this 2-day break from HD, irrespective of whether this day falls on a Monday or a Tuesday [2–4].

These increases in mortality and hospitalization are often greater where cardiac disease is the underlying cause. Postulated mechanisms include fluid overload resulting in the development of left ventricular hypertrophy and the need to remove more fluid during the dialysis session [5–7]. Peak concentrations of toxins including potassium [8] increase the risk of arrhythmias and sudden death manifesting in higher rates of sudden or out-of-hospital death [3, 9]. The more rapid shifts in fluid and electrolytes during the first HD session (HD1) of the week are associated with cardiovascular morbidity and mortality [10], likely through their promotion of myocardial stunning [11], arrhythmias [9] and post-dialysis hypotension [12].

Suggested interventions for the 2-day break problem worth exploring include modifying practices within the 3×W regime session such as prescribing longer HD sessions and differing fluid removal strategies [13], and increasing the number of HD sessions in a range of formats. The large-scale alteration of dialysis frequency comes with logistical issues, but the practice of extending dialysis treatment time is more widespread. Longer treatment times have been associated with better blood pressure control, improved metabolic parameters, reduced left ventricular hypertrophy and may facilitate more regular achievement of 'dry weight'—the patient's weight in the absence of overhydration [14–17]. Furthermore, longer sessions have the capacity to reduce the rate of fluid and potassium movement. These effects are appealing given the potential mechanisms for the excess adverse event rates after the 2-day break outlined above. Existing observational studies show that longer treatment times are associated with a reduction in mortality and hospitalization [16]. However, the association between longer treatment times and increased mortality and hospitalization on the first HD day of the week has not yet been explored. The study aims to first confirm the association between the 2-day break (long gap) and the endpoints of mortality, hospitalization, out-of-hospital death and hospitalization for heart failure/fluid overload. We then evaluate the association between longer treatment times and the risk of events after the 2-day break within the European in-centre HD patient population.

MATERIALS AND METHODS

Patients and data sources

The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a prospective cohort study of in-centre prevalent HD patients conducted across four continents [18, 19]. In this study, we included data on HD patients from seven European countries (Belgium, France, Germany, Italy, Sweden, Spain and the UK) recruited in DOPPS Phases I–IV between 1998 and 2011. Research staff at participating facilities code hospitalization using a standardized coding list developed for DOPPS, which includes diagnosis and procedure codes. Research staffs use a range of sources to determine these data including patient notes and discharge summaries. For each 4-month period of follow-up, more detailed information was collected on the last HD session including the date of the last collected blood tests. To assign the dialysis schedule, if the date reported of this HD session fell on Monday, Wednesday or Friday (Mon/Wed/Fri) in conjunction with a frequency of 3×W, then they were assigned a Mon/Wed/Fri dialysis schedule. If this date fell on Tuesday, Thursday and Saturday (Tue/Thu/Sat), then the schedule was defined in a similar manner. When this fell on a Sunday or no date was reported, schedules defined from previous or subsequent 4 month blocks were used. To avoid any day-of-the-week bias introduced by planned hospitalizations, all hospitalization analyses were limited to admissions longer than two nights and excluded hospitalizations coded as routine diagnostic tests or physical examinations relating maintenance dialysis care.

The day after the 2-day break (long gap)

Within all analyses, the day after the 2-day break (also referred to as the long gap) represents the HD1 after the two consecutive days without HD. This represents Monday in a patient dialysing on a Mon/Wed/Fri schedule and Tuesday in a patient dialysing on a Tue/Thu/Sat schedule.

Statistical analyses

Mortality and hospitalization on individual days of the week. Single event (mortality endpoints) and multiple event Andersen and Gill [20] (hospitalization endpoints) Cox regression analyses were used to evaluate the risk [hazard ratio (HR) and 95% confidence interval (CI)] on each day of the dialysis week compared with the day of the second HD session (HD2), censoring changes in dialysis frequency and modality, loss to follow-up or transfer to a facility not participating in the DOPPS. HD2 was chosen rather than the whole rest of the dialysis week because mortality and hospitalization are higher on the days the patient receives HD than non-HD days. In illustrative figures, we present the HR of individual days of the dialysis week compared with the day of the HD2 in Mon/Wed/Fri patients in order to explore any significant difference in risk profile between Mon/Wed/Fri and Tue/Thu/Sat patients. As both dialysis day of the week and treatment time vary during the follow-up period, we employed a time-varying approach that involved representing each individual day of follow-up as an observation. All analyses presented were stratified by country, study phase, age and HD schedule and adjusted for sex, race, 13 comorbid conditions (coronary heart disease, cancer other than skin, other cardiovascular disease, cerebrovascular disease, congestive heart failure, diabetes, gastrointestinal bleeding, hypertension, lung disease, neurological disease, psychiatric disorder, peripheral vascular disease and recurrent cellulitis), residual kidney function (>200 mL of urine per day at enrolment into DOPPS), body mass index (BMI), dialysis access blood flow and the time the patient had been receiving renal replacement therapy. Stratifying by rather than adjusting for some variables allows for different baseline hazards to be specified, which avoids violations of the proportional hazards assumption for these variables. Biochemical data, surrogates of volume expansion or ultrafiltration rate, were not included in models as they potentially lie in the causal pathway between treatment time length and endpoints [21]. All variables with the exception of residual kidney function and comorbid conditions were updated if they changed during follow-up. Facility clustering was taken into account using a robust sandwich covariance matrix estimator. To address missing covariate data, we performed multiple imputation by chained equations employing fully conditional specifications, reducing the proportion of patients with missing covariate data from 19.1% to 0% (detailed in Supplementary data, Table S1).

Mortality and hospitalization on individual days of the week by length of dialysis treatment time. In order to explore whether the relative and absolute increase in events after the 2-day break were similar across the range of observed treatment time groups, we assessed the mortality and hospitalization

event rates for 3×W in-centre HD patients separately. Four treatment time groups were defined that encompassed the most commonly prescribed treatment times (presented in brackets): <200 min (180), 200–225 min (210), 226–250 min (240) and >250 min (270 and 300) per HD session. Event rates were directly standardized for the age and comorbidity profile of the largest 226–250 min treatment time group [22]. Cox regression analysis employing the broader range of adjustment variables detailed above was used to evaluate the risk (HR and 95% CI) of mortality and hospitalization of the first HD day after the 2-day break compared with the second HD day, separately for each of the four treatment time groups. Note that this approach does not illustrate any effect of treatment time between groups, but only the risk from the 2-day break within a treatment time group.

To visualize the overall association between treatment time and mortality and hospitalization risk, specifically the day after the 2-day break and across the rest of the dialysis week, we evaluated the risk of these endpoints for each day across all four treatment time groups individually (i.e. 28 separate day/duration categories) compared with the second dialysis day in the 226–250 min group (reference group). These models were stratified and adjusted for the same variables as described above.

Sensitivity analyses. To screen for bias, additional sensitivity analyses were conducted to examine whether the effect estimates differed from our main results. First, we performed an instrumental variable analysis utilizing variation in treatment time practice across dialysis facilities as a form of pseudorandomization that can reduce bias [23]. To ensure that changes in treatment time immediately prior to mortality or hospitalization event did not bias our conclusions regarding treatment time, we analysed the treatment time from the preceding 4-month period (a lagged analysis). Second, hypothesizing that patients may receive short treatment times for palliative reasons, or that shorter treatment times employed in some facilities would not be generalizable and could introduce bias, we compared patients receiving 200–249 min HD treatment time with those receiving 250 min and longer. Finally, we repeated our hospitalization analyses retaining short inpatient admissions, and assessed the association between mortality and longer treatment time stratified by the presence of residual kidney function. These analyses are presented in Supplementary data.

All analyses were performed in STATA 14.2 (Stata Corp., College Station, TX, USA).

RESULTS

Study sample

From 21 880 European patients on HD recruited into EURODOPPS, 19 557 patients with data on treatment time were receiving in-centre HD and could be assigned a 3×W dialysis schedule. The mean follow-up was 18.5 months and 4052 patients died. The distribution of patient characteristics across the four treatment time groups at enrolment into EURODOPPS is shown in Table 1. Patients dialysing for more minutes were on average younger, more likely male and had a greater prevalence of comorbidities.

Mortality and hospitalization on individual days of the week

Figure 1 shows adjusted HRs and 95% CIs for mortality and hospitalization across the dialysis week compared with the HD2 of the week for the two HD schedules separately. The HD1 (most left in the figures) represents the first dialysis day after the 2-day break. Colour versions of this and subsequent figures are available as Supplementary data.

The mortality rate on HD1, the first dialysis day after the 2-day break was 17.0/100 patient-years compared with 14.0 for HD2. Variation in mortality by dialysis day of the week was greater in those dying out of hospital compared with those dying in hospital (Figure 2A and B). Out-of-hospital deaths accounted for 24.8% of total deaths, and had greater relative increases after the 2-day break (5.0 versus 2.8/100 patient-years, adjusted HR = 1.72, 95% CI 1.34–2.20).

Hospitalization rate was generally higher on the days patients attended for HD, with greatest increases seen on: 1.47 admissions per year after the 2-day break compared with 1.14 per year for HD2 (adjusted HR = 1.25, 95% CI 1.18–1.33). Although the HR for cardiovascular admissions across the dialysis week was similar to that of all-cause admissions, admissions for fluid overload/heart failure showed a higher risk after the 2-day break (Figure 2C and D): 6.4/year versus 2.3/year (adjusted HR = 2.70, 95% CI 2.07–3.52).

Mortality and hospitalization on individual days of the week by length of dialysis treatment time

Figure 3A shows the mortality and hospitalization event rates on the first and second HD days of the week, standardized to the patient characterstics of those receiving 226–250 min. These show a consistent association between reduced mortality endpoints and longer treatment times on both the first and second HD days; however, in patients receiving longer treatment times, the event rate on HD1 remains higher than that on HD2. With the exception of mortality in the shortest treatment time group, all four treatment time groups experienced similar relative increases in the endpoints on HD1 compared with HD2 (Figure 3B). Longer treatment times had less consistent associations with reduced hospitalization, but again similar relative increases after the 2-day break within treatment time groups.

Figure 4 explores the relative risk (HR and 95% CI) of mortality and hospitalization events across each day of the dialysis week for each of the four treatment time groups compared with the second dialysis day in the 226–250 min group. Notably, the overall risk of mortality in the shortest treatment time group was high across all days of the week and showed no 2-day break effect (Figure 4A). Event rates began to increase on the day prior to HD1, the second day of the 2-day break.

Sensitivity analyses

The instrumental variable analysis designed to reduce bias gave comparable results to our presented analyses (Supplementary data, Figure S1). In the 120 days prior to death,

Table 1. Demography and clinical characteristics of 3×W in-centre HD patients at first inclusion in EURODOPPS, stratified by session treatment time

	Overall	<200 min	200–225 min	226–250 min	>250 min	P-value
Number of patients, *n* (%)	19 557	2387 (12.2)	3268 (16.7)	10 241 (52.4)	3661 (18.7)	
Age, mean (SD), years	63.8 (14.9)	65.6 (15.5)	65.8 (14.7)	64.0 (14.8)	60.2 (14.3)	<0.001
Sex, male, *n* (%)	11 599 (59.3)	1185 (49.6)	1685 (51.6)	6138 (59.9)	2591 (70.8)	<0.001
Ethnicity, Caucasian, *n* (%)	18 545 (94.8)	2288 (95.6)	3118 (95.4)	9657 (94.3)	3482 (95.1)	0.004
Time on dialysis, mean, months	44.9	33.2 (61.2)	43.4 (64.1)	44.0 (63.0)	56.1 (71.3)	<0.001
BMI, mean, kg/m^2	25.1 (5.0)	23.8 (4.6)	24.2 (4.5)	25.2 (5.0)	26.7 (5.5)	<0.001
Residual kidney function, *n* (%)	8785 (49)	1403 (63.5)	1453 (47.9)	4441 (47.7)	1488 (44.1)	<0.001
Primary renal disease						<0.001
Cystic/hereditary/congenital diseases, *n* (%)	1857 (10.1)	230 (10.2)	295 (9.6)	989 (10.3)	343 (9.9)	
Diabetes, *n* (%)	3843 (20.9)	377 (16.7)	555 (18)	2030 (21.2)	881 (25.4)	
Glomerulonephritis, *n* (%)	3280 (17.9)	333 (14.8)	483 (15.7)	1709 (17.9)	755 (21.8)	
Hypertension/large vessel disease, *n* (%)	3047 (16.6)	397 (17.6)	547 (17.8)	1603 (16.7)	500 (14.4)	
Interstitial nephritis/pyelonephritis, *n* (%)	2211 (12)	324 (14.4)	408 (13.2)	1125 (11.8)	354 (10.2)	
Miscellaneous conditions, *n* (%)	2820 (15.3)	407 (18.1)	596 (19.4)	1419 (14.8)	398 (11.5)	
Neoplasms/tumors, *n* (%)	615 (3.3)	76 (3.4)	83 (2.7)	325 (3.4)	131 (3.8)	
Secondary glomerulonephritis/vasculitis, *n* (%)	700 (3.8)	110 (4.9)	113 (3.7)	373 (3.9)	104 (3)	
Comorbid conditions						
Diabetes, *n* (%)	5948 (30.4)	571 (23.9)	877 (26.8)	3166 (30.9)	1334 (36.4)	<0.001
Coronary artery disease, *n* (%)	7775 (39.8)	853 (35.7)	1150 (35.2)	4094 (40.0)	1678 (45.8)	<0.001
Heart failure, *n* (%)	5425 (27.7)	614 (25.7)	783 (24.0)	2894 (28.3)	1134 (31.0)	<0.001
Other cardiac, *n* (%)	7036 (36.2)	806 (33.9)	1114 (34.3)	3744 (36.8)	1372 (37.7)	0.001
Hypertension, *n* (%)	15 689 (80.8)	1826 (77)	2551 (78.8)	8258 (81.2)	3054 (84)	<0.001
Cerebrovascular disease, *n* (%)	3173 (16.3)	344 (14.5)	557 (17.2)	1699 (16.7)	573 (15.8)	0.025
Peripheral vascular disease, *n* (%)	5497 (28.3)	559 (23.5)	886 (27.3)	2966 (29.1)	1086 (29.9)	<0.001
Diabetes, *n* (%)	5948 (30.6)	571 (24.1)	877 (27.1)	3166 (31.1)	1334 (36.7)	<0.001
Lung disease, *n* (%)	2401 (12.4)	283 (11.9)	389 (12)	1344 (13.2)	385 (10.6)	<0.001
Cancer, *n* (%)	2718 (14.1)	314 (13.3)	416 (12.9)	1494 (14.7)	494 (13.7)	0.031
GI bleeding, *n* (%)	1056 (5.5)	141 (6)	160 (4.9)	562 (5.5)	193 (5.3)	0.354
Neurological condition, *n* (%)	1968 (10.1)	246 (10.4)	310 (9.6)	1065 (10.5)	347 (9.5)	0.267
Psychiatric condition, *n* (%)	3426 (17.6)	434 (18.3)	569 (17.5)	1774 (17.4)	649 (17.8)	0.775
Recurrent cellulitis, *n* (%)	1513 (7.8)	141 (5.9)	178 (5.5)	803 (7.9)	391 (10.8)	<0.001
Dialysis parameters						
Mon/Wed/Fri schedule, *n* (%)	10 862 (55.5)	1236 (51.8)	1745 (53.4)	5663 (55.3)	2218 (60.6)	<0.001
Access type						<0.001
Fistula, *n* (%)	12 618 (70.9)	1354 (66.1)	2137 (72)	6592 (70.3)	2535 (74.3)	
Graft, *n* (%)	1266 (7.1)	134 (6.5)	180 (6.1)	643 (6.9)	309 (9.1)	
Catheter, *n* (%)	3863 (21.7)	555 (27.1)	639 (21.5)	2110 (22.5)	559 (16.4)	
Blood flow, mean, mL/min	311.0 (60.8)	300.3 (67.1)	310.9 (56.8)	312.4 (58.8)	314.3 (64.4)	<0.001

P-value for differences between treatment time groups. Residual kidney function: <200 mL of urine per day at enrolment into DOPPS.

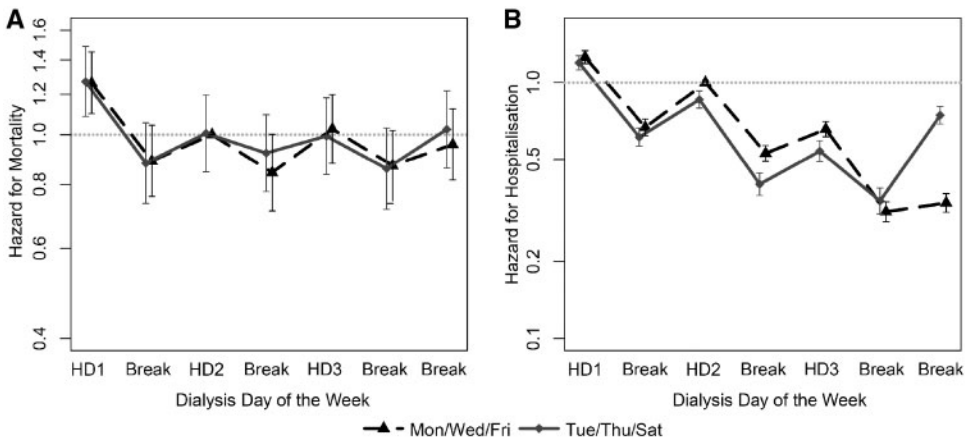

FIGURE 1: HRs and associated 95% CIs for mortality and hospitalization across the dialysis week in in-centre 3×W HD patients: (**A**) all-cause mortality by HD schedule (Mon/Wed/Fri and Tue/Thu/Sat regimes); (**B**) all-cause hospitalization by HD schedule adjusted for age, sex, race, 13 comorbid conditions, BMI, residual kidney function, dialysis access blood flow and time the patient has been receiving renal replacement therapy, country and DOPPS phase. Reference day: HD2 in Mon/Wed/Fri patients.

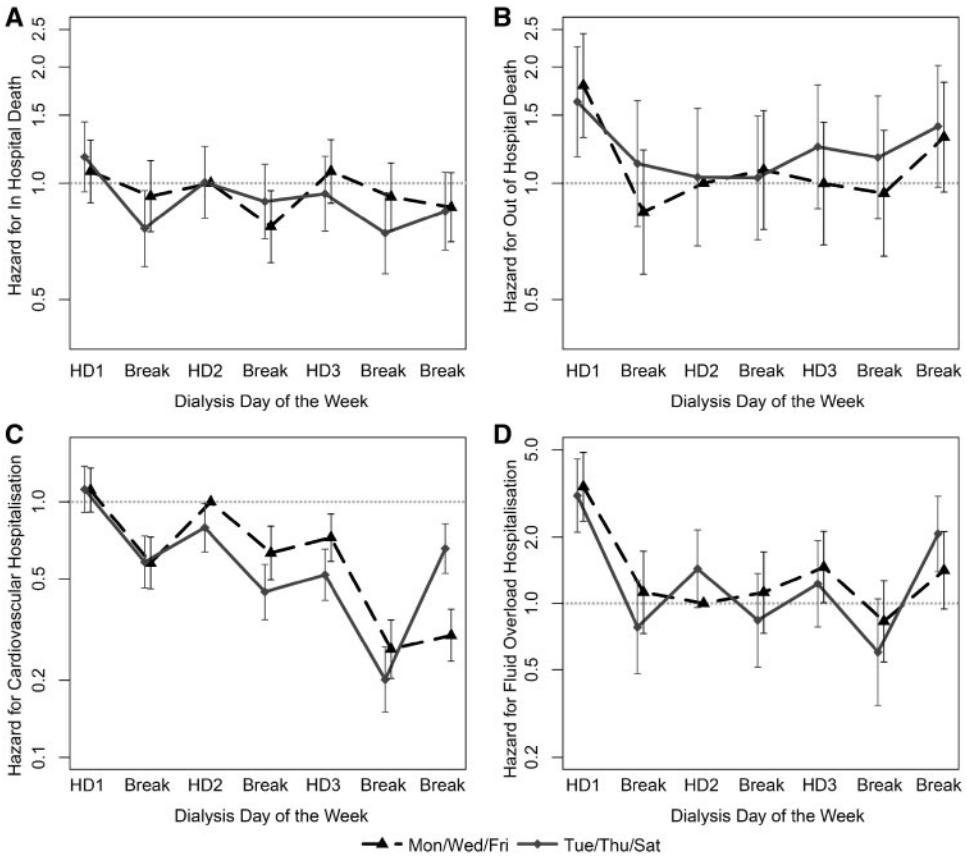

FIGURE 2: HRs and associated 95% CIs for cause-specific mortality and hospitalization across the dialysis week in in-centre 3×W HD patients: (**A**) in hospital, (**B**) out-of-hospital mortality by HD schedule (Mon/Wed/Fri and Tue/Thu/Sat regimes), (**C**) cardiovascular hospitalization and (**D**) fluid overload/heart failure hospitalization by dialysis schedule. Adjusted for age, sex, race, 13 comorbid conditions, BMI, residual kidney function, dialysis access blood flow and time the patient has been receiving renal replacement therapy, country and DOPPS phase. Reference day: HD2 in Mon/Wed/Fri patients.

26.3% of patients changed treatment time. Detailed results using the treatment time from 120 days prior to death in order to reduce bias from changes immediately prior to death (Supplementary data, Figure S2), and results with the shortest treatment group excluded (leaving 86.6% of the cohort) and with treatment time dichotomized into <250 and ≥ 250 min (Supplementary data, Figure S3) are available in Supplementary data. These showed a high risk of all endpoints after the 2-day break which persisted even in the longest treatment time group. Consistent findings were found following stratification by residual kidney function (Supplementary data, Figure S4), and with the inclusion of short-stay hospitalizations (Supplementary data, Figure S5).

DISCUSSION

The day-of-the-week variation in morbidity and mortality has been explored in a number of chronic diseases and healthcare settings [24–28], often focusing on the relationship with (often unobserved) variable provision of healthcare services. We explored the effect of the observed interruption in treatment during the 2-day break on outcomes and assessed for an association between extended HD sessions reduced adverse outcomes. We confirmed that the HD1 after the 2-day break is associated with increases in mortality and hospitalization [2–4], particularly in out-of-hospital death and hospitalization relating to cardiac failure and fluid overload in both Mon/Wed/Fri and Tue/Thu/Sat patients. Longer treatment times prescribed 3×W were associated with a decrease in mortality and hospitalization, both overall and specifically after the 2-day break [16, 29, 30]. Despite greater absolute improvements in mortality on HD1 with longer treatment times compared with other dialysis days, a relative increase in events on this day compared with the second dialysis day was evident even in the longest treatment time group.

This large cohort study explores an association between a potential intervention for the 2-day break problem that does not increase dialysis frequency, thereby maximizing acceptability to patients. In those bothered by fluid restriction, 33.5% of patients would be willing to increase their treatment time by 30 min, whereas 19.6% would be willing to add a fourth dialysis session [31]. By using time-dependent covariates including treatment time, we were able to take advantage of longitudinal data collected in EURODOPPS and allow for the real-world practice of extending treatment time during patients' dialysis careers. To explore potential confounding by indication in the analysis of the effect of treatment times, we employed facility as an instrumental variable, capitalizing on the variation in practice across the 189 participating European dialysis facilities to effectively pseudo-randomize patients to different treatment times.

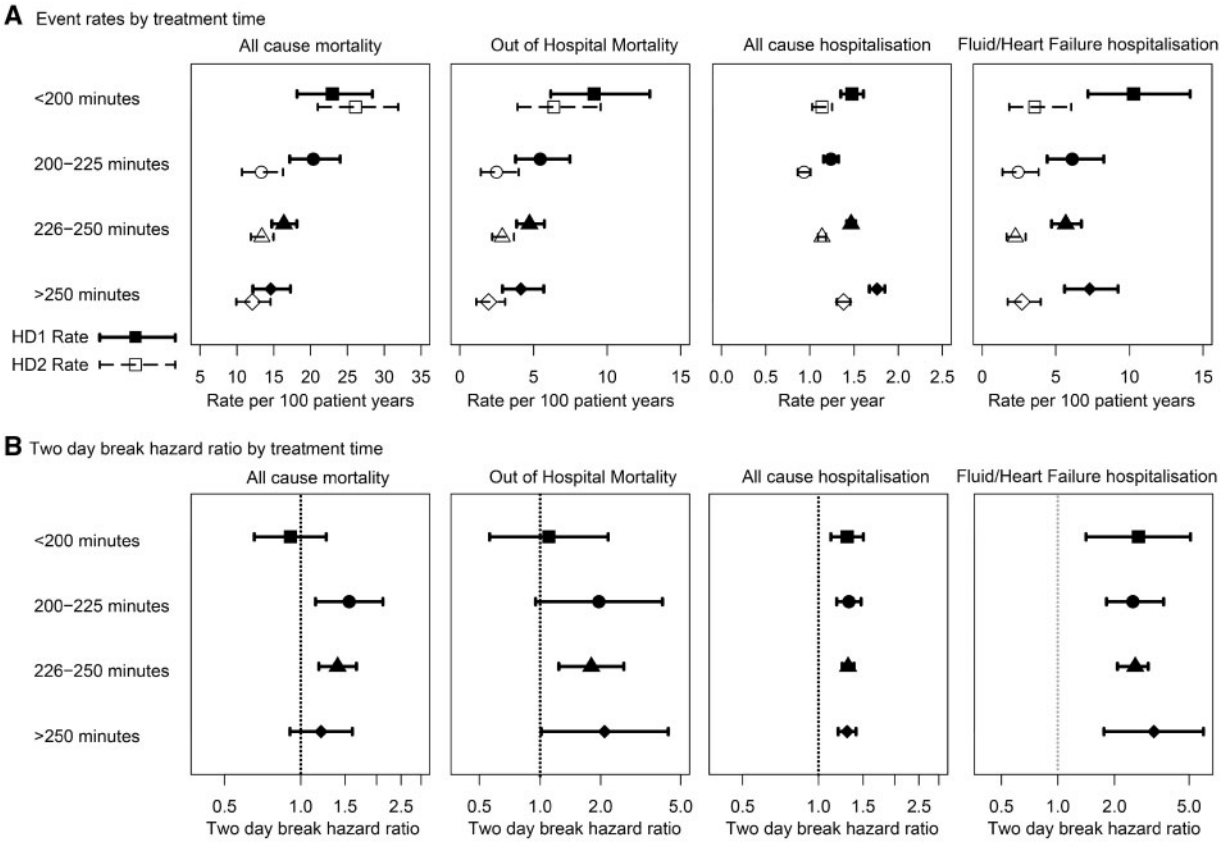

FIGURE 3: (**A**) Standardized event rates for mortality and hospitalization endpoints on the first and second HD days of the dialysis week and (**B**) the HR of the first HD day compared with the second according to per session HD treatment time in 3×W in-centre HD patients. Adjusted for age, sex, race, 13 comorbid conditions, residual kidney function, BMI, dialysis access blood flow and time the patient has been receiving renal replacement therapy, country, DOPPS phase and HD schedule.

Weaknesses of our observational study include confounding by indication and that despite the methods used residual confounding could persist. The data collection schedule in EURODOPPS only allows variables to change every 4 months, meaning we were unable to explore changes in these variables shortly ahead of hospitalization and mortality events in order to hypothesize mechanisms or develop early warning tools. As non-adherence is only captured immediately prior to enrolment in DOPPS, we are unable to explore if variable session adherence across the dialysis week is an explanation for the 2-day break problem.

The nature and size of the 2-day break problem in our study are in line with previous but not all publications [2–4]. We also confirmed the overall impact of longer treatment times: a global analysis of participants in DOPPS found more modest mortality benefits with longer treatment times overall and specifically in European participants (HR = 0.94, 95% CI 0.91–0.97/30 min extension of treatment time) [16], with other studies using cross-sectional and time-varying approaches reporting reductions in mortality more comparable to our study [29, 30]. The very high risk of mortality in patients receiving HD for ≤180 min per session could be explained by the usually high cardiovascular morbidity and all-cause mortality risk soon after the initiation of dialysis when treatment times are generally shortest [32, 33]. Also, treatment times may be shortened in patients in whom treatment strategies are entering a more palliative approach, or in those who become unstable on dialysis due to acute illness, a hypothesis supported by our lagged analysis (Supplementary data, Figure S2).

Based on our findings, clinicians aiming to fully neutralize the increase in mortality and hospitalization risk after the 2-day break might need to consider adding additional HD sessions. Even with the metabolic and volume benefits associated with longer treatment times, there is still twice as much time for waste products and fluid to re-accumulate over the 2-day break than during the other two interdialytic periods. Any large-scale change in either session frequency or treatment time would have an impact on policy surrounding the common 6 day opening of HD facilities and on overall dialysis capacity: of the 110 HD facilities participating in DOPPS Phase IV (2009–11), only 13 were open on both a Saturday and a Sunday. Half of facilities currently operate three dialysis shifts per day or more on some of the days they open, meaning extended hours (4.5 h) could not easily be offered to all patients without opening the unit for >16 h a day with early starts and late finishes for patients as a consequence. High serum potassium prior to the 2-day break has been shown to correlate with increased hospitalization over this period specifically [34], and the new pharmacological agents for potassium offer possible non-dialysis interventions. A study of 1678 arrythmias experienced in 44 of 66 patients participating in the Monitoring in Dialysis trial showed the highest arrhythmia rate immediately prior to and during the

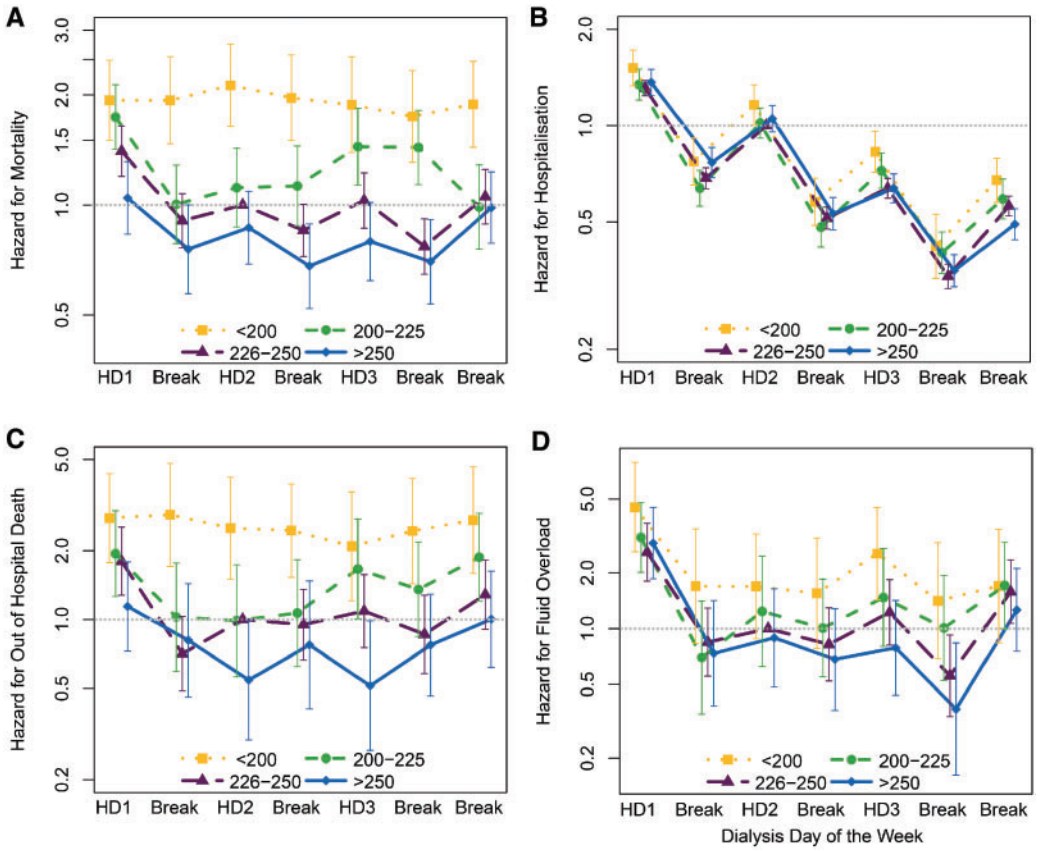

FIGURE 4: HRs with associated 95% CIs for (**A**) mortality, (**B**) all-cause hospitalization, (**C**) out-of-hospital death and (**D**) hospitalization due to fluid overload and heart failure across the dialysis week according to per session haemodialysis treatment time in 3×W in-centre HD patients (second HD day in patients receiving 226–250 min is the reference group). Adjusted for age, sex, race, 13 comorbid conditions, residual kidney function, BMI, dialysis access blood flow, time the patient has been receiving renal replacement therapy, country, DOPPS phase and HD schedule.

first session after the 2-day break, and that the use of cooled dialysate (<37°C) halved the overall event rate [35].

In conclusion, despite demonstrating an association between extended HD treatment times and a reduction in mortality and hospitalization, we showed the increased risk on the first HD day compared with the second persisted even in those patients receiving HD for ∼4.5 h per session three times a week. Future research should aim to address proposed mechanisms outside the 3×W paradigm, understand the benefits and risks of more frequent dialysis regimes in light of inconsistent observational and interventional study findings [36–38], and develop patient level and ideally HD session-level risk tools using more granular data to trigger an intervention. A solution for the 2-day break problem that is effective in preventing adverse events, individualized at a patient level, widely acceptable and cost effective, is needed.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

ACKNOWLEDGEMENTS

This article presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. The authors alone are responsible for the reporting and interpretation of EURODOPPS data used in the publication and they do not necessarily represent the decisions or policies of the ERA-EDTA or the DOPPS Programme.

FUNDING

The DOPPS Programme is supported by Amgen, Kyowa Hakko Kirin, AbbVie Inc., Sanofi Renal, Baxter Healthcare and Vifor Fresenius Medical Care Renal Pharma, Ltd. Additional support for specific projects and countries is also provided by the ERA-EDTA, Keryx Biopharmaceuticals, Inc., Merck Sharp & Dohme Corp., Proteon Therapeutics, Relypsa and F. Hoffmann-LaRoche Ltd; 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. All support is provided without restrictions on publications. J.F. is funded by a National Institute for Health Research Clinician Scientist Award.

AUTHORS' CONTRIBUTIONS

This analysis was developed by J.F., K.M., A.K. and M.W., and undertaken by J.F., A.S., V.S.S., K.M., A.K. and K.J.J. under guidance from B.B., Z.A.M. and B.M.R., on behalf

of EURODOPPS and the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry, which is an official body of the ERA-EDTA. The EURODOPPS Initiative is supported by the ERA-EDTA and the DOPPS Programme. All authors were involved in writing the manuscript, reviewed the final submission and had access to the study data.

CONFLICT OF INTEREST STATEMENT

Grants are made to Arbor Research Collaborative for Health and not to individual investigators. All authors declare that they have no relevant financial interests. The results presented in this article have not been published previously in whole or part, except in abstract form.

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Received: 3.7.2018; Editorial decision: 10.1.2019