Nephrol Dial Transplant (2020) 35: 488–495
doi: 10.1093/ndt/gfz208
Advance Access publication 18 November 2019

ORIGINAL ARTICLE

Survival of patients treated with extended-hours haemodialysis in Europe: an analysis of the ERA-EDTA Registry

Thijs T. Jansz [1,2], Marlies Noordzij[3], Anneke Kramer[3], Eric Laruelle[4,5], Cécile Couchoud[6], Frederic Collart[7], Aleix Cases [8,9], Mustafa Arici[10], Jaako Helve[11,12], Bård Waldum-Grevbo[13], Helena Rydell[14,15], Jamie P. Traynor[16], Carmine Zoccali[17], Ziad A. Massy[18,19], Kitty J. Jager[3] and Brigit C. van Jaarsveld[2,20]

[1]Department of Nephrology and Hypertension, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands, [2]Dianet Dialysis Centres, Utrecht, The Netherlands, [3]ERA-EDTA Registry, Department of Medical Informatics, Amsterdam Public Health Research Institute, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands, [4]AUB Sante Dialyse, Rennes, France, [5]Service de Nephrologie, CHU Rennes, Rennes, France, [6]REIN Registry, Agence de la biomédecine, Saint-Denis La Plaine, France, [7]French-Belgian ESRD Registry, Brussels, Belgium, [8]Nephrology Unit, Hospital Clinic, IDIBAPS, Universitat de Barcelona, Barcelona, Spain, [9]Registre de Malalts Renals de Catalunya, Barcelona, Spain, [10]Department of Nephrology, Faculty of Medicine, Hacettepe University, Ankara, Turkey, [11]Finnish Registry for Kidney Diseases, Helsinki, Finland, [12]Abdominal Center Nephrology, University of Helsinki and Helsinki University Hospital, Helsinki, Finland, [13]Department of Nephrology, Oslo University Hospital, Ullevål, Norway, [14]Department of Clinical Sciences Intervention and Technology, Karolinska Institutet, Huddinge, Sweden, [15]Swedish Renal Registry, Department of Internal Medicine, Ryhov County Hospital, Jönköping, Sweden, [16]Scottish Renal Registry Meridian Court, Information Services Division Scotland, Glasgow, UK, [17]Clinical Epidemiology and Physiopathology of Renal Diseases and Hypertension, CNR-Institute of Clinical Physiology, Reggio Calabria, Italy, [18]Division of Nephrology, Ambroise-Paré University Hospital, APHP, University of Paris Ouest-Versailles-St-Quentin-en-Yvelines, Boulogne-Billancourt/Paris, France, [19]Institut National de la Santé et de la Recherche Médicale U1018, Team 5, CESP UVSQ, University Paris Saclay, Villejuif, France and [20]Department of Nephrology and Cardiovascular Sciences, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands

Correspondence to: Brigit C. van Jaarsveld; E-mail b.jaarsveld@amsterdamumc.nl; Twitter handles: @ag_biomedecine, @EraEdtaRegistry, @jager_kitty, @carminezoccali

ABSTRACT

Background. Previous US studies have indicated that haemodialysis with ≥6-h sessions [extended-hours haemodialysis (EHD)] may improve patient survival. However, patient characteristics and treatment practices vary between the USA and Europe. We therefore investigated the effect of EHD three times weekly on survival compared with conventional haemodialysis (CHD) among European patients.

Methods. We included patients who were treated with haemodialysis between 2010 and 2017 from eight countries providing data to the European Renal Association–European Dialysis and Transplant Association Registry. Haemodialysis session duration and frequency were recorded once every year or at every change of haemodialysis prescription and were categorized into three groups: CHD (three times weekly, 3.5–4 h/treatment), EHD (three times weekly, ≥6 h/treatment) or other. In the primary analyses we attributed death to the treatment at the time of death and in secondary analyses to EHD if ever initiated. We compared mortality risk for EHD to CHD with causal inference from marginal structural models, using Cox proportional hazards models weighted for the inverse probability of treatment and censoring and adjusted for potential confounders.

Results. From a total of 142 460 patients, 1338 patients were ever treated with EHD (three times, 7.1 ± 0.8 h/week) and 89 819 patients were treated exclusively with CHD (three times, 3.9 ± 0.2 h/week). Crude mortality rates were 6.0 and 13.5/100 person-years. In the primary analyses, patients treated with EHD had an adjusted hazard ratio (HR) of 0.73 [95% confidence interval (CI) 0.62–0.85] compared with patients treated with CHD. When we attributed all deaths to EHD after initiation, the HR for EHD was comparable to the primary analyses [HR 0.80 (95% CI 0.71–0.90)].

Conclusions. EHD is associated with better survival in European patients treated with haemodialysis three times weekly.

Keywords: ERA-EDTA Registry, extended-hours, haemodialysis, nocturnal haemodialysis, survival

INTRODUCTION

Patients on dialysis have poor survival when compared with age-matched individuals from the general population [1–4]. Interestingly, various studies have shown lower mortality risks associated with haemodialysis treatment times of >4 h compared with shorter treatment times in patients from the USA, Australia/New Zealand and Europe [5–7]. This has prompted research into the effects of haemodialysis with session durations far beyond the conventional 3.5–4 h, that is, extended-hours haemodialysis (EHD), with ≥6-h sessions.

Several previous studies have demonstrated survival benefits of EHD. Two observational studies found better survival among patients treated with frequent EHD (≥4 times weekly) compared with conventional haemodialysis (CHD) [8, 9]. Yet this finding could not be confirmed by another observational study [10], a randomized controlled trial (RCT) that had a small sample size due to recruitment difficulties [11], and two post-trial observational studies[12, 13]. However, these studies did not distinguish between the effects of haemodialysis session duration and treatment frequency. Several observational studies investigating EHD three times weekly also demonstrated survival benefits compared with CHD three times weekly [14–17]. However, most of these studies were limited to the USA. In general, US patients treated with haemodialysis more often have diabetes, have shorter haemodialysis session durations with higher blood flow rates and less often use an arteriovenous fistula compared with European patients treated with haemodialysis [5, 18]. Thus far, no study has evaluated whether EHD three times weekly (with ≥6-h sessions) affects survival in European patients.

We aimed to study the effect of EHD three times weekly on survival compared with CHD among European patients. To this end, we used data from the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) Registry.

MATERIALS AND METHODS

Study population

The study cohort consisted of prevalent patients who were treated with haemodialysis between 2010 and 2017, derived from the ERA-EDTA Registry. The ERA-EDTA Registry collects data on renal replacement therapy (RRT) via national and regional renal registries in Europe on an annual basis. The core dataset includes date of birth, sex, primary kidney disease, date of start of RRT, dialysis modality at dialysis initiation and during follow-up and date and cause of death. In addition, several renal registries also provided additional clinical and biochemical data. For this study we included patients ≥20 years of age at any time during follow-up from the following eight national and regional registries that provided data including haemodialysis session duration and frequency: Austria, Catalonia (Spain), France and Scotland (the UK) (2010–17), the French-speaking part of Belgium, Finland, Norway and Sweden (2010–16). We excluded patients who were treated with haemodialysis for <120 days (4 months) in total, as mortality risk is highest in this early period after starting haemodialysis [19]. All patients were followed until death or censoring (i.e. recovery of renal function, transfer to peritoneal dialysis, kidney transplantation, loss to follow-up or end of administrative follow-up). End of administrative follow-up was 31 December 2016 for the French-speaking part of Belgium, Finland, Norway and Sweden and 31 December 2017 for Austria, Catalonia (Spain), France and Scotland (the UK).

Haemodialysis session duration and frequency

In the ERA-EDTA Registry, haemodialysis session duration and frequency were recorded once every year [Austria, the French-speaking part of Belgium, Catalonia (Spain), Finland, Norway, Sweden and Scotland (the UK)] or at every change in haemodialysis prescription (France). To investigate exclusively the association of extended haemodialysis session duration with survival, we categorized haemodialysis treatment into three groups: CHD (three times weekly, 3.5–4 h/treatment), EHD (three times weekly, ≥6 h/treatment) and other (not in any of the previous categories). We did not distinguish between haemodialysis, haemofiltration and haemodiafiltration. One registry (Austria) only recorded haemodialysis session frequency for treatments ≥18 h/week. For this registry, we therefore categorized haemodialysis treatment of 10.5–12 h/week as CHD (assuming treatment three times weekly) and any other treatment <18 h/week as other.

Mortality

In the primary analyses, we attributed mortality to the last-recorded haemodialysis treatment. If a patient's last event was 'limited care/stopped treatment (without recovery of renal function)', then we assumed that the patient died shortly thereafter. In secondary analyses, we attributed all deaths after initiation of EHD to EHD. We calculated person-time by summing all time attributed to each treatment.

Other variables

We calculated age at the first record of haemodialysis session duration and frequency. Primary kidney disease was classified according to the coding system of the ERA-EDTA [20]. We grouped patients into eight classes of primary kidney disease: glomerulonephritis, pyelonephritis, polycystic kidney disease, diabetes, hypertension, renal vascular disease, miscellaneous and unknown. We defined RRT vintage as the time between the first day of RRT and the first record of haemodialysis session duration and frequency. Dialysis vintage was defined as the time on RRT minus the time with a functioning kidney transplant. Definitions of comorbidities are available as Appendix 1.

Statistical analyses

We reported normally distributed numerical variables as mean ± standard deviation, non-normally distributed numerical variables as median with interquartile range and categorical variables as number (percentage). We tabulated patient characteristics at the time of their first record of haemodialysis session duration and frequency, stratified for patients exclusively treated with CHD, patients ever treated with EHD and patients

never treated with EHD but ever treated with other haemodialysis regimens.

We assessed the effect of EHD on survival with causal inference from marginal structural models using haemodialysis treatment as time-varying exposure. Marginal structural models are a class of causal models that can be used to estimate the causal effect of a time-varying exposure or treatment [21]. They are a powerful method for confounding control in longitudinal study designs with time-varying information on exposure and outcome [22]. In this study, this means that we assessed the association of total time spent on EHD with survival, even if treatment modality had been changed before death. Marginal structural models use estimators weighted for the inverse probability of treatment (IPTW) and censoring (IPCW), which we calculated with multinomial logistic regression models including the variables age (years), sex, primary renal disease, country, previous kidney transplantation (yes/no), dialysis vintage (years) and comorbidities (diabetes, cerebrovascular disease, ischaemic heart disease, peripheral vascular disease, congestive heart failure and malignancy) [23]. Weights were truncated at the 2nd and 98th percentiles. We adjusted the IPTW and IPCW Cox proportional hazard models for age (years), sex, primary renal disease, country, previous kidney transplantation (yes/no), dialysis vintage (years) and comorbidities (diabetes, cerebrovascular disease, ischaemic heart disease, peripheral vascular disease, congestive heart failure and malignancy), with CHD as a reference group. We also present results from unweighted, unadjusted Cox proportional hazard models with haemodialysis treatment as time-varying exposure. We present hazard ratios (HRs) for EHD only because of the heterogeneity of the other haemodialysis regimens and the ensuing limited interpretability.

The completeness of comorbidity data varied, ranging from 11% missing for diabetes to 22% missing for congestive heart failure. We therefore imputed missing comorbidity data using the R aregImpute function with 10 imputations with predictive mean matching. Variables in the imputation model included age at each record (years), age at the start of dialysis (years), sex, primary renal disease, previous kidney transplantation (yes/no), dialysis vintage (years), time on RRT (years), time since transplantation (years), indicators of censoring, transplantation and death at each record and at any time during follow-up, indicators of treatment at each record and during follow-up and comorbidities (diabetes, cerebrovascular disease, ischemic heart disease, peripheral vascular disease, congestive heart failure and malignancy). We analysed each of the imputed datasets separately and pooled the results according to Rubin's rules [24].

As patients from France constituted most of the study population (71% of all patients), we repeated all analyses excluding data from this registry. Furthermore, we repeated all analyses excluding patients with missing comorbidity data, excluding patients that were ever treated with home haemodialysis and exclusively including incident patients treated with haemodialysis (RRT vintage $<$180 days). Finally, we conducted a propensity score matched analysis, matching patients ever treated with EHD with up to 20 patients exclusively treated with CHD using propensity scores as calculated for the IPTWs, within a 0.1 caliper.

We reported HRs with 95% confidence intervals (CIs). Furthermore, we created Kaplan–Meier curves weighted for the product of IPTW and IPCW [25]. We considered $P \leq 0.05$ (two-tailed) statistically significant and used R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) for all analyses.

RESULTS

Our cohort included a total of 142 640 prevalent patients from eight European countries treated with haemodialysis between 2010 and 2017. Of them, 89 819 were exclusively treated with CHD, 1338 were ever treated with EHD and 51 483 were ever treated with other haemodialysis regimens but never with EHD (Table 1). Of note, the latter group included 109 patients ever treated with frequent EHD (four or more times weekly, $\geq$6 h/treatment). These treatments were also classified as other haemodialysis regimens because of their limited occurrence. Compared with patients exclusively treated with CHD, patients ever treated with EHD were generally younger (mean 55 versus 67 years), had been on dialysis longer (median 1.7 versus 0.4 years), were more often treated at home (6% versus 0%) and more often had a previous kidney transplantation (26% versus 9%). Also, patients ever treated with EHD less often had comorbidities, such as diabetes and cardiovascular diseases, and less often had diabetes or hypertension as primary renal disease.

Haemodialysis session duration and frequency

CHD was delivered three times weekly for, on average, 3.9 $\pm$ 0.2 h per session (11.8 $\pm$ 0.5 h weekly), whereas EHD was delivered three times weekly for 7.1 $\pm$ 0.8 h per session (21.4 $\pm$ 2.5 h weekly) (Figure 1). Other haemodialysis regimens were delivered, on average, 3.0 $\pm$ 0.8 times weekly (range 1–7) for a mean of 3.9 $\pm$ 0.8 h per session (range 0.1–10), amounting to a mean of 11.6 $\pm$ 3.5 h weekly (range 0.1–56).

Mortality

A total of 41 892 patients died while treated with CHD (13.5/100 person-years), whereas 179 patients died while treated with EHD (6.0/100 person-years) and 16 421 patients died while treated with other haemodialysis regimens (16.1/100 person-years). A total of 17 963 patients received a kidney transplant while treated with CHD (5.8/100 person-years), whereas 308 patients received a kidney transplant while treated with EHD (10.4/100 person-years) and 5977 while on other haemodialysis regimens (5.9/100 person-years). From the total of 1338 patients ever treated with EHD, 468 (35%) transferred from EHD to CHD or other haemodialysis regimens, after an average recorded treatment duration of 2.5 $\pm$ 1.8 years. The mortality rates (with deaths attributed to EHD after initiation) were similar for patients that initiated EHD but transferred from EHD to CHD or other haemodialysis regimens (7.5/100 person-years) and for patients that initiated EHD and did not transfer (7.5/100 person-years).

In the primary analyses, we attributed death to the treatment at time of death. In an ordinary unweighted, unadjusted Cox

Table 1. Characteristics of patients exclusively treated with CHD, patients ever treated with EHD and patients treated with other haemodialysis regimens, at the time of the first record of haemodialysis session duration and frequency

Characteristics	Exclusively treated with CHD ($n = 89\,819$)	Ever treated with EHD ($n = 1338$)	Ever treated with other haemodialysis regimen[a] ($n = 51\,483$)
Age (years), mean ± SD	67 ±15	55 ±15	67 ±16
Male, *n* (%)	56 360 (63)	993 (74)	32 229 (63)
Primary renal disease, *n* (%)			
Glomerulonephritis	12 500 (14)	363 (27)	7244 (14)
Pyelonephritis	5080 (6)	103 (8)	3078 (6)
Polycystic kidney disease	5675 (6)	129 (10)	3295 (6)
Diabetes	20 871 (23)	235 (18)	11 870 (23)
Hypertension	18 675 (21)	158 (12)	10 334 (20)
Renal vascular disease	2053 (2)	15 (1)	1113 (2)
Miscellaneous	13 672 (15)	243 (18)	8233 (16)
Unknown	11 293 (13)	92 (7)	6316 (12)
Dialysis vintage (years), median (IQR)	0.4 (0.0–2.4)	1.7 (0.0–5.3)	0.5 (0.0–2.6)
Time on RRT (years), median (IQR)	0.4 (0.0–3.0)	2.4 (0.0–10.5)	0.5 (0.0–3.2)
Previous transplantation, *n* (%)	8348 (9)	347 (26)	5321 (10)
Ever treated with home haemodialysis, *n* (%)	233 (0)	77 (6)	1407 (3)
Comorbidities[b], *n* (%)			
Diabetes mellitus	35 201 (39)	390 (29)	20 323 (40)
Cerebrovascular disease	10 015 (11)	63 (5)	5934 (12)
Ischaemic heart disease	21 323 (24)	197 (15)	12 246 (24)
Peripheral vascular disease	17 015 (19)	150 (11)	9205 (18)
Congestive heart failure	19 582 (22)	165 (12)	10 752 (23)
Malignancy	9475 (11)	106 (8)	5540 (11)
Country, *n* (%)			
Austria	5792 (6)	28 (2)	3313 (6)
Belgium, French-speaking	3166 (4)	112 (8)	1048 (2)
Catalonia (Spain)	6769 (8)	95 (7)	3076 (6)
Finland	1443 (2)	22 (2)	2009 (4)
France	66 552 (74)	910 (68)	33 418 (65)
Norway	1329 (2)	0 (0)	1725 (3)
Sweden	2409 (3)	73 (5)	4599 (9)
Scotland (the UK)	2359 (3)	98 (7)	2295 (5)

SD, standard deviation; IQR, interquartile range.
[a]Patients in this category were never treated with EHD but were ever treated with other haemodialysis regimens.
[b]Comorbidity data were incomplete and missing comorbidity data were therefore imputed. Percentage missing comorbidity data: diabetes mellitus, 11%; cerebrovascular disease, 13%, ischaemic heart disease, 13%; peripheral vascular disease, 13%; congestive heart failure, 22%; malignancy, 13%.

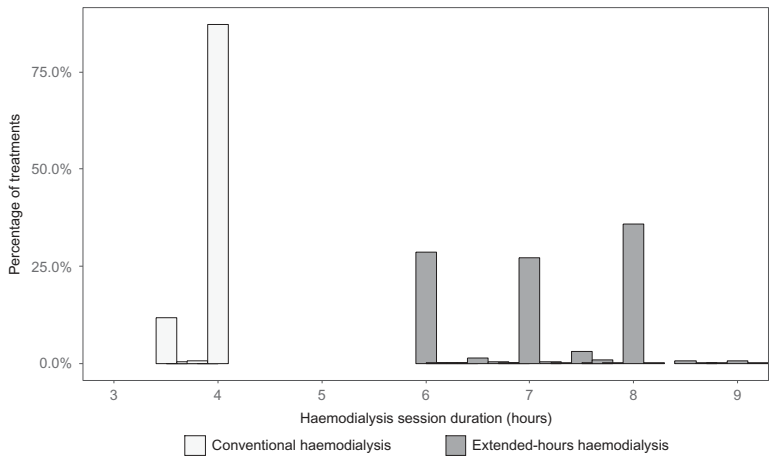

FIGURE 1: Distribution of haemodialysis session duration in treatment with CHD (grey bars, 383 204 records) and EHD (black bars, 3111 records), as a percentage of the total number of records per treatment group.

proportional hazard model, EHD was associated with a mortality HR of 0.41 (95% CI 0.36–0.48) compared with CHD. Using marginal structural models adjusted for case-mix factors and treatment history, we found that patients treated with EHD had a mortality HR of 0.73 (95% CI 0.62–0.85) compared with patients treated with CHD (Figure 2 and Table 2).

In the secondary analyses, we attributed all deaths that occurred after a patient had ever been treated with EHD to EHD,

regardless of the treatment at time of death. In the unweighted, unadjusted Cox proportional hazard model, EHD was associated with a mortality HR of 0.50 (95% CI 0.45–0.56) compared with CHD. Using marginal structural models adjusted for case-mix factors and treatment history, we found that patients treated with EHD had a mortality HR of 0.80 (95% CI 0.71–0.90) compared with patients treated with CHD.

Sensitivity analyses excluding data from France confirmed our finding that patients treated with EHD had a lower mortality risk compared with patients treated with CHD (Supplementary data, Table S1). Although the effect estimates for EHD were even larger when excluding data from France, characteristics of patients treated with CHD or EHD were largely similar in the French registry and other registries (data not shown). Furthermore, we repeated the primary and secondary analyses adjusted for RRT vintage instead of dialysis vintage, which yielded numerically similar results (data not shown). Our finding of lower mortality risk with EHD was also confirmed by sensitivity analyses excluding patients with missing comorbidity data (Supplementary data, Table S2), sensitivity analyses excluding patients ever treated with home haemodialysis (Supplementary data Table S3), sensitivity analyses exclusively including incident patients treated with haemodialysis (Supplementary data, Table S4) and a propensity score matched analysis (Supplementary data, Tables S5 and S6).

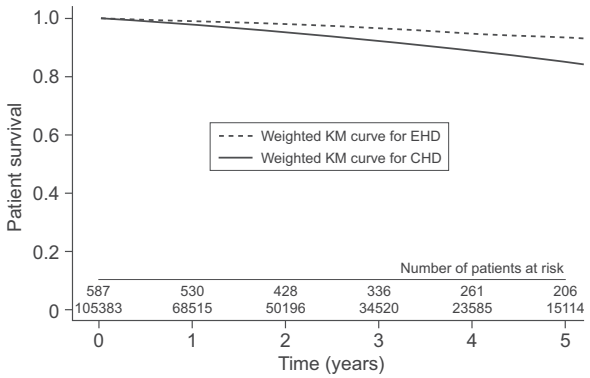

FIGURE 2: Weighted (IPT and IPC) Kaplan–Meier (KM) curves for EHD (dashed line) and CHD (solid line). We show the number of patients at risk of death per year at the bottom of the graph for EHD (top row) and CHD (bottom row).

DISCUSSION

In this cohort of prevalent patients from eight European countries treated with haemodialysis three times weekly, we found that patients treated with EHD had a significantly lower mortality risk than patients treated with CHD. Our findings extend those of previous studies in patients from the USA to European patients treated with haemodialysis and support the hypothesis that EHD improves survival.

To our knowledge, this is the first study to investigate the effect of EHD (three times weekly, ≥6 h/treatment) on survival in a European population. Previously the Frequent Hemodialysis Network: Nocturnal Trial investigated the effect of frequent nocturnal haemodialysis (six times weekly, ≥6 h/treatment) on survival, which was non-significant [11]. However, this trial was underpowered due to recruitment difficulties. Other trials with different endpoints include a Canadian trial and the A Clinical Trial of IntensiVE Dialysis (ACTIVE) dialysis trial. The Canadian trial randomized patients to in-centre or home haemodialysis three times weekly and nocturnal haemodialysis six times weekly and found reductions in left ventricular mass, systolic blood pressure, serum phosphate and parathyroid hormone [26]. The ACTIVE dialysis trial randomized patients to haemodialysis 12–18 h/week and ≥24 h/week and found reductions in serum phosphate and prescriptions of antihypertensives, but no improvements in quality of life [27]. A recent analysis of the ACTIVE dialysis trial showed no survival benefit for EHD 4 years post-intervention. However, the ACTIVE trial was not powered to detect mortality differences, and only very few patients in the EHD group were treated for ≥24 h/week post-intervention [13]. Moreover, these three trials were not designed to assess the impact of haemodialysis session duration separately from frequency. These limitations emphasize the need for thorough analyses of haemodialysis cohorts.

Several observational studies have investigated the effect of EHD three times weekly among haemodialysis cohorts in the USA [14–16] and Turkey [17], with greatly varying effect estimates from 10 to 72%. Our data showed ∼ 20% lower mortality risk for EHD three times weekly compared with CHD. This variation may be due to differences in study design, analytical approach, health care systems and population. For example, our estimates are smaller than a large recent study that used a similar analytical approach but investigated patients from the USA [16]. Nevertheless, estimates of this study and previous studies are all in the same direction, indicating a robust effect of EHD.

Table 2. Mortality risk in EHD compared with CHD in prevalent patients treated with haemodialysis in eight European countries between 2010 and 2017 ($n = 142\,640$)

Variable	Number of deaths	Person-years	Mortality rate[a]	Adjusted HR (95% CI)[b]
Death attributed to the treatment at time of death (primary analysis)				
CHD	41 892	310 712	13.5	1.0 (ref.)
EHD	179	2966	6.0	0.73 (0.62–0.85)
All deaths attributed to EHD after initiation (secondary analysis)				
CHD	41 832	310 275	13.5	1.0 (ref.)
EHD	303	4039	7.5	0.80 (0.71–0.90)

[a]Per 100 person-years.
[b]HR from marginal structural model with Cox regression, adjusted for age (years), sex, primary renal disease, country, previous kidney transplantation (yes/no), dialysis vintage (years) and comorbidities (diabetes, cerebrovascular disease, ischaemic heart disease, peripheral vascular disease, congestive heart failure and malignancy). Reference group is CHD.

The reduced mortality in EHD may develop through several mechanisms. Several studies have shown associations of EHD with lower phosphate levels [28]. High phosphate levels are associated with vascular calcification and arterial stiffness [29], which are risk factors for left ventricular dysfunction and heart failure among patients with chronic kidney disease [30], and thus mortality. Indeed, some studies, including one randomized trial, have suggested reductions of left ventricular mass with EHD [17, 26, 31–33], although this was not confirmed in two other randomized trials [11, 27]. Furthermore, high phosphate levels are associated with endothelial dysfunction, which may predispose to atherosclerosis [34]. EHD is also associated with higher removal of fibroblast growth factor 23 [35], which is associated with left ventricular hypertrophy and mortality [36]. On the other hand, EHD allows for a substantially lower ultrafiltration rate than CHD. High ultrafiltration rates in CHD are associated with myocardial stunning, which over time results in impaired segmental and global left ventricular function [37]. Slower fluid removal is associated with lower blood pressure and reduced mortality [38], an association that was also observed by Charra *et al.* [39], who were one of the first to report low mortality rates among patients treated with EHD.

Our findings support the hypothesis that extending haemodialysis hours during treatment three times weekly improves survival. Still, all prior studies [14–17], including ours, have been observational, which cannot prove causation. Importantly, patients opting for EHD are generally a selected subgroup. Although there may be various reasons for initiating EHD, such as pregnancy or calciphylaxis, often patients initiating EHD are younger, treated at home, healthier, more motivated and more likely to adhere to treatment. Indeed, patients treated with EHD had higher transplantation rates and less often had comorbidities such as cerebrovascular disease and ischaemic heart disease compared with patients treated with CHD. We therefore accounted for censoring and comorbidities in our analyses, which yielded much lower estimates compared with unadjusted, unweighted analyses. Nevertheless, unmeasured confounders may have led to improved survival independent of the treatment, such as fitness, for which transplantation eligibility could be a proxy. Although RCTs could overcome this issue, a previous trial that randomly assigned patients to frequent nocturnal haemodialysis failed to recruit sufficient patients [11], as did another trial that randomly assigned patients to haemodialysis and peritoneal dialysis [40]. This indicates that patients are generally reluctant to be randomized to treatments such as dialysis modalities that have a tremendous impact on daily life. It is therefore questionable whether an adequately powered RCT investigating the effect of EHD on mortality will take place.

In this study, we investigated the effect of EHD separate from treatment frequency. Two observational studies investigating more frequent ($\geq$4$\times$ weekly) EHD compared with CHD reported larger mortality risk reductions compared with our study (45 and 66%) [8, 9]. However, these estimates are not directly comparable to ours due to differences in population and study design. Moreover, frequent haemodialysis increases the risk of vascular access complications [41]. Therefore further study into the added value of frequent treatment in EHD would be useful.

The major strength of this study is that by using data from population-based national and regional registries contributing to the ERA-EDTA Registry, our cohort covered all adult patients treated with haemodialysis in the respective countries and regions, thus representing a large, unselected population. We therefore believe our results are generalizable to a broad population of European patients treated with haemodialysis. Also, we used marginal structural models for causal inference, which are sophisticated statistical methods to account for the propensity of healthier patients to survive to transfer to EHD. Nevertheless, our findings should also be viewed within the context of certain limitations. The ERA-EDTA Registry depends on data provided by national and regional registries, which did not include haemodialysis session duration and frequency in many registries. In addition, we studied prevalent patients treated with haemodialysis, which may have introduced survivor bias. Furthermore, data on reasons for transfer to EHD were not available. This may have included a full-time job or other daily activities that are accompanied by more favourable outcomes, introducing potential indication bias. Other limitations include unavailable data on clinical information, including vascular access type, type of dialysis membrane, ultrafiltration rate, actual amount of delivered haemodialysis and transplantation eligibility. Also, we did not distinguish between haemodialysis and haemodiafiltration, which could have led to lower estimates due to potentially more frequent haemodiafiltration in conventional regimens, which may improve survival [42]. Nevertheless, every observational study is limited by potentially unmeasured confounders and selection bias.

In conclusion, European patients treated with EHD three times weekly have a lower mortality risk compared with patients treated with CHD. This indicates that extending haemodialysis to $\geq$6 h during treatment three times weekly may improve survival. Further studies could investigate the added value of frequent treatment in EHD.

SUPPLEMENTARY DATA

Supplementary data are available at ndt online.

ACKNOWLEDGEMENTS

We would like to thank the patients and the staff of the dialysis and transplant units for contributing the data via their national and regional renal registries. Furthermore, we gratefully acknowledge the following registries and persons for their contributions of data: Austrian Dialysis and Transplant Registry (R. Kramar); French-speaking Belgian Society of Nephrology (J.M. des Grottes); Finnish Registry for Kidney Diseases (P. Finne, A. Pylsy and P.H. Groop); France: The Epidemiology and Information Network in Nephrology (REIN) (M. Lassalle); Norwegian Renal Registry (T. Leivestad, A.V. Reisæter and A. Åsberg); Swedish Renal Registry (K.G. Prütz, M. Stendahl, M. Evans, S. Schön, T. Lundgren and M. Segelmark); Scottish Renal Registry (all of the Scottish renal units); and the regional registry of Catalonia (E. Arcos, J. Comas and J. Tort) and the other ERA-EDTA Registry Committee members not mentioned

above for their advice in the analysis and the drafting of this article: P. Ambühl, J. De Meester, M. Evans, P. Finne, J. Harambat, L. Mercadal, M. Nordio, S.S. Sørensen and E. Vidal; and M. Pippias and V.S. Stel in the AMC Registry office for data collection and management. The ERA-EDTA Registry is funded by the ERA-EDTA.
This article was written by T. Jansz, M. Noordzij, A. Kramer, E. Laruelle, C. Couchoud, F. Collart, A. Cases, M. Arici, J. Helve, B. Waldum-Grevbo, H. Rydell, J. Traynor, C. Zoccali, Z.A. Massy, K.J. Jager and B.C. van Jaarsveld on behalf of the ERA-EDTA Registry, which is an official body of the ERA-EDTA.

CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published previously in whole or part.

REFERENCES

1. Kramer A, Pippias M, Noordzij M *et al.* The European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry Annual Report 2015: a summary. *Clin Kidney J* 2018; 11: 108–122
2. de Jager DJ, Grootendorst DC, Jager KJ *et al.* Cardiovascular and noncardiovascular mortality among patients starting dialysis. *JAMA* 2009; 302: 1782–1789
3. Vogelzang JL, van Stralen KJ, Noordzij M *et al.* Mortality from infections and malignancies in patients treated with renal replacement therapy: data from the ERA-EDTA registry. *Nephrol Dial Transplant* 2015; 30: 1028–1037
4. Couchoud C, Dantony E, Elsensohn MH *et al.* Restricted mean survival time over 15 years for patients starting renal replacement therapy. *Nephrol Dial Transplant* 2017; 32: ii60–ii67
5. Tentori F, Zhang J, Li Y *et al.* Longer dialysis session length is associated with better intermediate outcomes and survival among patients on in-center three times per week hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 2012; 27: 4180–4188
6. Marshall MR, Polkinghorne KR, Kerr PG *et al.* Intensive hemodialysis and mortality risk in Australian and New Zealand populations. *Am J Kidney Dis* 2016; 67: 617–628
7. Fotheringham J, Sajjad A, Stel VS *et al.* The association between longer haemodialysis treatment times and hospitalization and mortality after the two-day break in individuals receiving three times a week haemodialysis. *Nephrol Dial Transplant* 2019; 34: 1577–1584
8. Johansen KL, Zhang R, Huang Y *et al.* Survival and hospitalization among patients using nocturnal and short daily compared to conventional hemodialysis: a USRDS study. *Kidney Int* 2009; 76: 984–990
9. Nesrallah GE, Lindsay RM, Cuerden MS *et al.* Intensive hemodialysis associates with improved survival compared with conventional hemodialysis. *J Am Soc Nephrol* 2012; 23: 696–705
10. Tennankore KK, Na Y, Wald R *et al.* Short daily-, nocturnal- and conventional-home hemodialysis have similar patient and treatment survival. *Kidney Int* 2018; 93: 188–194
11. Rocco MV, Lockridge RS Jr, Beck GJ *et al.* The effects of frequent nocturnal home hemodialysis: the Frequent Hemodialysis Network Nocturnal Trial. *Kidney Int* 2011; 80: 1080–1091
12. Rocco MV, Daugirdas JT, Greene T *et al.* Long-term effects of frequent nocturnal hemodialysis on mortality: the Frequent Hemodialysis Network (FHN) Nocturnal Trial. *Am J Kidney Dis* 2015; 66: 459–468
13. Smyth B, Zuo L, Gray NA *et al.* Long-term follow-up of a randomized controlled trial of extended-hours hemodialysis: the ACTIVE dialysis study. Presented at the International Society of Nephrology World Congress of Nephrology, Melbourne, Australia, 12–15 April 2019
14. Lacson E Jr, Wang W, Lester K *et al.* Outcomes associated with in-center nocturnal hemodialysis from a large multicenter program. *Clin J Am Soc Nephrol* 2010; 5: 220–226
15. Lacson E Jr, Xu J, Suri RS *et al.* Survival with three-times weekly in-center nocturnal versus conventional hemodialysis. *J Am Soc Nephrol* 2012; 23: 687–695
16. Rivara MB, Adams SV, Kuttykrishnan S *et al.* Extended-hours hemodialysis is associated with lower mortality risk in patients with end-stage renal disease. *Kidney Int* 2016; 90: 1312–1320
17. Ok E, Duman S, Asci G *et al.* Comparison of 4- and 8-h dialysis sessions in thrice-weekly in-centre haemodialysis: a prospective, case-controlled study. *Nephrol Dial Transplant* 2011; 26: 1287–1296
18. Pisoni RL, Zepel L, Fluck R *et al.* International differences in the location and use of arteriovenous accesses created for hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Am J Kidney Dis* 2018; 71: 469–478
19. Robinson BM, Zhang J, Morgenstern H *et al.* Worldwide, mortality risk is high soon after initiation of hemodialysis. *Kidney Int* 2014; 85: 158–165
20. van Dijk PC, Jager KJ, de Charro F *et al.* Renal replacement therapy in Europe: the results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. *Nephrol Dial Transplant* 2001; 16: 1120–1129
21. Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; 11: 550–560
22. Williamson T, Ravani P. Marginal structural models in clinical research: when and how to use them? *Nephrol Dial Transplant* 2017; 32: ii84–ii90
23. van der Wal WM, Geskus RB. ipw: an R package for inverse probability weighting. *J Stat Soft* 2011; 43: 1–23
24. Rubin DB, Schenker N. Multiple imputation for interval estimation from simple random samples with ignorable nonresponse. *J Am Stat Assoc* 1986; 81: 366–374
25. Cole SR, Hernan MA. Adjusted survival curves with inverse probability weights. *Comput Methods Programs Biomed* 2004; 75: 45–49
26. Culleton BF, Walsh M, Klarenbach SW *et al.* Effect of frequent nocturnal hemodialysis vs conventional hemodialysis on left ventricular mass and quality of life: a randomized controlled trial. *JAMA* 2007; 298: 1291–1299
27. Jardine MJ, Zuo L, Gray NA *et al.* A trial of extending hemodialysis hours and quality of life. *J Am Soc Nephrol* 2017; 28: 1898–1911
28. Wong B, Collister D, Muneer M *et al.* In-center nocturnal hemodialysis versus conventional hemodialysis: a systematic review of the evidence. *Am J Kidney Dis* 2017; 70: 218–234
29. Raggi P, Boulay A, Chasan-Taber S *et al.* Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? *J Am Coll Cardiol* 2002; 39: 695–701
30. Moody WE, Edwards NC, Chue CD *et al.* Arterial disease in chronic kidney disease. *Heart* 2013; 99: 365–372
31. Jin X, Rong S, Mei C *et al.* Effects of thrice-weekly in-center nocturnal vs. conventional hemodialysis on integrated backscatter of myocardial tissue. *Hemodial Int* 2011; 15: 200–210
32. Wald R, Goldstein MB, Perl J *et al.* The association between conversion to in-centre nocturnal hemodialysis and left ventricular mass regression in patients with end-stage renal disease. *Can J Cardiol* 2016; 32: 369–377
33. Weinreich T, de los Rios T, Gauly A *et al.* Effects of an increase in time vs. frequency on cardiovascular parameters in chronic hemodialysis patients. *Clin Nephrol* 2006; 66: 433–439
34. Gross P, Six I, Kamel S *et al.* Vascular toxicity of phosphate in chronic kidney disease: beyond vascular calcification. *Circ J* 2014; 78: 2339–2346
35. Cornelis T, van der Sande FM, Eloot S *et al.* Acute hemodynamic response and uremic toxin removal in conventional and extended hemodialysis and hemodiafiltration: a randomized crossover study. *Am J Kidney Dis* 2014; 64: 247–256
36. Kuczera P, Adamczak M, Wiecek A. Fibroblast growth factor-23—a potential uremic toxin. *Toxins (Basel)* 2016; 8: 369
37. Burton JO, Jefferies HJ, Selby NM *et al.* Hemodialysis-induced repetitive myocardial injury results in global and segmental reduction in systolic cardiac function. *Clin J Am Soc Nephrol* 2009; 4: 1925–1931
38. Saran R, Bragg-Gresham JL, Levin NW *et al.* Longer treatment time and slower ultrafiltration in hemodialysis: associations with reduced mortality in the DOPPS. *Kidney Int* 2006; 69: 1222–1228
39. Charra B, Chazot C, Jean G *et al.* Long, slow dialysis. *Miner Electrolyte Metab* 1999; 25: 391–396

40. Korevaar JC, Feith GW, Dekker FW *et al*. Effect of starting with hemodialysis compared with peritoneal dialysis in patients new on dialysis treatment: a randomized controlled trial. *Kidney Int* 2003; 64: 2222–2228
41. Suri RS, Larive B, Sherer S *et al*. Risk of vascular access complications with frequent hemodialysis. *J Am Soc Nephrol* 2013; 24: 498–505
42. Peters SA, Bots ML, Canaud B *et al*. Haemodiafiltration and mortality in end-stage kidney disease patients: a pooled individual participant data analysis from four randomized controlled trials. *Nephrol Dial Transplant* 2016; 31: 978–984

Received: 28.6.2019; Editorial decision: 13.9.2019

Nephrol Dial Transplant (2020) 35: 495–502
doi: 10.1093/ndt/gfz222
Advance Access publication 18 November 2019

ORIGINAL ARTICLE

Dialysis initiation improves calcification propensity

Belen Ponte[1,2], Menno Pruijm[3], Andreas Pasch[4], Anne Dufey-Teso[1], Pierre-Yves Martin[1] and Sophie de Seigneux[1]

[1]Nephrology Service, Department of Medicine, University Hospital of Geneva, Geneva, Switzerland, [2]Institute of Social and Preventive Medicine, University Center of General Medicine and Public Health, Lausanne, Switzerland, [3]Nephrology and Hypertension Service, Department of Medicine, University Hospital of Lausanne, Lausanne, Switzerland and [4]Calciscon AG, Nidau, Switzerland

Correspondence to: Sophie De Seigneux; E-mail: sophie.deseigneux@hcuge.ch

ABSTRACT

Background. Cardiovascular morbidity and mortality is high in patients starting dialysis and could be related to modifications of calcification inducers and inhibitors by dialysis, promoting cardiovascular events. The impact of dialysis initiation on serum calcification propensity evolution and arterial stiffness is unknown. We therefore prospectively determined the evolution of the one-half maximal transition time (T_{50}) value and its main determinants as well as pulse wave velocity over the first 3 months of dialysis initiation.

Methods. We analysed the evolution of T_{50}, fetuin-A and mineral metabolism parameters before dialysis initiation (M0) and monthly until Month 3 (M3) in incident patients starting haemodialysis (HD) or peritoneal dialysis (PD) in two tertiary Swiss university hospitals. Arterial stiffness was assessed by pulse tonometry at M0 and M3 and biological parameters were compared between M0 and M3 and before/after HD. Linear mixed models were used to assess parameter evolution over time, taking into account repeated measures and other influencing variables.

Results. Forty-six patients on HD and 12 on PD were followed. Among them, 45 were male (78%) with a median age of 67 years (25th–75th quartile range 54–77). T_{50} significantly increased between M0 and M3 from 183 (120–266) to 246 min (175–330) ($P < 0.001$). Fetuin-A, calcium and magnesium also increased while phosphate decreased. Factors associated with T_{50} changes over time were fetuin-A, phosphate and magnesium ($P < 0.001$). Fetuin-A changes were associated with inflammation-related factors (albumin, C-reactive protein) but not calcium and phosphate levels. Arterial stiffness was not significantly modified over 3 months. PD and HD initiation showed similar trends.

Conclusions. Dialysis initiation significantly improves calcification propensity and fetuin-A levels. These modifications do not explain the high mortality related to dialysis initiation. The clinical relevance of using T_{50} values to initiate dialysis awaits further studies.

Keywords: calcification, dialysis initiation, fetuin-A

INTRODUCTION

Chronic kidney disease (CKD) engenders major cardiovascular (CV) mortality [1]. Haemodialysis (HD) and peritoneal dialysis (PD) are initiated at CKD Stage 5 mostly in symptomatic uraemic patients to mitigate complications. However, an excessively high mortality rate is observed during the first 3 months after dialysis initiation as compared with the period thereafter, mainly due to CV events [2]. For this reason, the issue of timing of dialysis initiation is still debated and has not been settled [3, 4]. Why dialysis initiation is associated with a high rate of CV events is incompletely understood. Several hypotheses have been proposed, such as vascular access problems or dialysis-induced myocardial dysfunction or stunning [5]. Others have suggested that cardiovascular events are triggered by acute alterations in mineral metabolism that favour vascular stiffness and calcifications, but prospective studies that have focused on these properties in the early dialysis period are largely lacking. Also, until recently, no clinical tests have been available to assess the propensity of blood to promote or inhibit vascular calcifications [6, 7].

The one-half maximal transition time (T_{50}) test [8] was developed for the assessment of serum calcification propensity.