

# Association between pre-transplant dialysis modality and patient and graft survival after kidney transplantation

Anneke Kramer<sup>1</sup>, Kitty J. Jager<sup>1</sup>, Damian G. Fogarty<sup>2</sup>, Pietro Ravani<sup>3</sup>, Patrik Finne<sup>4</sup>, Jordi Pérez-Panadés<sup>5</sup>, Karl G. Prütz<sup>6</sup>, Manuel Arias<sup>7</sup>, James G. Heaf<sup>8</sup>, Christoph Wanner<sup>9</sup> and Vianda S. Stel<sup>1</sup>

<sup>1</sup>ERA–EDTA Registry, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands, <sup>2</sup>Nephrology Research Group, Centre for Public Health, Queen's University and Regional Nephrology Unit, Belfast City Hospital, Belfast, UK, <sup>3</sup>Department of Medicine and Community Health Science, University of Calgary, Calgary, Alberta, Canada, <sup>4</sup>Finnish Registry for Kidney Diseases, Helsinki, Finland, <sup>5</sup>Àrea de Epidemiologia, Direcció General de Salut Pública, Conselleria de Sanitat, Generalitat Valenciana, Spain, <sup>6</sup>Department of Nephrology and Transplantation, Skåne University Hospital, Malmö, Sweden, <sup>7</sup>Department of Nephrology, Hospital Universitario Marqués de Valdecilla, Santander, Spain, <sup>8</sup>Department of Nephrology, University of Copenhagen Herlev Hospital, Herlev, Denmark and <sup>9</sup>Division of Nephrology, University Clinic, University of Würzburg, Würzburg, Germany

Correspondence and offprint requests to: Anneke Kramer; E-mail: a.kramer@amc.uva.nl

## Abstract

**Background.** Previous studies have found inconsistent associations between pre-transplant dialysis modality and subsequent post-transplant survival. We aimed to examine this relationship using the instrumental variable method and to compare the results with standard Cox regression.

**Methods.** We included 29 088 patients (age >20 years) from 16 European national or regional renal registries who received a first kidney transplant between 1 January 1999 and 31 December 2008 and were on dialysis before transplantation for a period between 90 days and 10 years. Standard multivariable Cox regression examined the association of individually assigned pre-transplant dialysis modality with post-transplant patient and graft survival. To decrease confounding-by-indication through unmeasured factors, we applied the instrumental variable method that used the case-mix adjusted centre percentage of peritoneal dialysis (PD) as predictor variable.

**Results.** Standard analyses adjusted for age, sex, primary renal disease, donor type, duration of dialysis, year of transplantation and country suggested that PD before transplantation was associated with better patient [hazard ratio, HR (95% CI) = 0.83 (0.76–0.91)] and graft survival [HR (95% CI) 0.90 (0.84–0.96)] when compared with haemodialysis (HD). In contrast, the instrumental variable analysis showed that a 10% increase in the case-mix adjusted centre percentage of patients on PD was neither associated with post-transplant patient survival [HR (95% CI) = 1.00 (0.97–1.04)] nor with graft survival [HR (95% CI) = 1.01 (0.98–1.04)].

**Conclusions.** The instrumental variable method failed to confirm the associations found in standard Cox regression between pre-transplant dialysis modality and patient and graft survival after transplantation. The lack of association in instrumental variable analysis may be due to better control of residual confounding.

**Keywords:** confounding; dialysis; Europe; instrumental variable; kidney transplantation; survival

## Introduction

While awaiting a donor kidney most end-stage renal disease patients need to initiate dialysis. There has been debate on whether the choice of dialysis modality may affect prognosis of these patients. Studies examining the association between dialysis modality, i.e. haemodialysis (HD) or peritoneal dialysis (PD), before kidney transplantation, and patient and graft survival after transplantation have shown conflicting results [1–8]. Goldfarb-Rumyantzev *et al.* [1] studied the survival of 92 844 US kidney transplant recipients and concluded that patients on PD before transplantation had a 6% lower risk of death and a 3% lower risk of (death-censored) graft failure than HD patients. In contrast, Snyder *et al.* [2] studied the survival of 22 776 US kidney transplant recipients and reported that dialysis modality prior to transplantation was not associated with patient survival after transplantation, but that PD patients had a 15% increased risk of death-censored graft failure. On the other hand, other much smaller, and therefore less powered, studies (up to 3464 patients) in different populations [3–8] reported that there was no association between dialysis modality prior to transplantation and the patient and graft survival after transplantation.

However, any association between dialysis modality before transplantation and the survival after transplantation potentially suffers from confounding-by-indication, as patients may have been selected to start with HD or PD because of observed or unobserved prognostic factors [9]. For example, in many countries, patients on PD tend to be healthier than those on HD [10–12]. Previous studies addressed this problem by matching HD and PD patients

for age and gender [3, 4], or by adjusting for patient characteristics such as the presence of co-morbidities [1, 2]. However, these methods may insufficiently account for differences in health status. In observational studies, the instrumental variable method is increasingly being used as an approach to reduce confounding-by-indication due to unmeasured factors [13–19]. Using this method, patients are grouped by organizational unit (the instrumental variable), rather than by the treatment assigned to each individual patient.

The aim of this study was to examine the association between pre-transplant dialysis modality and patient and graft survival after the first kidney transplantation in a large cohort of living and deceased donor kidney transplant recipients in Europe. In addition to standard regression analyses, we also applied the instrumental variable method that used the case-mix adjusted centre percentage of PD as predictor to minimize potential bias due to unmeasured confounders.

## Materials and methods

### Data collection

Sixteen national or regional renal registries that annually submit individual patient data to the European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) Registry, and had data available from 1999 to 2008, participated in this study, including the national registries of Austria, Denmark, England/Wales (UK), Finland, Greece, Norway, Scotland (UK), Sweden, the Netherlands, and the regional registries of Dutch and French-speaking Belgium, and Asturias, Basque country, Cantabria, Catalonia and the Valencian region (together covering 35% of Spain). The details of the database and the methods used for data collection and data processing have been reported previously [20].

Patients satisfying the following criteria were included in the study cohort: (i) being on dialysis before transplantation for at least 90 days and no longer than 10 years; (ii) receiving a first kidney transplant from a living or deceased kidney donor between 1 January 1999 and 31 December 2008 and (iii) being >20 years of age at the time of first transplantation.

### Statistical analysis

The differences in patient characteristics between groups were examined using the Chi-square test (for categorical variables) and the Wilcoxon–Mann–Whitney test (for continuous variables). For both the analyses with patient survival and graft survival after transplantation, the date of transplantation was the starting point. For *patient survival*, death was the event studied, and reasons for censoring were loss to follow-up and the end of the follow-up period (31 December 2008 or 5 years after transplantation, whichever came first). For the *graft survival*, the events studied were graft failure and patient death, and censored observations were loss to follow-up and the end of the follow-up period.

Primary renal diseases were defined according to the ERA–EDTA coding system [20] and classified into four groups. SAS 9.1 software was used for all statistical analyses.

**Standard analyses.** Although in this paper we considered the instrumental variable method as our primary analysis strategy, we first analysed the data using ‘standard’ multivariable regression analysis to facilitate comparison with results from previous studies. All patients were stratified into ‘HD patients’ and ‘PD patients’ according to their dialysis modality at 90 days after dialysis initiation. This first dialysis modality was the primary predictor variable for survival after transplantation. We used the predominant dialysis modality (defined as modality used for >50% of the time on dialysis before transplantation) and the last dialysis modality before transplantation (defined as modality before transplantation that continued for at least 60 days) as additional predictor variables. Using Cox regression, the survival analyses were adjusted for age at transplantation, sex, primary renal disease, duration of

dialysis before transplantation, year of transplantation, donor type and country.

**Instrumental variable analyses.** The differences in patient survival between PD and HD patients may arise from unmeasured factors. To address the confounding-by-indication thereby introduced in the association between the pre-transplant dialysis modality and post-transplant patient and graft survival, we used an instrumental variable approach [13, 18, 21, 22]. Using this method one chooses a variable—the instrumental variable—that can be considered to be allocated to a patient at random, thus independent of individual patient characteristics. The random allocation of this variable can be considered as a ‘natural experiment’. In this study, we chose the percentage of PD patients in the patient’s treatment centre as the instrumental variable. In patients without specific preferences or contraindications for one of the dialysis modalities, the preference of the nephrologist/centre may influence the final choice for PD or HD [23]. As patients tend to visit a treatment centre in the direct neighbourhood of their homes, in principle, the treatment centre can be considered to be allocated at random and serve as an instrumental variable. However, as being treated by a particular centre may still not be fully at random, it is customary to nonetheless account for differences in case-mix between centres. Therefore, we adjusted the centre percentage of PD patients for centre case-mix. This required the following steps [13, 14]. First, a logistic regression model was developed to predict the chance of PD for each patient based on their age at the start of renal replacement therapy (RRT) sex, primary renal disease and country. Then for each centre, the expected percentage of patients on PD was calculated as the average of all individual predicted chances for PD. Thereafter, we calculated the ratio between the observed percentage of patients on PD and the expected percentage of PD for each centre. This ratio can be considered as a measure for how often PD is provided relative to what would be expected based on the characteristics of the patient population in that centre. Thus, in centres with more PD than expected based on the patient population, this ratio was >1, and vice versa. This ratio was then multiplied by the overall percentage of patients on PD (34.8%), generating a case-mix adjusted percentage of patients on PD on Day 90 after the start of dialysis for each centre. We tested the assumptions [21] related to the use of the instrumental variable method: (i) the instrumental variable must be related to the treatment individually assigned; (ii) the instrumental variable must be unrelated to observed and unobserved prognostic factors and (iii) the instrumental variable must be unrelated to outcome, except through pathways that operate via the treatment individually assigned.

Cox regression analyses were performed as described in the paragraph on standard analyses, except that the pre-transplant dialysis modality of each individual patient was substituted by the instrumental variable, i.e. the case-mix adjusted percentage of patients treated with PD on Day 90 at the centre in which the patient was treated on Day 90. Thus, these analyses did not examine the dialysis modality at Day 90 for that individual patient per se, but instead they used the case-mix adjusted centre percentage of PD at Day 90 as a patient characteristic for all dialysis patients in that centre. Only patients on dialysis in countries from which we received centre identification and patients from centres that had at least 30 patients on dialysis and that had patients on both PD and HD were included in the instrumental variable analyses. Analyses were adjusted for patient’s individual age at transplantation, sex, primary renal disease, duration of dialysis before transplantation, year of transplantation and donor type, and accounted for effects of facility clustering using robust standard error estimation techniques based on the sandwich estimator [24].

Additional analyses were performed stratified by year after transplantation to check whether the proportional hazards assumption was fulfilled. We also examined the presence of interaction between the kidney donor source (deceased/living), year of transplantation and dialysis modality in the association with patient and graft survival after transplantation.

## Results

### Standard analysis

In total, 29 088 adults who received a first kidney transplant from a living ( $N=4947$ ) or deceased kidney donor ( $N=24\,141$ ) between 1999 and 2008 were included in the

standard analyses. An overview of the baseline characteristics of these patients is shown in Table 1. Overall, 34.8% of the patients were on PD on Day 90 after dialysis initiation. When compared with HD patients, patients on PD were younger at the start of dialysis and at the time of transplantation, they were more often female, had a slightly different primary renal disease distribution and their time spent on dialysis before transplantation was ~1 month shorter.

Table 2 shows the unadjusted and adjusted hazard ratios (HR) for patient and graft survival resulting from the standard Cox regression analyses with PD as pre-transplant dialysis modality. After adjustment for relevant confounders, the risk of post-transplant death on PD was 17% lower than that for being on HD [HR (95% CI) = 0.83 (0.76–0.91)] and the risk of graft failure was 10% lower for PD patients [adjusted HR 0.90 (95% CI 0.84–0.96)]. Similar results were obtained with PD as either the predominant dialysis modality before transplantation or as the last dialysis modality before transplantation.

### Instrumental variable analyses

To address confounding-by-indication, in Cox regression analyses, we used the instrumental variable for patient characteristic, i.e. the case-mix adjusted percentage of PD patients at the centre in which the patient was treated on Day 90, instead of the individual patient's dialysis modality on Day 90. Analyses were restricted to patients from national and regional renal registries with centre data available and who were treated in centres with >30 patients ( $N=19\,755$ ). The patients who were excluded in this way ( $N=9333$ ) had similar patient characteristics when compared with those remaining in the analyses. In total, there were 228 centres with >30 dialysis patients which had patients both on HD and PD. The median (interquartile range) of the case-mix adjusted centre percentage of patients on PD at Day 90 was 43% [32–53%]. Table 3 provides an overview of the baseline characteristics of patients treated in centres with a case-mix adjusted percentage of patients on PD above and below the median (43%). It shows that when compared according to

**Table 1.** Descriptive characteristics of all patients, and of patients on PD or HD on Day 90 after dialysis initiation

Characteristics	All patients $N=29\,088$	Dialysis modality at Day 90		P value
		PD $N=10\,135$	HD $N=18\,953$	
Age, in years				
At start of dialysis, median (Q1–Q3)	48.5 (37.8–57.7)	46.7 (36.4–56.2)	49.5 (38.7–58.5)	<0.001
At first transplantation, median (Q1–Q3)	51.3 (41.2–61.3)	49.3 (38.9–59.0)	52.3 (41.2–61.3)	<0.001
Sex				
Males, %	63.3	60.6	64.8	<0.001
Females, %	36.7	39.4	35.2	
Primary renal disease				
Diabetes, %	13.7	15.6	12.7	<0.001
Hypertension/renal vascular disease, %	10.5	9.4	11.1	<0.001
Glomerulonephritis, %	24.7	26.1	23.9	<0.001
Other diseases, %	51.1	48.9	52.3	<0.001
Kidney donor source				
Living donor, %	17.0	18.9	16.0	<0.001
Deceased donor, %	83.0	81.1	84.0	
Time on dialysis before transplantation, in years				
In total, median (Q1–Q3)	2.2 (1.2–3.7)	2.1 (1.2–3.6)	2.2 (1.2–3.7)	0.003
On PD, median (Q1–Q3)	0.0 (0.0–1.1)	1.7 (0.9–2.8)	0.0 (0.0–0.0)	NA
On HD, median (Q1–Q3)	1.3 (0.1–2.9)	0.0 (0.0–0.2)	2.1 (1.1–3.6)	NA

Q1, 25th percentile; Q3, 75th percentile; PD, peritoneal dialysis; HD, haemodialysis; NA, not applicable.

**Table 2.** HR for patient and graft survival after transplantation in patients with PD as pre-transplant dialysis modality

Dialysis modality	Patient survival			Graft survival including death as event		
	$N_{\text{total}}$	$N_{\text{events}}$	HR (95% CI)	$N_{\text{total}}$	$N_{\text{events}}$	HR (95% CI)
PD at Day 90, unadjusted	29 088	2669	0.74 (0.68–0.80)	29 088	4947	0.88 (0.83–0.94)
PD at Day 90, adjusted <sup>a</sup>	29 088	2669	0.83 (0.76–0.91)	29 088	4947	0.90 (0.84–0.96)
PD predominant before Tx, adjusted <sup>a</sup>	29 088	2669	0.83 (0.76–0.91)	29 088	4947	0.88 (0.83–0.94)
PD prior to Tx, adjusted <sup>a</sup>	28 827	2661	0.85 (0.77–0.93)	28 827	4911	0.88 (0.82–0.94)

PD, peritoneal dialysis; Tx, transplantation; PRD, primary renal disease.

<sup>a</sup>Analysis adjusted for age at transplantation, sex, PRD distribution, donor type, duration of dialysis before transplantation, year of transplantation and country.

the case-mix adjusted centre percentage of PD, the patient groups were much more similar than when compared according to the individual patient's dialysis modality (as in Table 1): those treated in centres with a case-mix adjusted percentage of PD above the median were about 1 year younger at the start of dialysis and at the time of transplantation and only had a slightly higher percentage of glomerulonephritis as a cause of renal failure. This

suggests that our instrumental variable indeed functioned as a 'pseudo-randomizer' [25].

Table 4 shows the HR of patients on dialysis in centres with a 10% higher case-mix adjusted centre percentage of PD. There was no association between the case-mix adjusted centre percentage of PD and patient survival after transplantation [HR per 10% increase of PD: 1.00 (0.97–1.04)] and graft survival [HR per 10% increase of PD:

**Table 3.** Descriptive characteristics of all patients and of patients treated in centres with case-mix adjusted percentages of PD above or below the median

Characteristics	All patients <i>N</i> = 19 755	Patients on dialysis in centres with a case-mix adjusted percentage of PD		
		>Median (43%) <i>N</i> = 9791	<Median (43%) <i>N</i> = 9964	P value
Age, in years				
At start of dialysis, median (Q1–Q3)	48.2 (37.4–57.5)	47.7 (36.8–57.1)	48.6 (37.9–57.7)	0.001
At first transplantation, median (Q1–Q3)	50.9 (40.1–60.4)	50.4 (39.6–60.0)	51.4 (40.4–60.6)	0.003
Sex				
Males, %	62.6	62.8	62.3	0.461
Females, %	37.4	37.2	37.7	
Primary renal disease				
Diabetes, %	13.7	13.8	13.7	0.808
Hypertension/renal vascular disease, %	10.7	10.7	10.8	0.775
Glomerulonephritis, %	24.3	23.6	24.9	0.004
Other diseases, %	51.2	51.9	50.6	0.002
Kidney donor source				
Living donor, %	19.3	19.4	19.2	0.727
Deceased donor, %	80.7	80.6	80.8	
Time on dialysis before transplantation, in years				
In total, median (Q1–Q3)	2.2 (1.2–3.7)	2.3 (1.2–3.8)	2.2 (1.2–3.7)	0.006
On PD, median (Q1–Q3)	0.0 (0.0–1.5)	0.5 (0.0–1.9)	0.0 (0.0–1.0)	NA
On HD, median (Q1–Q3)	1.2 (0.0–2.7)	0.7 (0.0–2.4)	1.4 (0.3–2.9)	NA

Q1, 25th percentile; Q3, 75th percentile; PD, peritoneal dialysis; HD, haemodialysis; NA, not applicable.

**Table 4.** HR for patient and graft survival after transplantation with the case-mix adjusted percentage of patients treated with PD on Day 90 after the start of dialysis at a centre as instrumental variable

	Patient survival			Graft survival including death as event		
	<i>N</i> <sub>total</sub>	<i>N</i> <sub>events</sub>	HR (95% CI)	<i>N</i> <sub>total</sub>	<i>N</i> <sub>events</sub>	HR (95% CI)
Case-mix adjusted percentage of PD per centre, per 10% increase, adjusted <sup>a</sup>	19 755	1847	1.00 (0.97–1.04)	19 755	3391	1.01 (0.98–1.04)
Case-mix adjusted percentage of PD per centre, above versus below median (43%), adjusted <sup>a</sup>	19 755	1847	0.98 (0.88–1.10)	19 755	3391	0.99 (0.90–1.08)
Case-mix adjusted percentage of PD per centre, Q2 versus Q1, adjusted <sup>a</sup>	9964	934	1.04 (0.89–1.22)	9964	1701	1.06 (0.93–1.20)
Case-mix adjusted percentage of PD per centre, Q3 versus Q1, adjusted <sup>a</sup>	9848	887	1.02 (0.86–1.20)	9848	1632	1.05 (0.93–1.19)
Case-mix adjusted percentage of PD per centre, Q4 versus Q1, adjusted <sup>a</sup>	9933	942	1.05 (0.91–1.22)	9933	1680	1.07 (0.95–1.21)

Q1: patients on dialysis in centres with case-mix adjusted percentage of PD patients within the lowest quartile (reference).

Q2: patients on dialysis in centres with case-mix adjusted percentage of PD patients within the second quartile.

Q3: patients on dialysis in centres with case-mix adjusted percentage of PD patients within the third quartile.

Q4: patients on dialysis in centres with case-mix adjusted percentage of PD patients within the highest quartile.

PD, peritoneal dialysis; PRD, primary renal disease.

<sup>a</sup>Analyses were adjusted for individual patient characteristics (age at transplantation, sex, PRD distribution, donor type, duration of dialysis before transplantation and year of transplantation), and accounted for facility clustering.



1.01 (0.98–1.04)]. In addition, Table 4 shows the HR of patients treated in centres with a case-mix adjusted percentage of patients on PD above versus below the median and HR comparing patients on dialysis in centres with a case-mix adjusted percentage of patients on PD in the second, third and fourth quartile with those in the lowest first quartile. Again there was no statistically significant association with patient and graft survival after transplantation.

The first assumption regarding instrumental variable analysis—stating that the instrumental variable must be related to the treatment individually assigned—was fulfilled: the median of the case-mix adjusted centre percentage of PD was higher in patients who were on PD at Day 90 than in patients who were on HD at Day 90 (47% and 39%, respectively,  $P < 0.001$ ). The second assumption—stating that the instrumental variable must be unrelated to observed and unobserved prognostic factors—was at least partially fulfilled: the differences in observed prognostic factors were substantially reduced if patients were compared on the basis of case-mix adjusted centre percentage of PD instead of on the basis of individual pre-transplant dialysis modality (Table 3 versus Table 1). The third assumption requires the case-mix adjusted centre percentage of PD to be unrelated to survival after transplantation, except through the individually assigned treatment under study. We have only few data to show that this is probably the case. However, the kidney donor source (living versus deceased) could be considered as centre characteristic. As kidney donor source was equally distributed in patients treated in centres with case-mix adjusted centre percentages below and above the median, we also assumed that other centre practices, such as the provision of immunosuppressive regimens, followed a similar random distribution and are thus independent of the case-mix adjusted centre percentage of PD.

The assessment of interaction showed that any effect of dialysis modality before transplantation was not different in deceased or living donor kidney recipients, in different years of transplantation, or in different years of follow-up.

## Discussion

Previous reports suggested that dialysis modality before the first kidney transplantation might influence both patient and graft survival after transplantation [1, 2] with effects ranging from a 6% lower to a 15% higher risk of death for PD patients. In this study which included 29 088 patients from Europe, we examined the association of dialysis modality before the first kidney transplantation with patient and graft survival after transplantation. In standard analyses, with the individual pre-transplant dialysis modality as a patient characteristic, PD before transplantation was associated with better patient survival and graft survival. However, this is potentially confounded by indication and standard analysis may fail to sufficiently account for differences in health status. In contrast, the instrumental variable method using the case-mix adjusted centre percentage of PD failed to show a higher risk of death and graft failure for patients treated in centres with

higher case-mix adjusted centre percentages of PD. This suggests that the results from standard analyses were confounded by indication, and that there is likely no difference in mortality and graft failure.

Previous papers suggested reasons as to why dialysis modality before the first kidney transplantation might influence both patient and graft survival after transplantation [1, 2]. However, for each of these potential reasons, the data in the literature are inconsistent.

For example, it has been hypothesized that residual renal function may be better preserved in PD patients [26, 27], and consequently PD patients may have a higher glomerular filtration rate (GFR) at the point of kidney transplantation. Nevertheless, two studies examining the association of estimated GFR of the recipient's own kidney before transplantation with patient and graft survival after pre-emptive kidney transplantation did not find any relationship [28, 29].

Also, it has been suggested that the occurrence of infections after transplantation may differ between PD and HD patients. Studies, however, reported conflicting results. Passalacqua *et al.* [30] concluded that PD patients had a higher risk of intra-abdominal, bloodstream and wound site infections after transplantation. On the other hand, Miemois-Foley *et al.* [31] reported less bacterial infections in PD patients after transplantation and Yang *et al.* [8] reported less hepatitis infections in PD patients after transplantation, and a similar rate of other infections in HD and PD patients.

In addition, delayed graft function (DGF) after transplantation, which is a predictor of graft failure [32], was suggested to be higher for HD patients [33–35], possibly due to the worse hydration status of HD patients. However, other studies did not find a difference between HD and PD patients with regard to the risk of DGF after transplantation [8, 36].

Furthermore, the development of post-transplant diabetes mellitus (PTDM) may be associated with the pre-transplant treatment modality due to the glucose load resulting from PD. However, results were also conflicting in this respect. Whereas Madziarska *et al.* [37] and Seifi *et al.* [38] reported higher rates of PTDM in the former PD patients, Courivaud *et al.* [39] reported similar rates of PTDM between those who were on HD or PD before transplantation.

Graft thrombosis has also been put forward as a potential explanation. Both Ojo *et al.* [40] and Palomar *et al.* [41] reported a higher incidence of graft thrombosis after transplantation among PD patients. They proposed possible mechanisms including increased levels of various coagulation factors in PD patients, as well as a higher risk of haemoconcentration in PD patients as opposed to HD patients. On the other hand, Pérez Fontán *et al.* [42] reported that PD is not a risk factor for graft thrombosis after transplantation.

Finally, it has been speculated that immunologic differences between HD and PD patients may play a role in graft survival after transplantation. It has been shown that HD patients have elevated levels of natural killer cells and production of cytokines [43, 44] although the mechanisms through which this could influence survival after transplantation are unclear.

### Standard analysis

When considering the results of our standard analyses using individual pre-transplant dialysis modality as a patient characteristic, our results were in line with those from the largest US-based study ( $N=92\,844$ ) by Goldfarb-Rumyantsev *et al.* [1], who found a patient survival benefit (HR PD (95% CI) = 0.94 (0.91–0.97)) for transplant recipients who had PD as last dialysis modality before transplantation. On the other hand, another large US study ( $N=22\,776$ ) by Snyder *et al.* [2] reported that dialysis modality prior to transplantation was not associated with patient survival after transplantation [HR PD (95% CI) = 0.95 (0.85–1.06)]. Our patient-based analyses of graft survival using pre-transplant dialysis modality as a patient characteristic revealed a lower risk of graft failure for PD patients, which was in line with the results of Goldfarb-Rumyantsev *et al.* [1] [HR PD (95% CI) = 0.97 (0.94–1.00)], but not with the results of Snyder *et al.* [2] who reported a higher risk of graft failure for PD patients [HR (95% CI) = 1.15 (1.04–1.26)]. However, a difference in the post-transplant outcome or any other outcome between HD and PD patients may result from confounding-by-indication as patients on PD tend to be healthier than those on HD [10–12]. The conflicting results of our standard analyses and instrumental variable analyses regarding patient survival suggest that the adjustment in the standard multivariable analyses for age at transplantation, sex, primary renal disease, donor type, duration of dialysis before transplantation, year of transplantation and country may have been insufficient to largely eliminate differences in health status between patients on PD and HD. In comparison with our study, the studies of Goldfarb-Rumyantsev *et al.* [1] and Snyder *et al.* [2] were able to adjust their models for more variables, like co-morbidity. Nevertheless, adjustment for confounders in their standard analysis may not take away selection bias, because it is not possible to adjust for confounders that are not measured (or even unknown) and for confounders that have been measured insufficiently. Only randomization of dialysis modality may fully prevent this form of selection bias, but randomization for dialysis modality is extremely difficult [45], and information from randomized trials is currently not available.

### Instrumental variable analyses

One way to simulate random assignment in observational studies is the use of an instrumental variable. In this study, we used the case-mix adjusted centre percentage of PD patients as instrumental variable. The allocation of a centre to a patient may be considered as a natural experiment, as patients tend to visit a centre in their direct neighbourhood. The case-mix adjusted centre percentage of PD may be viewed as a measure for how often PD is provided relative to what would be expected based on the characteristics of the patient population in that centre. Thus, subsequently, the allocation of a centre to a patient where PD is provided relatively frequently, and where the patient has a higher probability of starting dialysis with PD independent of the patient's age, gender and primary renal disease, may be considered as random. In this way,

the effects of confounding-by-indication may have been substantially reduced.

### Limitations of the study

The case-mix adjustment of the centre percentage of PD was based on relatively few variables. Patient co-morbidity for example could not be taken into account. A previous study, however, has shown that once age, gender and primary renal disease are included in models for patient survival on RRT, co-morbidity may add relatively little to the variance in mortality [46]. As for other unobserved prognostic factors, the instrumental variable approach has increased the likelihood that they were more evenly distributed between the patient groups.

Nevertheless, the assumptions related to the instrumental variable analysis may not entirely hold. When using the instrumental variable method, the differences in measured baseline characteristics for patients treated in centres with case-mix adjusted percentages of PD above or below the median were strongly reduced, but did not disappear completely for some variables. Furthermore, although the kidney donor source was equally distributed in patients treated in centres with case-mix adjusted centre percentages of PD below and above the median, we could not test this for other centre characteristics. Therefore, the possibility remains that the case-mix adjusted centre percentage of PD may be associated with other patient characteristics (e.g. socioeconomic status) and other centre practice patterns that could contribute to the risk of death and graft failure. Thus, the instrumental variable method seems to have taken away substantial residual confounding compared with standard Cox regression, but some residual confounding may have remained.

### Conclusion

Using instrumental variable analysis, a method that in observational studies is used to approximate randomization of treatment, we found that patients on dialysis in centres where PD was provided more frequently had a similar patient and graft survival when compared with patients treated in centres in which PD was provided less frequently. This suggests that there is no association between the pre-transplant dialysis modality and patient and graft survival after transplantation. However, the instrumental variable method may still not fully correct for confounding-by-indication, and therefore, we cannot exclude the possibility that pre-transplant PD may affect survival after kidney transplantation. Nevertheless, we cannot think of any biological hypothesis as to why it would do so. We therefore conclude that previous studies as well as our own standard analyses using individual pre-transplant dialysis modality as a determinant for outcomes after transplantation may have suffered from confounding-by-indication, and that there is likely no association between the pre-transplant dialysis modality and patient and graft survival after transplantation.

**Acknowledgements.** We would like to thank the patients and staff of all the dialysis and transplant units who have contributed data via their national and regional renal registries. Furthermore, we gratefully acknowledge the following registries and persons for their participation in the data collection: R. Alonso de la Torre, Á. Roces and E. Sánchez (Asturias Renal Registry); R. Kramar [Austrian Dialysis and Transplant Registry (OEDTR)]; Á. Magaz, J. Aranzabal, I. Lampreabe and J. Arrieta (Basque Country Renal Registry); J. González Cotorruelo and O. García Ruiz (Cantabrian Renal registry); E. Arcos, J. Comas, R. Deulofeu and J. Twose [Catalan Renal Registry (RMRC) and Catalan Transplant Organisation (OCATT)]; H. Augustijn, B. de Moor and J. de Meester [Dutch-Belgian Nephrology Registry (NBVN)]; D. Ansell, C. Tomson, J. Gilg and R. Steenkamp (UK Renal Registry); C. Grönghagen-Riska (Finnish Registry for Kidney Diseases); J-M. des Grottes and F. Collart (French-speaking Belgium Registry); G.A. Ioannidis (Greek national Renal Registry); T. Leivestad (Norwegian Renal Registry); W. Metcalfe and K. Simpson (Scottish Renal Registry); L. Bäckman, S. Schön, A. Seeberger and B. Rippe [Swedish Renal Registry (SNR)]; A. Hemke [Dutch End-Stage Renal Disease Registry (RENINE)]; and O. Zurriaga Llorens and M. Ferrer [Registro de Enfermos Renales de la Comunidad Valenciana (REMRENAL)] for providing data. In addition, we would like to thank A. Hoitsma (The Netherlands); P. Finne (Finland); Frederic Collart (Belgium) and E. Verrina (Italy) for providing critical revision for important intellectual content of the article. The ERA-EDTA Registry is funded by the ERA-EDTA.

**Conflict of interest statement.** None declared. The results presented in this paper have not been published previously in whole or part, except in abstract format.

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*Received for publication: 5.8.2012; Accepted in revised form: 8.8.2012*