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Improved survival associated with acetate-free haemodialysis in elderly: a registry-based study

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ORIGINAL ARTICLE

ABSTRACT

Background. Acetate-free dialysis (AFD) improves haemodynamic stability during dialysis, compared with standard haemodialysis (HD) with a small amount of acetic acid. Using the national REIN registry, we classified 15 160 incident patients who started HD from 2008 to 2010 into three exposure categories according to the type of dialysate used in their dialysis unit: standard dialysate only (reference), both standard and AFD (mixed unit) or HCl dialysate only (100% HCl unit).

Methods. Cox survival analysis was adjusted for 15 baseline comorbidities, laboratory data and haemodiafiltration (HDF). We took patient clustering within units into account, used age as the time scale and treated patient exposure to AFD and to HDF as time-dependent variables.

Results. Median age (interquartile range) was 70.5 years (58.1–78.8). Over a median follow-up of 1.8 years (1.2–2.6), 658 patients were dialysed in a 100% HCl unit, 3021 in a mixed unit and 11 481 were never exposed to AFD. The relation between AFD and mortality was not constant with age (Schoenfeld residuals test P = 0.01 for mixed group and P = 0.03 for 100%HCl group). Patients older than 70 years had a significantly lower mortality risk associated with AFD [hazard ratio (HR) = 0.79, 95% confidence interval (CI) = 0.67 to 0.94 for patients exposed in a 100% HCl unit; HR = 0.83, 95% CI = 0.74 to 0.94 for patients exposed in a mixed unit], but no association was found in younger patients.

Conclusions. AFD was associated with improved survival independent of comorbidities and HDF in patients aged 70 years and older but not in patient younger than 70 years.

Keywords: acetate-free haemodialysis, haemodialysis, intradialytic haemodynamic, registry

INTRODUCTION

Haemodialysis has historically used acetate buffer in dialysate. High concentrations, up to 40 mmol/L, result in bicarbonate generation after liver metabolization. Nonetheless, at such concentrations, acetate is a potent vasodilator and myocardial depressor and can cause intradialytic hypotension. Acetate has therefore been replaced over time by bicarbonate. However, the mix of bicarbonate and calcium requires a small amount of acid to avoid insoluble precipitation of calcium carbonate. Adding 3–8 mmol/L of acetic acid to the mixture enables the generation of substantially more calcium bicarbonate than calcium carbonate.

This small amount of acetic acid is metabolized into acetate when mixed with bicarbonate and, despite its small quantity, significantly increases the physiologic blood acetate concentration during dialysis sessions [1–4]. The acetate concentration increases rapidly during the first hour of dialysis to reach a plateau [2, 3], the level of which depends on liver acetate metabolization. Patients with slow liver metabolism, including women and those with diabetes or liver disease, are exposed to higher intradialytic acetate concentrations; haemodiafiltration (HDF) raises this acetate level still higher, due to the substitution fluid volume.

Several acetate-free dialysis (AFD) techniques are now available. Acetate-free biofiltration (AFB) uses a buffer-free dialysate and a postdilution bicarbonate infusion. Acetic acid may be replaced in the dialysate by either hydrochloric acid (HCl) or citric acid. Studies comparing AFB and standard dialysis suggest that the use of AFD has clinical benefits, particularly for

patients with diabetes [5–9]. Haemodynamic studies show that cardiac output decreases more markedly during a session with standard dialysis than with AFD [3, 10, 11]. The difference in the impact on cardiac output is detected early during the dialysis session and lasts from the first hour to the end [3–5]. In addition, troponin T peaks at higher levels in standard dialysis than in AFD [4, 12]. Peripheral resistance increases sufficiently in most patients, thus limiting the risk of intradialytic hypotension, but the stimulating effect of acetate on nitric oxide synthetase can cause vasodilation in some patients [13–15]. Acetate's cumulative effect on cardiac output and peripheral resistance is thought to cause intradialytic hypotension. One randomized multicenter trial of 400 patients, which compared AFB with standard dialysis, confirmed the improvement in intradialytic haemodynamic stability but found no survival benefit for either cardiovascular or all causes of death [16]. That trial, however, considered only AFB for selected patients, and its statistical power appears to have been low (n = 84 deaths from cardiovascular causes).

We therefore used the nationwide Renal Epidemiology and Information Network (REIN) end-stage renal disease registry to test the hypothesis that AFD, specifically HCl dialysate use and AFB, the two techniques available in France at the time of the study, is associated with a lower mortality rate than standard HD in real-life conditions.

MATERIALS AND METHODS

Population

The REIN registry includes all ESRD patients in France on chronic renal replacement therapy—either on dialysis or transplanted. The details of methods and quality control of the REIN Registry have been described elsewhere [17]. This study included all adult incident haemodialysis patients who started hemodialysis in 2008, 2009 or 2010 and continued >3 months. Because of the higher mortality rate during the first 90 days of dialysis treatment [18], patients with chronic kidney disease who died before a period of dialysis <3 months have been analysed separately. Of a total of 23 671 incident patients, we analysed 15 160 incident patients dialysed in the 13 French regions where at least one unit used AFD for at least 1 year in 2008–11, when follow-up ended (Figure 1).

Data

Baseline data at dialysis initiation included age, gender, primary renal disease, comorbidities, disability status, body mass index (BMI), initial dialysis conditions (including emergency status and catheter use) and laboratory results (serum albumin, haemoglobin level and estimated glomerular filtration rate). Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) equation. Comorbidities included diabetes, heart failure, coronary heart disease, stroke, peripheral vascular disease, chronic respiratory disease, obesity (BMI $\geq$ 30 kg/m^2), active malignancy, cirrhosis, smoking and mobility status.

Technical data included the frequency and duration of dialysis, HDF use, facility type (in-centre dialysis unit, satellite unit or self-dialysis) and dialysis unit legal status (for-profit versus not-for-profit).

Events including renal transplantation, changes in dialysis unit, changes in modality of dialysis, recovery of renal function and death are collected prospectively and reported from the first day of treatment.

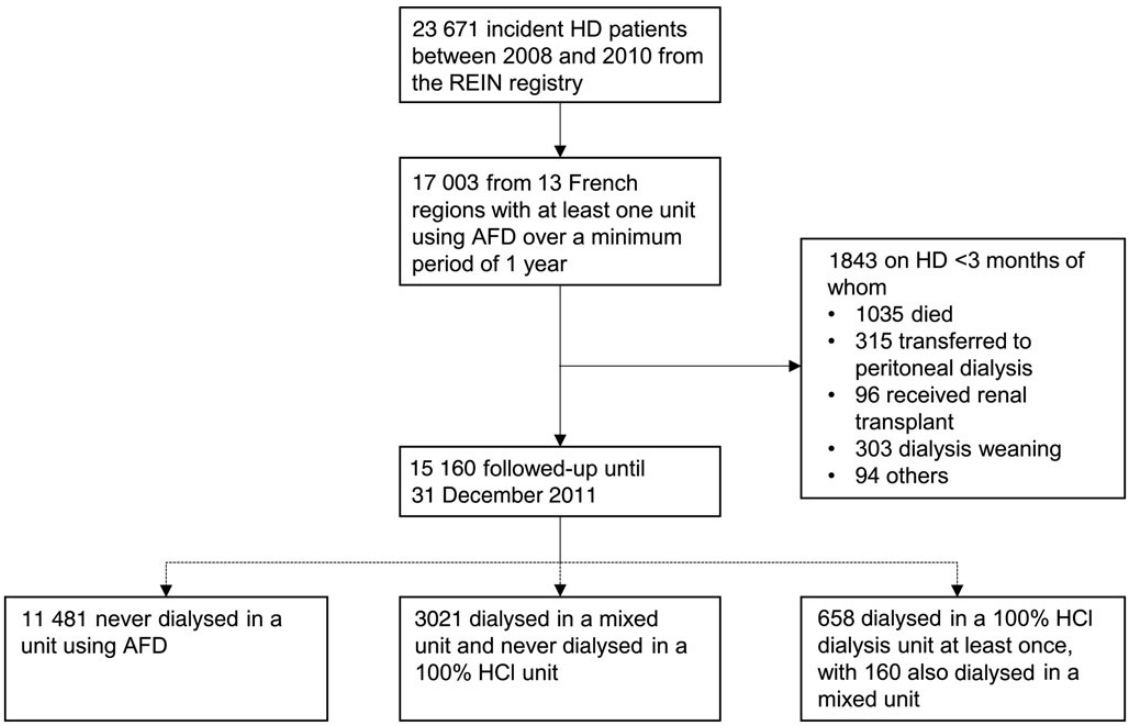

FIGURE 1: Flow chart of the study. AFD, acetate-free dialysis; HD, haemodialysis.

Assessment of patient exposure to AFD

AFD can be either performed with AFB or hydrochloric acid dialysate (HCl). During the study period, citric acid dialysate was used in only a few patients in France and was therefore not included in the analysis. Industrial manufacturers (Bellco, Hospal, Hemotech, Baxter and Fresenius) provided yearly AFD volume sold to each dialysis unit during the study period. The date of first use was calculated from the sales and the number of dialysed patients by unit. Using these sales, each unit was classified by time periods over 2008–11 into three groups: units using standard dialysis, units using both standard dialysis and AFD (HCl or AFB, referred to as mixed units), and units using AFD exclusively (100% HCl unit). The information on AFD use at the unit level was assigned at the patient level by time periods.

Statistical analysis

Patients' baseline characteristics were compared for three AFD exposure groups: never dialysed in a unit using AFD, dialyzed in a mixed unit but never dialysed in a 100% HCl unit and dialysed in a 100% HCl unit. These comparisons used χ^2 or Wilcoxon two-sample tests, as appropriate. Crude survival analysis with the Kaplan–Meier method compared the three AFD exposure groups by log-rank tests. Patients were censored for renal transplantation, dialysis weaning, loss to follow-up, transfer to peritoneal dialysis or moving out of France.

Adjusted overall mortality was analysed by time-dependent Cox proportional hazard models, with age as the time scale [19, 20] and stratified by facility type. AFD exposure was studied as a time-dependent covariate with multiple entries, taking into account changes in patients' dialysis units and AFD status changes within the units. Analysis was adjusted for HDF at a patient level as a time-dependent variable.

As some unknown patient characteristics and medical practice patterns may vary by unit, robust variance estimates (by a sandwich estimator) were used to account for unit clustering effects [21, 22]. The proportionality hazards assumption was tested by the Schoenfeld residual method. The results showed that the risk associated with AFD exposure was not constant with age. Considering that the age cutoff provided by the Schoenfeld method was close to the median age of the population, the data set was split at the median age permitting to have two groups of equal effective: younger than 70 years, or 70 years and older at study entry. Adjusted HRs of mortality according to AFD exposure were assessed using two separate Cox models.

Interactions were tested between AFD exposure and diabetes, cardiovascular comorbidities, and HDF. In the final models, multiple imputations using a Markov chain Monte Carlo approach was used [23]. A run length of 500 iterations was used and 20 imputed datasets were created to take into account uncertainty caused by missing data (PROC MI procedure of SAS) [24]. The variables included in the imputation procedure were diabetes, heart failure, peripheral vascular disease, stroke, myocardial infarction, chronic respiratory disease, active malignancy, cirrhosis, smoking status, mobility status, BMI, first dialysis with catheter, albuminemia and creatinine. There was no missing data for age, sex, dialysis modality and facility type. There were 4–8% missing data for diabetes, comorbidities and haemodialysis start conditions, 21% for eGFR, 25% for haemoglobin, 31% for BMI and 49% for albuminemia. The results of the analyses through the 20 complete imputated datasets were combined, and the final results were averaged across these sets (PROC MIANALYZE Procedure of SAS). This procedure is a generalization of the approach of Rubin and Schenker [25] and Schafer [26]. As sensitivity analyses, we studied the overall mortality of the early dialysis period (<3 months) and cardiovascular mortality. The analyses were repeated for patients dialysed only in in-centre dialysis units and for patients exposed to AFD for >1 month.

Two-sided significance tests were used and P-values <0.05 were considered significant. All statistical analyses were performed with the SAS 9.4 and R statistical packages.

RESULTS

Patient characteristics by dialysate exposure

AFD use expanded markedly during the study period (Supplementary data, Figure 1). Of a total of 15 160 patients, 11 481 were never exposed to AFD, 3021 were treated in mixed dialysis units and never in a 100% HCl unit, while 658 were treated in 100% HCl dialysis units (Figure 1). At dialysis start, the latter group was distributed throughout eight regions, with more than one-third in Basse-Normandie (Figure 2). The median (interquartile range) follow-up was 1.75 years (1.12–2.59) for the never exposed group, 1.95 years (1.28–2.82) for the mixed-unit group and 1.96 years (1.30–2.73) for those exposed in 100% HCl units. The patients exposed only in mixed dialysis units were exposed to AFD for a median of 0.97 (0.39–1.59) year and spent 61% of their dialysis vintage in mixed dialysis units (Table 1). The patients exposed in the 100% HCl unit were exposed to AFD for a median of 1.00 (0.46–1.65) year and spent 66% of their dialysis vintage in a 100% HCl dialysis unit (Table 1). These patients were also exposed in a mixed unit for 17% of their dialysis vintage (Table 1). Ten patients in 100% HCl units (1.5%) and 104 in mixed units (3.4%) were exposed <1 month.

Patients exposed to AFD were older, had more cardiac and vascular comorbidities, had cirrhosis and mobility problems more often, were less likely to have polycystic kidney disease and more likely to have a vascular kidney disease, and had started dialysis more frequently in an emergency situation, with a catheter and in a hospital-based unit (Table 2). The patients in the 100% HCl exposure group had their first dialysis session on HDF more often than the patients in other exposure groups. Laboratory data at dialysis start were similar except for a slightly higher eGFR in the mixed exposure group and conversely a lower eGFR in the 100% HCl exposure group. Patients never exposed to AFD had a significantly higher kidney transplantation rate (Table 1).

Mortality according to AFD exposure

In the crude analysis, Kaplan–Meier survival curves comparing the three dialysis exposure groups showed a significant survival benefit associated with exposure to AFD (log-rank

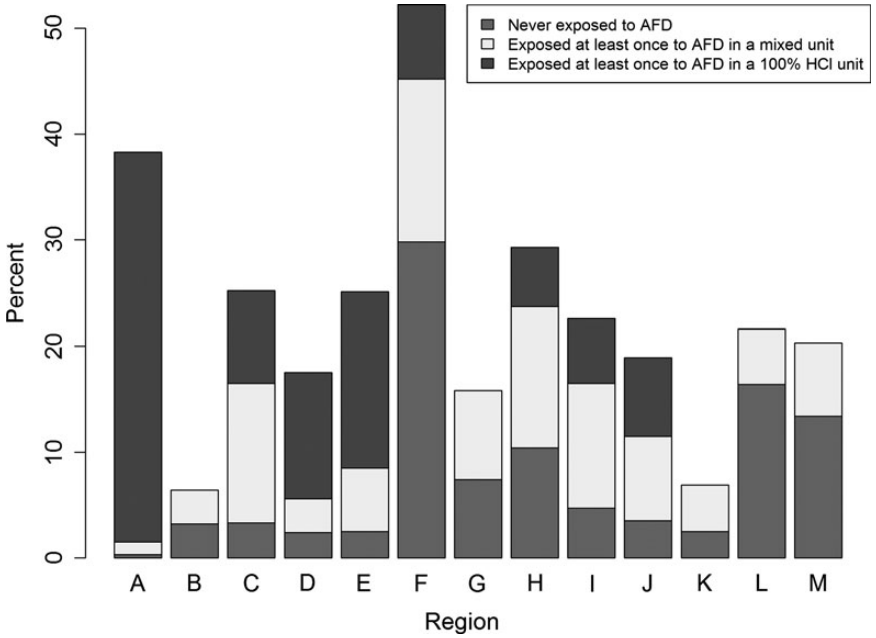

FIGURE 2: Distribution of patient AFD exposure group according to their region at dialysis start. For each exposure category, the sum of all the regions is equal to 100%. (**A**) Basse-Normandie; (**B**) Bourgogne; (**C**) Bretagne; (**D**) Champagne-Ardenne; (**E**) Haute-Normandie; (**F**) Ile de France; (**G**) Languedoc-Roussillon; (**H**) Nord-Pas-de-Calais; (**I**) Pays de Loire; (**J**) Picardie; (**K**) Poitou-Charentes; (**L**) Provence-Alpes-Côte d'Azur; (**M**) Rhône-Alpes.

Table 1. Number of person-years and events by AFD exposure group

	Never exposed to AFD (n = 11 481)	Exposed to AFD in a mixed unit (n = 3021)	Exposed to AFD in a 100% HCl unit (n = 658)
Person-years			
Person-years unexposed to AFD	18 553.0	2136.0	196.9
Person-years exposed in a mixed unit	0	3287.2	201.3
Person-years exposed in a 100% HCl unit	0	0	774.7
Events % (n)			
Deaths	25.3 (2909)	24.5 (739)	21.7 (143)
Cardiovascular deaths	5.5 (636)	5.5 (176)	5.6 (37)
Loss to follow-up	1.3 (145)	0.6 (17)	0.3 (2)
Kidney transplantation	12.2 (1404)	9.6 (289)	8.7 (57)
Dialysis weaning	2.4 (275)	2.8 (84)	2.0 (13)
Transfer to peritoneal dialysis	0.7 (82)	0.7 (22)	0.9 (6)
Rates (per 100 person-years)			
Mortality rate	15.7	13.6	12.2[a]
Kidney transplantation rate	7.6	5.3	4.9[a]

[a]Log-rank test P-value <0.001.

P-value <0.0001; Figure 3). At 1 year, the crude probability of survival was 0.88 (95% CI = 0.89 to 0.92) for patients never exposed to AFD, 0.91 (95% CI = 0.90 to 0.92) for patients exposed in a mixed unit and 0.91 (95% CI = 0.88 to 0.93) for patients exposed in a 100% HCl unit, and at 2 years, respectively, 0.76 (95% CI = 0.75 to 0.77), 0.79 (95% CI = 0.78 to 0.81) and 0.82 (95% CI = 0.79 to 0.85).

In the multivariate Cox model, the mortality risk associated with AFD exposure was not constant with age (Figure 4) (Schoenfeld residuals test, P-value = 0.01 for mixed group and P-value = 0.03 for 100% HCl group). Dialysis in a mixed or a 100% HCl unit was not associated with better survival for patients younger than 70 years (Table 3). In contrast, for patients aged 70 and older, AFD exposure was associated with a significant reduction of the mortality risk: 0.81 (95% CI = 0.68 to 0.96) in a 100% HCl unit and 0.82 (95% CI = 0.73 to 0.92, Table 3) in a mixed unit. The mortality HRs without adjustment for HDF were very similar, equal to 0.77 (95% CI = 0.65–0.90) for being exposed in a 100% HCl unit and 0.83 (95% CI = 0.74–0.94) in a mixed unit. Interactions between AFD and HDF, cardiovascular comorbidities, diabetes and facility types were not significant.

HDF was also associated with a significant mortality risk reduction: 0.73 (95% CI = 0.59 to 0.90) for patients younger than

Table 2. Baseline characteristics of 15 160 incident patients from the REIN registry, according to acetate-free dialysis (AFD) exposure status

Items	Never exposed to AFD (n = 11 481)	Exposed to AFD in a mixed unit (n = 3021)	Exposed to AFD in a 100% HCl unit (n = 658)	P-value[a]
Age (years)	70.0 (57.5–78.6)	72.4 (59.9–79.6)	70.9 (59.8–78.6)	<0.001
Male sex	63.7 (7311)	60.4 (1825)	58.8 (387)	<0.001
Comorbidities				
Diabetes	39.3 (4513)	40.0 (1209)	39.5 (260)	0.78
Heart failure	25.4 (2744)	27.2 (792)	30.8 (187)	0.002
Coronary heart disease	24.9 (2674)	26.6 (771)	29.3 (175)	0.013
Active malignancy	11.3 (1221)	10.4 (302)	10.9 (66)	0.36
Peripheral vascular disease	21.2 (2274)	23.7 (675)	24.1 (137)	0.007
Stroke	9.7 (1050)	12.2 (356)	13.4 (80)	<0.001
Chronic respiratory disease	11.1 (1278)	14.9 (450)	12.27 (73)	<0.001
Myocardial infarction	10.6 (1140)	12.1 (354)	12.9 (77)	0.017
Obesity (BMI ≥ 30 kg/m^2)	20.2 (1548)	22.2 (521)	24.9 (129)	0.006
Smoking				0.092
Never smoker	60.8 (5790)	58.9 (1528)	60.4 (356)	
Former smoker	28.1 (2679)	30.9 (801)	29.4 (173)	
Current smoker	11.1 (1053)	10.3 (267)	10.2 (60)	
Cirrhosis	2.1 (232)	3.1 (89)	3.3 (20)	0.005
Mobility				0.016
Need assistance with mobility	13.7 (1323)	14.0 (385)	8.8 (50)	
Totally dependent for transfers	4.0 (382)	4.1 (112)	3.9 (22)	
Primary renal disease				<0.001
Polycystic kidneys	6.6 (762)	5.6 (168)	3.8 (25)	
Hypertension	26.0 (2989)	25.6 (772)	24.0 (158)	
Diabetic nephropathy	23.2 (2662)	23.0 (694)	25.1 (165)	
Glomerulonephritis	11.1 (1275)	11.5 (347)	9.9 (65)	
Pyelonephritis	4.0 (462)	3.9 (117)	4.7 (31)	
Vascular nephropathy	1.1 (132)	2.4 (74)	3.8 (25)	
Other and unknown	27.9 (3199)	28.1 (849)	28.7 (189)	
Haemodialysis start				
Unplanned	28.7 (3006)	32.7 (937)	35.6 (218)	<0.001
With catheter	45.8 (5254)	51.0 (1541)	53.2 (350)	<0.001
Facility type				<0.001
In-centre dialysis unit	88.8 (10 200)	91 (2750)	95.7 (630)	
Satellite unit	3.1 (354)	2.9 (89)	1.1 (7)	
Self-dialysis	8.1 (927)	5.6 (169)	3.2 (34)	
Haemodiafiltration	9.3 (1062)	9.0 (273)	21.4 (141)	<0.001
Laboratory variables				
Albuminaemia (g/L)	33.1 (28.8–37.4)	33.3 (29.2–37.2)	32.8 (29.0–37.5)	0.38
Hemoglobin (g/dL)	10.2 (9.0–11.3)	10.3 (9.1–11.3)	10.2 (9.1–11.4)	0.52
eGFR (mL/min/1.73 m^2)	8.4 (6.2–11.2)	8.6 (6.4–11.4)	8.1 (6.0–10.8)	<0.001

Data are presented as median (IQR) or % (n).
BMI, body mass index; eGFR, estimated glomerular filtration rate (by the modification of diet in renal disease equation); IQR, interquartile range.
[a]Calculated with χ^2 or Wilcoxon two-sample test.

70 years and 0.85 (95% CI = 0.76 to 0.96) for older patients (Supplementary data, S1).

Factors associated with mortality were sex, heart failure, peripheral vascular and chronic respiratory diseases, stroke, cirrhosis, active malignancy, smoking, disability, serum albumin under 35 g/L, eGFR greater than 15 mL/min/1.73 m^2 and HDF (Supplementary data, S1).

Sensitivity analyses

The mortality during the early dialysis period (<3 months) was not influenced by AFD exposure (data not shown). The risk of cardiovascular death did not differ significantly between the three dialysate exposures. At 1 year, AFD-associated mortality risks in mixed and 100% HCl units were similar to those at 4 years, significant for the mixed units and borderline significant for 100% HCl units (Table 3). The results were unchanged if considering only patients dialysed in in-centre dialysis units who accounted for around 90% of the dataset and had the most important burden of comorbidities. Considering patients exposed to AFD for >1 month, the mortality HRs were equal to 0.76 (95% CI = 0.64–0.89) for being exposed in a 100% HCl unit and 0.81 (95% CI = 0.71–0.92) in a mixed unit.

DISCUSSION

This study showed that AFD use is spreading fast and may improve survival compared with standard haemodialysis, at least in ESRD patients aged 70 years or older. The benefit was borderline significant at 1 year and persisted at 4 years with the same

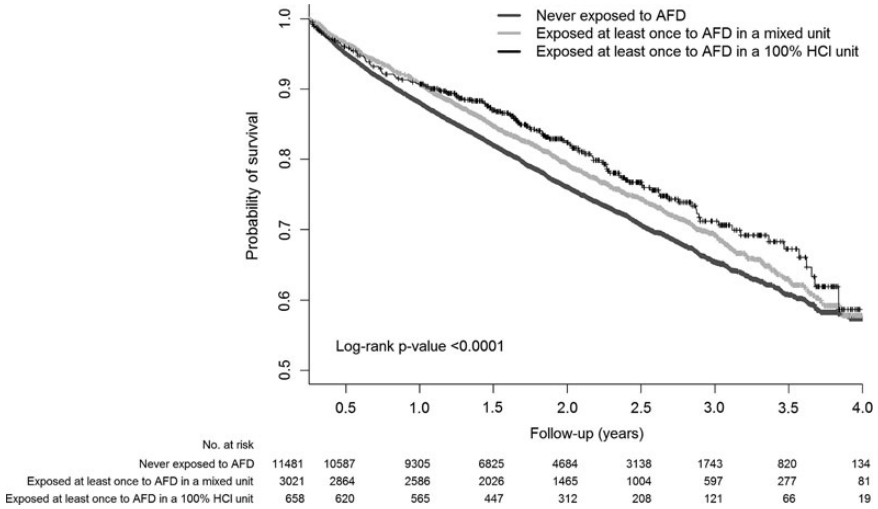

FIGURE 3: Kaplan–Meier curves for 4-year survival by AFD exposure group defined over all monitoring (P-value <0.0001 by the log-rank test).

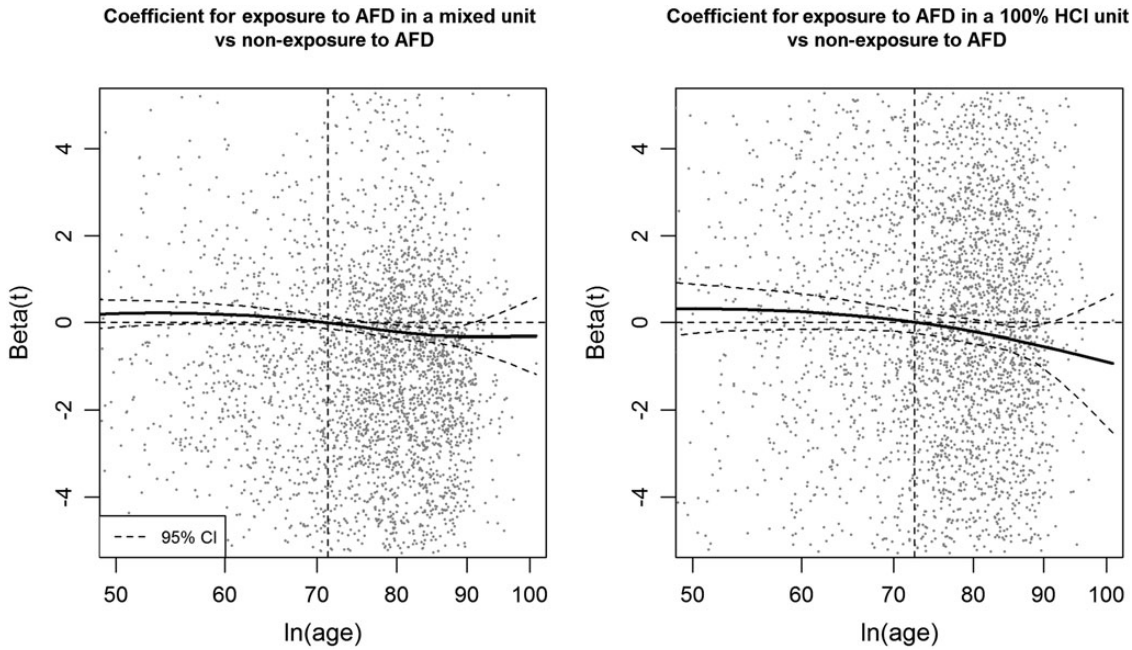

FIGURE 4: Time-dependent coefficient of mortality associated with AFD categories by log-transformed age. Schoenfeld residuals test, P-value = 0.01 for mixed group and P-value = 0.03 for 100% HCl group.

amplitude. Although observational in nature, these findings are important because they are independent of patient case-mix and based on a large unselected ESRD registry population, quasi-random exposure to AFD. Quasi-randomization results here from the patient's assignment to the AFD exposure group at the provider rather than the individual level, which limits indication bias. These results are also consistent with the current body of evidence that the haemodynamic tolerance in ESRD patients is better in AFD than in standard dialysis and should thus encourage changes in dialysis options for the oldest patients.

AFD was proposed 30 years ago with AFB [27]. Two randomized studies clearly showed the haemodynamic improvement associated with this technique [6, 16]. The development of dialysate without acetate, first with hydrochloric and later with citric acid, provides additional evidence that the small amount of acetate nonetheless present in standard dialysate still influences cardiac output, peripheral resistance and therefore intradialytic haemodynamic [10, 11]. Acetate is also implicated in bioincompatibility at high—and to a lesser extent at lower—concentrations, by its stimulation of interleukin-1 secretion and monocyte activation [13, 14, 28], which may have some long-term deleterious nutritional consequences [29].

In our study, survival improved only among patients aged 70 years and older. The haemodynamic improvement might be the main reason that this population, which has more cardiovascular comorbidities, benefits more from AFD. Among the older patient group, 59% had at least one cardiac comorbidity, compared with 36% of the younger patients. In the largest randomized trial of AFB (194 patients on standard dialysis

Table 3. Multivariate adjusted hazard ratio (HR) for all-cause mortality according to AFD exposure status, by age group

	Model fully adjusted	
	HR (95% CI) < 70 years	HR (95% CI) ≥ 70 years
Mortality at 1 year		
Exposure to AFD (ref. unexposed to AFD)		
Exposed in a mixed unit	1.25 (0.96–1.64)	0.78 (0.66–0.91)
Exposed in a 100% HCl unit	1.46 (0.88–2.42)	0.76 (0.54–1.08)
Mortality at 4 years		
Exposure to AFD (ref. unexposed to AFD)		
Exposed in a mixed unit	1.02 (0.85–1.23)	0.82 (0.73–0.92)
Exposed in a 100% HCl unit	1.17 (0.80–1.70)	0.81 (0.69–0.96)

Adjustments for region of first dialysis, sex, diabetes, heart failure, coronary heart disease, peripheral vascular disease, stroke, myocardial infarction, chronic respiratory disease, obesity, cirrhosis, active malignancy, smoking, mobility, albuminaemia (<25, [25,30], [30,35] and ≥35 g/L), eGFR (<15 and ≥15 mL/min/1.73 m^2), HDF, public or private status, stratification by facility type. Use of robust variance estimates to account for unit-clustering effects.
AFD, acetate-free dialysis; HDF, haemodiafiltration.

compared with 177 on AFB), no survival benefit was observed in the overall cohort, but the long-term case fatality rate after major cardiovascular events was halved [16]. This benefit could not have been linked to the convection volume of AFB being around 10 L and considered as low in the light of the HDF randomized studies. We looked in particular at the mortality associated with AFD in patients with diabetes, but we could not find any interaction between AFD and diabetes or other cardiovascular comorbidities. Previous publications have suggested a potential additional benefit of HDF with an acetate-free dialysate [3]. We found that survival improved with both HDF and AFD. The absence of interaction between these techniques indicates that the benefit of AFD is similar in patients dialysed with AFD-HDF and those dialysed with AFD-HD. Moreover, adjusting for HDF did not change the relation between AFD and mortality.

All the various AFD techniques present the advantage of the lack of acetate loading, but each may also have individual advantages and disadvantages. AFB, for example, is the sole technique without carbon dioxide in the dialysate, which could be advantageous in patients with respiratory insufficiency and hypercapnic acidosis. Moreover, AFB is the sole dialysis technique allowing unlimited bicarbonate delivery, for this depends only on the bicarbonate infusion rate and the patient's tolerance for alkalization. Finally, the absence of calcium carbonate in the dialysate circuit may minimize its bacterial contamination [30] and reduce the need to use acid for its maintenance. The major drawback limiting routine AFB prescription is the cost and burden on nurses, for as many as 9–10 L of bagged bicarbonate must be hung at the dialysis monitor. AFB with more highly concentrated bicarbonate (84‰) has been proposed to make it possible to decrease the infusion volume, but strong security would then be needed to maintain the bicarbonate infusion rate [31]. Accordingly, hypochloric and citric acid dialysate have unsurprisingly replaced AFB and become the main techniques for AFD. The survival advantage of AFD that we showed in this study was related principally to HCl dialysate, which became fairly widespread in France during this period.

The main disadvantage of HCl dialysate is its low pH, which may expose staff to accidents while handling it. It also requires a greater amount of bicarbonate. Citric acid dialysate is the newest acetate-free dialysate on the European market and has a potential, but still controversial, effect on dialytic anticoagulation requirements [32]. Additionally, citrate dialysate needs adjustment for the calcium dialysate concentration. The anticoagulation effect and the haemodynamic effect both depend on this adjustment [11]. To obtain a calcium load similar to standard HD, a calcium concentration 0.1– 0.2 mmol/L higher with citrate dialysate is warranted. When the citrate dialysate is used in HDF, its calcium concentration could be similar to the one used in standard HD, the convection volume being responsible of an additional calcium load.

Major strengths of this study include its large sample size, the unselected nature and representativity of its registry-based population, as well as detailed patient comorbidities. This allowed us to study various potential interactions and to adjust for many confounders.

The study also has limitations. First, its observational design can result in indication bias or other confounding. However, although indication bias cannot be ruled out in hazard ratio (HR) estimates for those treated in mixed dialysis units, where some patients may be assigned to AFD due to their condition, this is not the case for both those on dialysis in 100% HCl dialysis units and those never exposed. In the latter situations, patients may be considered as quasi-randomly assigned to either type of dialysis because only residence, and not condition, determines whether a patient starts dialysis in a 100% HCl unit or a standard unit. Multiple adjustments for a number of relevant comorbidities as well as for HDF are also likely to have reduced confounding bias.

Second, the growth of AFD use during the study period may have indirectly induced survival bias. In the earliest cohorts, patients of an older dialysis vintage were more likely to be assigned to AFD than their counterparts with shorter durations of treatment. To reduce this bias, both AFD exposure categories and HDF modality were treated as time-dependent covariates in the Cox model so that estimated mortality HRs took changes in dialysis modalities over time into account. Finally, although exposure misclassification is unlikely in the two categories where patients were either 100% exposed or 100% unexposed, given the reliability of yearly AFD sales volumes, misclassification is present in the mixed-unit category, where only a percentage of patients are exposed. The lower HR observed in this category, compared with that of 100% HCl units, may have

resulted from a dilution effect. Although sales data were easy to obtain and reliable, collection of this information in facility questionnaires, as planned in the REIN registry, would facilitate and improve the monitoring and assessment of AFD use. The results also have to be confirmed with a longer follow-up.

In summary, substantial progress has been made toward more biocompatible dialysate and more physiological haemodialysis for ESRD patients. Several acetate-free dialysates are now available and used in a large number of dialysis facilities, despite their higher cost and the insufficiency of their assessment. Using REIN registry data, AFD was associated with improved survival independent of comorbidities and HDF in patients aged 70 years and older but not in younger patients.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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CONFLICT OF INTEREST STATEMENT

L.M. is implicated as the principal investigator in a study sponsored by Bellco. B.S. received honoraria from MSD for a scientific presentation.

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ORIGINAL ARTICLE

Encapsulating peritoneal sclerosis is associated with T-cell activation

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ABSTRACT

Background. Encapsulating peritoneal sclerosis (EPS) is an excessive fibrotic response of the peritoneum that may occur after long-term peritoneal dialysis (PD). The underlying pathophysiology is poorly understood, but involvement of peritoneal inflammatory T helper 1 cells may be pivotal.
Methods. Soluble interleukin-2 receptor alpha (sCD25) concentration was measured as a marker for T-cell activation in serum and ascites from EPS patients and various control patient groups. Peritoneal biopsies were stained for the presence of T cells, and T cells isolated from ascites of EPS patients were characterized in detail for differentiation status and cytokine expression.
Results. Serum sCD25 concentrations are significantly and specifically increased in EPS patients compared with haemodialysis, PD and predialysis patients. Peritoneal effluent of stable PD patients contains very low levels of sCD25, while sCD25 levels in ascites of EPS patients are high and indicative of local production. In the years preceding the diagnosis of EPS, the serum sCD25 concentrations increased while remaining at stable levels in control PD patients. The peritoneum and ascites of EPS patients showed a significant influx of T cells with relatively increased numbers of $CD4^+$ T cells. These T cells were fully differentiated and displayed a T helper 1 cell type with a pro-inflammatory cytokine profile.
Conclusions. Increased serum sCD25 concentrations and peritoneal lymphocytosis in EPS patients indicate the involvement of activated T cells in the pathophysiology of excessive fibrosis.

Keywords: biomarker, encapsulating peritoneal sclerosis, peritoneal dialysis, sCD25, T cells

INTRODUCTION

Encapsulating peritoneal sclerosis (EPS) is a rare but devastating complication of peritoneal dialysis (PD). The most important risk factor for EPS is duration of PD treatment, and associations have been found with younger age, frequent