Long-term effects of citric acid-based bicarbonate haemodialysis on patient outcomes: a survival propensity score–matched study in western France

Jacky Potier, Thibault Dolley-Hitze, Didier Hamel, Isabelle Landru, Erick Cardineau, Guillaume Queffeulou, Elie Zagdoun, Eric Renaudineau, Nicolas Molinari, Lucie Gamon, et al.

Long-term effects of citric acid-based bicarbonate haemodialysis on patient outcomes: a survival propensity score–matched study in western France

Jacky Potier[1], Thibault Dolley-Hitze[2], Didier Hamel[2], Isabelle Landru[3], Erick Cardineau[4], Guillaume Queffeulou[1], Elie Zagdoun[5], Eric Renaudineau[6], Nicolas Molinari[7], Lucie Gamon[8], Marion Morena[9], Jean-Paul Cristol[9,10] and Bernard Canaud[11,12]

[1]Department of Nephrology and Hemodialysis, Centre Hospitalier Public du Cotentin, Cherbourg, France, [2]AUB Santé, Dialysis Unit, Saint-Malo, France, [3]Department of Nephrology and Hemodialysis, Centre Hospitalier Robert Bisson, Lisieux, France, [4]Department of Nephrology and Hemodialysis, Centre Hospitalier Intercommunal Alencon-Mamers, Alençon, France, [5]Department of Nephrology and Hemodialysis, Centre Hospitalier Mémorial France Etats-Unis, Saint-Lô, France, [6]Department of Nephrology and Hemodialysis, Centre Hospitalier Broussais, Saint-Malo, France, [7]IMAG, CNRS, Centre Hospitalier Universitaire de Montpellier, University of Montpellier, Montpellier, France, [8]Clinical Research and Epidemiology Unit, Centre Hospitalier Universitaire de Montpellier, University of Montpellier, Montpellier, France, [9]PhyMedExp. INSERM, CNRS, Université de Montpellier, Montpellier, France, [10]Département de Biochimie et Hormonologie, Centre Hospitalier Universitaire de Montpellier, Montpellier, France, [11]School of Medicine, Montpellier University, Montpellier, France and [12]FMC, Global Medical Office, Bad Homburg, Germany

Correspondence to: Jacky Potier; E-mail: jacky.potier2@wanadoo.fr

ABSTRACT

Background. Citric acid–based bicarbonate haemodialysis (CIT-HD) has gained more clinical acceptance over the last few years in France and is a substitute for other acidifiers [e.g. acetic acid (CH_3COOH) and hydrochloric acid (HCl)]. This trend was justified by several clinical benefits compared with CH_3COOH as well as the desire to avoid the consequences of the corrosive action of HCl, but a nationwide clinical report raised concerns about the long-term safety of CIT-HD. The aim of this study was to assess the long-term effects of CIT-HD exposure on patient outcomes in western France.

Methods. This is a population-based retrospective multicentre observational study performed in 1132 incident end-stage kidney disease patients in five sanitary territories in western France who started their renal replacement therapy after 1 January 2008 and followed up through 15 October 2018. Relevant data, collected prospectively with the same medical software, were anonymously aggregated for the purposes of the study. The primary goal of this study was to investigate the effects of citrate exposure on all-cause mortality. To provide a control group to CIT-HD one, propensity score matching (PSM) at 2:1 was performed in two steps: the first analysis was intended to be exploratory, comparing patients who received citrate ≤80% of the time (CIT-HD ≤80) versus those who received citrate >80% of the time (CIT-HD >80), while the second analysis was intended to be explanatory in comparing patients with 0% (CIT-HD0) versus 100% citrate time exposure (CIT-HD100).

Results. After PSM, in the exploratory part of the analysis, 432 CIT-HD ≤80 patients were compared with 216 CIT-HD >80 patients and no difference was found for all-cause mortality using the Kaplan–Meier model (log-rank 0.97), univariate Cox regression analysis {hazard ratio [HR] 1.01 [95% confidence interval (CI) 0.71–1.40]} and multivariate Cox regression analysis [HR 1.11 (95% CI 0.76–1.61)] when adjusted for nine variables with clinical pertinence and high statistical relevance in the univariate analysis. In the explanatory part of the analysis, 316 CIT-HD0 patients were then compared with 158 CIT-HD100 patients and no difference was found using the Kaplan–Meier model (log-rank 0.06), univariate Cox regression analysis [HR 0.69 (95% CI 0.47–1.03)] and multivariate Cox regression analysis [HR 0.87 (95% CI 0.57–1.33)] when adjusted for seven variables with clinical pertinence and high statistical relevance in the univariate analysis.

Conclusions. Findings of this study support the notion that CIT-HD exposure ≤6 years has no significant effect on all-cause mortality in HD patients. This finding remains true for patients receiving high-volume online haemodiafiltration, a modality most frequently prescribed in this cohort.

Keywords: chronic haemodialysis, citrate, HDF, mortality

INTRODUCTION

Bicarbonate (HCO_3) haemodialysis (HD) requires acidification of dialysis fluid to prevent calcium (Ca) and magnesium (Mg)

precipitation to keep their concentration constant. Three acids (i.e. acidifiers—acetic acid (CH_3COOH), hydrochloric acid (HCl) and citric acid ($C_6H_8O_7$; CIT)] are currently used at low concentration in HD. CH_3COOH was the first to be used. CH_3COOH-based HCO_3 haemodialysis (CH_3COOH-HD) was associated with haemodynamic instability, particularly in high-efficiency HD and online haemodiafiltration (HDF) with sub-optimal biocompatibility marked by cell toxicity [1]. Hydrochloric-based HCO_3 haemodialysis (HCl-HD) was introduced subsequently to correct side effects of CH_3COOH. On the positive side, HCl-HD was shown to improve haemodynamic tolerance in short-term studies, with potential survival benefits in long-term observational studies [2]. In contrast, HCl-HD was associated with premature ageing of concentrate piping and damage to dialysis machine (e.g. pump and tubing); furthermore, HCl was recognized as being more difficult to transport and store. CIT was the third acidifier to be introduced. CIT is known to chelate ionized Ca (iCa) and magnesium (iMg) conferring anticoagulant activity in different settings (e.g. blood bank storage for transfusion, catheter locking solution and regional citrate–Ca anticoagulation). CIT-based HCO_3 haemodialysis (CIT-HD) was introduced to solve issues observed with other acids. CIT dissociates into citrate, a naturally existing anion that acts as an indirect buffer base after conversion to HCO_3 through its metabolic pathway—not modified by chronic renal failure [3]—in muscle and especially the liver, whose dysfunction prohibits its use. In CIT-HD, despite low concentrations (0.8–1.0 mmol/L), citrate reduces dialysate Ca (dCa) and Mg (dMg) concentrations, then diffuses through the membrane and further decreases plasma iCa and iMg concentrations, a mechanism that tends to reduce the divalent ion mass balance. In this context, reduced iCa concentrations have no anticoagulant effect [4], while it may negatively impact long-term Ca and Mg mass balance [5]. Specific effects of CIT-HD on Ca mass balance have been well described in landmark studies, both in acute studies showing a reduction in iCa concentrations and in long-term studies where it is associated with an increase in intact parathyroid hormone (iPTH) [6, 7]. The chelation effect of CIT-HD on divalent ions has prompted the manufacturer to compensate for this negative mass balance effect by increasing dCa up to 0.15–0.25 mmol/L, not considering adjustment for dMg. CIT-HD has been used in the USA [8] for more than a decade and worldwide without particular concerns. Minor side effects (e.g. cramps) of CIT-HD observed initially were not completely abolished despite an increase in dCa [9]. Furthermore, in the same study, it was shown that low total protein and albumin (Alb) concentrations might play an essential role in these side effects.

To the best of our knowledge, all CIT-HD-related studies have been acute or short-term studies focusing on biological and clinical consequences; none of them have explored long-term patient outcomes.

CIT-HD was introduced in 2013 in France, with rapid acceptance and no major concerns until a safety concern was recently raised by a retrospective national database study from the Renal Epidemiology and Information Network registry (Mercadal *et al.*, oral presentation, annual meeting of Société Francophone de Néphrologie, Dialyse et Transplantation, October 2018, Lille, France and abstract, MON-110, World Congress of Nephrology, Melbourne, NSW, Australia, 2019). The French National Agency for Medicines and Health Products Safety (ANSM) initiated several database studies from dialysis care providers to assess the safety of CIT-HD. In conjunction with this request, the ANSM asked us to perform this retrospective observational multicentre study exploiting a large database of dialysis patients treated in western France. The objective of the study was to explore the long-term effect of CIT-HD on HD patient outcomes.

MATERIALS AND METHODS

Study design and objectives

This retrospective observational study had two parts. The first part of the study was exploratory and consisted of selecting patients with CIT-HD exposure—calculated as the ratio of the prescription duration to the total observational period: >80% (CIT-HD >80) or ≤80% (CIT-HD ≤80). Patient outcome was analysed over a 10-year period before and after propensity score matching (PSM) on main patient characteristics to minimize selection biases. The second part of the study was explanatory, centering on the role of CIT. It consisted of selecting patients who received exclusively CIT acidifier over the observation period (CIT-HD100) versus those who never received CIT (CIT-HD0). Patient outcome was analysed over the same 10-year period before and after PSM on the main patient and treatment characteristics.

Data source

This was a retrospective study performed on a dataset of incident HD patients treated in western France. Data of interest were extracted from patient electronic medical records, de-identified and anonymized to create a workable subset of data. A total of 1132 incident end-stage kidney disease (ESKD) patients on HD from dialysis facilities in five sanitary territories were included in the final dataset. Data capturing, storage and analysis rely on a common electronic medical record integrated into Dialog7 software, allowing the optimized collection of data. These dialysis facilities offer all renal replacement therapy options, from in-centre HD (HDC), medicalized dialysis units (UDMs) and self-care dialysis units (UADs) to home therapy (peritoneal dialysis and HD), including access to renal transplantation. Each sanitary territory is managed by a chief medical nephrologist supported by his staff and caregivers and provides full service to dialysis patients through a public and non-profit association healthcare system.

Study population

The patient inclusion period started on 1 January 2008 for four sanitary territories and on 1 January 2010 for the last one (Saint-Lô). The follow-up period was extended to 15 October 2018 for four sanitary territories and to 15 May 2018 for one (Saint-Malo) due to a software change. All ESKD patients starting dialysis in this time frame and having provided written informed consent on secondary use of their clinical data for

research purposes and eligible for study inclusion were included after 90 days of regular dialysis treatment and stabilization.

Main patient characteristics and laboratory data were collected at dialysis initiation, including age, gender, causal nephropathy, dry weight, body mass index (BMI), Charlson comorbidity index (CCI), diabetes mellitus (DM) status, cardiovascular disease (CVD), vascular access (VA) type and laboratory data including serum Alb, C-reactive protein (CRP), creatinine index, haemoglobin (Hb), ferritin and iPTH.

The mean weekly dialysis time (WDT) was calculated. Exposure to treatment modality was expressed as the percentage of time spent on each modality for each patient, including the treatment option (HD, online HDF $<50\%$ and $\geq 50\%$ exposure) and dialysis facility (HDC/UDM, UAD/home HD, considering $\geq 50\%$ time exposure). Prescribed dialysate HCO_3 ($dHCO_3$), dCa and, in the case of CIT-HD, the 'effective' diffusive dialysate Ca (eff-dCa)—estimated from the manufacturer's Ca nominal concentration by subtracting 0.15 mmol/L, accounting for 10% of iCa chelation estimate [10]—were averaged on the observation period and used as time-averaged values (TAVs). Angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker (ACEi/ARB) prescription, expressed as the percentage of time spent on these medications, was also used as a potential marker of cardiovascular severity.

TAVs for lab tests included Alb, C Reactive Protein (CRP), erythropoietin resistance index (ERI), creatinine index, Hb, ferritin, Ca, corrected Ca for Alb, phosphorus (P), iPTH, pre- and post-dialysis HCO_3- and eqK_t/V.

Renal replacement modalities and operating procedures

All patients were treated with high-flux synthetic membranes and under conditions of ultrapure dialysis fluid, whatever the modality (e.g. HD or online HDF) and type of dialysis unit (e.g. HDC, UDM and UAD). HCl acidifier was predominant (e.g. 75%) in all these dialysis units before 2014. After 2014, HCl acidifier was steadily substituted by CIT (from 17% in May 2014 to 57% in May 2018) according to dialysis provider policy. The dialysate CIT concentration was 1.0 and 0.8 mmol/L for 96 and 4% of CIT exposure, respectively. The renal replacement treatment schedule (e.g. number of dialysis sessions and treatment duration) was prescribed and adjusted to residual kidney function and patient needs. The choice of dialysis modality and facility type relied on a medical decision, accounting for comorbid conditions, medical risk and patient's choice.

Calculations and statistics

Data are presented as mean ± standard deviation (SD), median with interquartile range (IQR; 25th–75th percentile) or frequency as appropriate. Comparisons between groups were performed with the chi-squared test for categorical data or the Mann–Whitney U test for non-parametric data.

The first 'exploratory' part of the study analysed the outcomes of patients partially exposed to citrate acidifier ($\leq 80\%$ or $>80\%$ treatment time, whole population). The second 'explanatory' part of the study was focused on the outcome of patients who received citrate acidifier exclusively (CIT-HD100) versus those who had never been exposed to citrate acidifier (CIT-HD0).

Due to the retrospective observational nature of the study and to minimize differences between groups, PSM analyses were performed (matched population) in both cases in a 2:1 ratio including the following patient characteristics: age, gender, BMI, CCI, DM (yes/no), CVD (yes/no) and initial VA (tunnelled catheter versus arteriovenous fistula or graft). Validation of the paired match was ascertained by comparing variables using McNemar or Wilcoxon tests as appropriate.

Survival analysis was performed according to the Kaplan–Meier method and compared with the log-rank test. Multivariate Cox regression analysis analysed the hazard ratio (HR) of receiving citrate or non-citrate acidifier, including variables statistically significant in univariate analysis and with clinical pertinence. Statistical analyses were performed with SAS software version 9.1 (SAS Institute, Cary, NC, USA). All analyses were considered significant for $P < 0.05$.

RESULTS

Exploratory analysis

The initial cohort of incident HD patients consisted of 1132 subjects. In the first part of the study, based on limited time exposure to citrate acidifier, 898 patients were in the CIT-HD ≤ 80 group and 234 in the CIT-HD >80 group (whole population). After PSM with a 2:1 ratio, 432 were assigned to the CIT-HD ≤ 80 group and 216 to the CIT-HD >80 group and then compared (matched population) (Figure 1). The median follow-up period was 29 (IQR 16.7–52) and 22 (IQR 9–34.5) months, respectively. Data are presented in Table 1. Kaplan–Meier survival analysis revealed no difference, as shown by virtually superimposable curves (Figure 2) with a log-rank $P = 0.97$. The unadjusted Cox regression model showed no difference in all-cause mortality between CIT-HD ≤ 80 and CIT-HD >80 {HR 1.01 [95% confidence interval (CI) 0.72–1.40]}. Adjusted multivariate analysis including age, BMI, CCI, CVD (yes/no) as initial demographic variables, VA initiation, Alb initiation and CRP initiation, facility type, dialysis modality exposure (HD, online HDF <50 and $\geq 50\%$) and WDT variables did not change the results [HR 1.11 (95% CI 0.76–1.61)] (Table 2).

Explanatory analysis

In the second part of the study, 731 patients who met the selection criteria were identified: 549 patients were never exposed to citrate (CIT-HD0), while 182 patients received citrate throughout the observational period (CIT-HD100). After PSM with a 2:1 ratio, 316 patients were assigned to the CIT-HD0 group and 158 patients to the CIT-HD100 group. The median follow-up period was 22 (IQR 13–37) and 20 (IQR 9–33) months, respectively. Data are presented in Table 3. Kaplan–Meier survival analysis did not reveal a significant difference between CIT-HD0 and CIT-HD100 (Figure 3), with a log-rank $P = 0.06$. The unadjusted Cox model showed no significant difference in all-cause mortality between CIT-HD0 and CIT-HD100 [HR 0.69 (95% CI 0.47–1.03)]. Adjusted multivariate analysis including age, BMI, CCI, CVD (yes/no) as initial

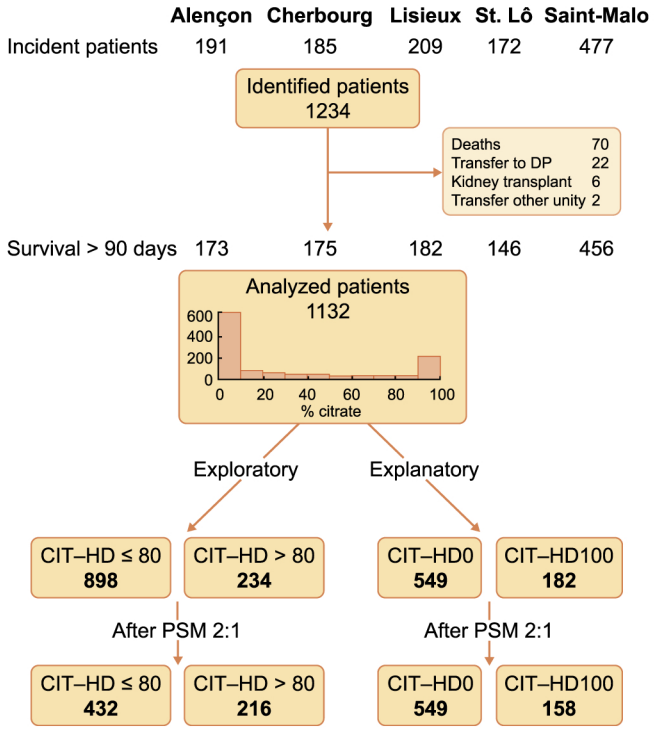

FIGURE 1: Study design flow diagram.

demographic variables, facility type, dialysis modality exposure (HD, online HDF <50 and ≥50%) and WDT variables did not modify the results [HR 0.87 (95% CI 0.57–1.33)] (Table 4).

After PSM, some differences persisted and concerned mainly HD prescription parameters: first, a higher HDC:UDM ratio in the CIT-HD100 group explained by earlier provision of citrate in HDC due to a clinical pre-assessment before CIT was deployed or generalized in other facilities; second, a higher percentage of patients receiving online HDF ≥50% in the CIT-HD100 group due to concomitant prevalent increase of both CIT-HD and online HDF; third, a shorter WDT in the CIT-HD group related to the shorter median follow-up with a probable better residual renal function allowing a lower dose of dialysis; fourth, a higher proportion of patients receiving ACEis/ARBs in the CIT-HD100 group, suggesting on one hand a poor initial cardiovascular condition and on the other a potential protective effect over the long term. A few other variables were slightly different, including dCa and eff-dCa, as well as low molecular weight heparin dosing. The last finding confirms that CIT acidifier choice was not indicated for its anticoagulant activity in this cohort.

Lab test values are presented in Table 5 as TAVs over the observation period. Serum Alb concentration was significantly lower in the CIT-HD100 group but within the same range as it was at baseline, indicating no time change. Hb concentration was lower in the CIT-HD100 group but still in the target range >11 g/dL. ERI was significantly lower in the CIT-HD100 group. Regarding bone mineral markers, total Ca was lower in the CIT-HD100 group. Interestingly, this difference disappeared when Ca was corrected for Alb concentrations. We acknowledge that iCa dosages would have been more pertinent for interpreting intermediary outcomes, but unfortunately iCa was not routinely performed in our current practice. Otherwise the most important finding is the fact that iPTH, a sensitive indicator of Ca imbalance, did not differ between the two groups. As shown, iPTH concentrations ranged between 130 and 585 ng/L and were not different between groups. Furthermore, iPTH, which was similar in the two groups, initially remained stable over time until the end of the observation period. As shown, the last iPTH concentrations remained similar in both groups (CIT-HD0 305.5 ± 244 versus CIT-HD100 307.1 ± 195 ng/L), suggesting that parathyroid glands were not stimulated. Predialysis HCO_3 concentration was lower in the CIT-HD100 group while remaining in the target range, but this value should be interpreted in light of a lower dialysate plasma HCO_3 gradient due to reduced $dHCO_3$ prescription. In addition, the lower post-dialysis HCO_3 concentration observed in the CIT-HD100 group is in agreement with previous studies [9, 10].

DISCUSSION

CIT-HD is an interesting option for dialysis that was developed with the intent of improving haemodynamic tolerance of dialysis sessions, particularly in high-risk patients. As shown from a market survey, CIT-HD is gaining more clinical acceptance worldwide. Most previous studies on CIT-HD have focused on short- or mid-term effects and never considered long-term outcomes, highlighting the importance of our retrospective long-term observational study.

Direct clinical comparisons of HD with various acidifiers are difficult to interpret considering the variety of dialysate compositions that include citrate concentrations ranging between 0.66 and 1 mmol/L, CH_3COOH-HD acetate concentrations ranging between 2.5 and 11 mmol/L and dCa or dMg adjusted or not to CIT-HD. Interestingly, in a recent prospective randomized study, lower intradialytic blood pressure (BP) and other minor adverse events (e.g. cramps and fatigue) were reported through the first 2 weeks of CIT-HD exposure then vanished afterwards, suggesting an adaptation to the new dialysis condition [9]. Despite the lower BP observed in patients exposed to CIT-HD, the overall haemodynamic effects of CIT-HD were considered beneficial (e.g. lower peripheral vascular resistance and stable stroke index), particularly for patients presenting with intradialytic hypertension in another interventional study [11]. An increase in symptomatic intradialytic hypotensive episodes and cramps was observed, particularly when CIT-HD is associated with low dCa (1.25 mmol/L) and probably low dMg [12]. Overall, CIT-HD is considered as safe as CH_3COOH-HD and some studies have reported better tolerance (e.g. less malaise) [13] and an improved subjective patient perception [11].

Thrombogenicity of the extracorporeal circuit and heparin consumption tend to be reduced with CIT-HD use. The antithrombotic effect of citrate results from a possible partial local Ca-chelating effect within the extracorporeal circuit even though iCa never reaches anticoagulant levels (e.g. iCa <0.40 mmol/L) [4]. Although controversial [14, 15], this property may explain why CIT-HD is frequently indicated in high bleeding risk patients to decrease heparin needs [16, 17]. CIT-HD contributes to improve overall dialysis efficiency [8, 10, 11, 17] by preserving membrane permeability and facilitates dialyser reuse [12]. The

Table 1. Baseline characteristics and HD parameters of the CIT-HD ≤80 and CIT-HD >80 patients before and after PSM

Characteristics	Whole cohort			Matched cohort		
	CIT-HD ≤80	CIT-HD >80	P-value	CIT-HD ≤80	CIT-HD >80	P-value
n	898	234		432	216	
Demographics						
Age (years)	69.52 ± 14.38	69.12 ± 13.83	0.4709	68.77 ± 13.97	69.03 ± 13.51	0.7825
Gender (female), %	38.08	40.60	0.4818	37.73	38.89	0.7132
Weight (kg)	75.60 ± 18.14	77.71 ± 20.27	0.3424	79.66 ± 18.04	78.57 ± 20.38	0.3573
BMI (kg/m^2)	27.43 ± 6.22	28.56 ± 7.02	0.0669	28.80 ± 6.18	28.56 ± 7.02	0.4917
CCI	7.32 ± 2.29	6.66 ± 2.12	**<0.0001**	6.77 ± 2.12	6.74 ± 2.14	0.4411
Renal disease, %			0.1588			0.3126
Cystic disease	6.68	9.40		6.71	9.72	
Diabetes	20.38	22.65		24.07	22.69	
Glomerulonephritis	11.92	9.40		12.04	9.72	
Interstitial	9.91	12.39		8.56	11.11	
Vascular and hypertension	31.63	32.48		29.40	32.87	
Unknown and other	19.49	13.68		19.21	13.89	
DM, %	33.30	41.03	**0.0271**	42.82	42.59	0.9376
CVD, %	32.63	25.21	**0.0291**	25.00	25.93	0.7389
HD parameters, %						
VA catheter initiation	32.81	29.49	0.3320	28.24	31.48	0.2829
Facility type, %			0.1966			0.0704
HDC/UDM	84.53	87.97		81.94	87.50	
UAD/home HD	15.47	12.13		18.06	12.50	
Online HDF	62.4	69.9	**0.0335**	61.8	73.1	**0.0042**
HD parameters (TAV)						
WDT (min)	605 ± 114	563 ± 112	**<0.0001**	609 ± 112	567 ± 113	**<0.0001**
Anti-Xa (IU/session)	3467 ± 1375	3786 ± 1398	**0.0005**	3578 ± 1344	3831 ± 1425	**0.0269**
Other treatments						
ACEi/ARB, %	38.14 ± 42.06	47.59 ± 42.35	**0.0046**	39.86 ± 42.23	49.15 ± 42.33	**0.0028**
Laboratory initiation						
Alb (g/L)	33.73 ± 5.83	33.04 ± 6.01	0.2118	33.83 ± 5.60	33.09 ± 6.02	**0.0291**
CRP (mg/L), median (IQR)	7.2(2.2–23.0)	8.0(2.0–28.5)	0.9649	7.7(2.9–21.0)	8.0(2.0–29.0)	**0.0150**
Hb (g/dL)	10.18 ± 1.52	10.05 ± 1.50	0.1720	10.21 ± 1.50	10.06 ± 1.50	**0.0131**
Creatinine index (mg/kg/day)	16.83 ± 3.25	16.87 ± 2.44	0.9915	17.10 ± 3.15	16.86 ± 2.49	0.0757
iPTH (ng/L)	324.5 ± 254.9	322.7 ± 221.8	0.4602	340.1 ± 265.9	313.4 ± 207.3	0.6574
Ferritin (µg/L)	277.2 ± 262.5	250.8 ± 251.7	0.4167	263.6 ± 249.9	254.3 ± 259.6	0.2877

Data are presented as mean ± SD unless stated otherwise. The interquartile range (IQR) is the 25th–75th percentile.
Note: Statistical significant of *P*-values are in bold.

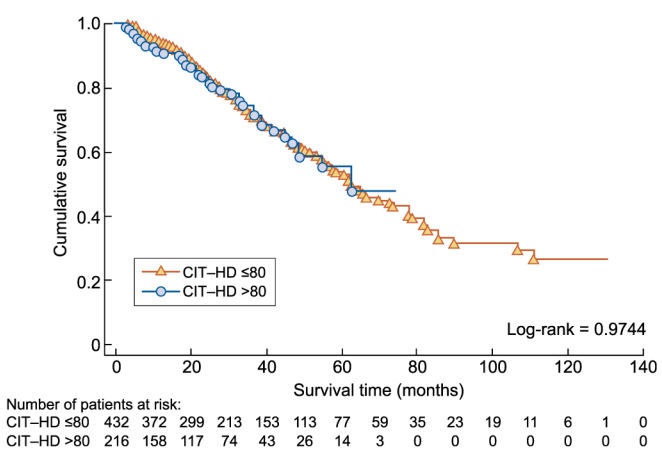

FIGURE 2: Kaplan–Meier analysis comparing all-cause mortality between the CIT-HD ≤80 and CIT-HD >80 study groups after PSM.

effect of CIT-HD on acid–base status was a concern in frail patients. However, due to the relatively slow metabolization of CIT, plasma HCO_3 increases steadily during the dialysis session but the risk of post-dialysis alkalosis appears quite limited [9]. This property has interest in patients suffering from chronic respiratory disease [18]. Recent studies with CIT-HD have confirmed that pre-dialysis HCO_3 was not modified or only slightly increased over time but remained in the optimal target range [9–11].

Aside from these clinical benefits, it must be underlined that CIT-HD has a negative significant impact on dialysis Ca mass balance [5, 6]. From recent studies, one can estimate that 10–20% of available diffusive Ca is reduced when CIT-HD is used [5]. As a rule of thumb, an equivalent Ca mass balance should be maintained with CIT-HD as compared with CH_3COOH-HD or HCl-HD and baseline dCa should be increased by 0.15–0.25 mmol/L. Mg is similarly affected by citrate complexing phenomenon, meaning that Mg mass balance is potentially reduced [5]. In the long run, recurrent negative Ca and Mg dialysis mass balance are likely to induce iPTH hormone release and to exacerbate secondary hyperparathyroidism [5, 6].

Our current study on CIT-HD provides original and interesting findings that are discussed and kept in their current clinical context. The use of CIT-HD has increased over the last

Table 2. Comparison between CIT-HD ≤80 and CIT-HD >80

Characteristics	Univariate		Multivariate	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	1.06 (1.04–1.07)	**<0.0001**	1.03 (1.01–1.05)	**0.0008**
BMI (kg/m^2)	0.97 (0.95–0.99)	**0.0033**	0.98 (0.95–1.00)	0.0582
CCI	1.21 (1.14–1.28)	**<0.0001**	1.07 (0.96–1.19)	0.2001
CVD (ref. no) yes	1.86 (1.40–2.46)	**<0.0001**	1.69 (1.22–2.34)	**0.0018**
VA initiation (ref. catheter) no catheter	0.67 (0.50–0.91)	**0.0107**	0.66 (0.47–0.92)	**0.0143**
Dialysis modality (ref. HD)		**0.0060**		**<0.0001**
Online HDF <50%	0.60 (0.37–0.97)		0.96 (0.55–1.68)	
Online HDF ≥50%	0.52 (0.35–0.78)		0.34 (0.21–0.57)	
Facility type (ref. HDC/UDM) UAD/home HD	0.16 (0.08–0.32)	**<0.0001**	0.16 (0.08–0.34)	**<0.0001**
WDT (min) (TAV)	0.97 (0.96–0.98)	**<0.0001**	0.98 (0.97–1.00)	**0.0138**
Alb initiation (ref. ≤35) >35 (g/L)	0.71 (0.25–0.96)	**0.0250**	0.81 (0.58–1.14)	0.2208
CRP initiation (ref. <10) ≥10 (mg/L)	1.62 (1.22–2.16)	**0.0009**	1.15 (0.82–1.61)	0.4198
(ref. CIT-HD ≤80) CIT-HD >80	1.01 (0.72–1.40)	0.9744	1.11 (0.76–1.61)	0.6003
All-cause mortality				

Univariate and multivariate Cox regression analysis for all-cause mortality.
Note: Statistical significant of *P*-values are in bold.

Table 3. Baseline characteristics and HD parameters of the CIT-HD0 and CIT-HD100 patients before and after PSM

Characteristics	Whole cohort			Matched cohort		
	CIT-HD0 ($n = 549$)	CIT-HD100 ($n = 182$)	P-value	CIT-HD0 ($n = 316$)	CIT-HD100 ($n = 158$)	P-value
Demographic variables						
Age (years)	70.16 ± 14.67	69.23 ± 13.55	0.1974	68.84 ± 14.79	69.14 ± 13.24	0.9254
Gender (female), %	39.34	43.41	0.3330	40.19	40.51	0.9338
Weight (kg)	74.29 ± 17.96	77.41 ± 20.58	0.1609	78.36 ± 17.93	77.20 ± 19.61	0.3515
BMI (kg/m^2)	26.96 ± 6.20	28.92 ± 7.49	**0.0050**	28.24 ± 6.15	28.28 ± 6.65	0.8012
CCI	7.43 ± 2.35	6.53 ± 2.14	**<0.0001**	6.75 ± 2.21	6.67 ± 2.20	0.6954
Renal disease, %			0.5066			0.4614
Cystic disease	8.38	7.69		9.49	7.59	
Diabetes	18.94	23.63		21.52	23.42	
Glomerulonephritis	9.65	10.44		11.71	11.39	
Interstitial	10.20	10.99		8.86	9.49	
Vascular and hypertension	31.33	31.87		28.48	31.65	
Unknown and other	21.49	15.38		19.94	16.46	
DM, %	32.60	41.76	**0.0247**	140.51	43.04	0.5108
CVD, %	32.24	24.73	0.0560	24.37	25.32	0.7797
HD parameters, %						
VA catheter initiation	36.93	29.67	0.0756	29.43	32.91	0.3213
Facility type, %			**0.0225**			**0.0002**
HDC/UDM	87.25	93.41		84.49	93.67	
UAD/home HD	12.75	6.59		15.51	6.33	
Online HDF	57.7	73.4	**0.0001**	60.4	79.7	**0.0001**
HD parameters (TAV)						
WDT (min)	605 ± 114	563 ± 112	**<0.0001**	601 ± 113	559 ± 109	**0.0001**
dCa (mmol/L)	1.50 ± 0.05	1.62 ± 0.10	**<0.0001**	1.51 ± 0.05	1.63 ± 0.10	**<0.0001**
Eff-dCa (mmol/L)	1.50 ± 0.05	1.47 ± 0.09	**<0.0001**	1.51 ± 0.05	1.47 ± 0.10	**<0.0001**
$dHCO_3$ (mmol/L)	34.8 ± 1.6	33.5 ± 1.5	**<0.0001**	34.8 ± 1.3	33.6 ± 1.5	**<0.0001**
Anti-Xa (IU/session)	3447 ± 1335	3855 ± 1410	**0.0004**	3500 ± 1342	3887 ± 1430	**0.0039**
Other treatments						
ACEi/ARB, %	36.37 ± 42.47	50.01 ± 42.53	**0.0004**	40.35 ± 42.91	52.48 ± 42.45	**0.0006**
Laboratory initiation						
Alb (g/L)	33.44 ± 5.89	32.55 ± 5.88	0.0962	34.14 ± 5.85	32.61 ± 5.89	**0.0037**
CRP (mg/L), median (IQR)	9.0(2.5–23.3)	7.0(2.0–26.2)	0.3814	7.0(2.0–20.5)	7.0(2.0–27.0)	0.3748
Hb (g/dL)	10.16 ± 1.50	10.01 ± 1.49	0.1312	10.18 ± 1.54	10.03 ± 1.49	0.0655
Creatinine index (mg/kg/day)	16.79 ± 3.32	16.85 ± 2.39	0.9968	17.05 ± 3.06	16.86 ± 2.49	0.2710
iPTH (ng/L)	328.1 ± 258.6	319.2 ± 219.3	0.6857	341.8 ± 272.0	309.0 ± 200.6	0.7654
Ferritin (μg/L)	278.0 ± 258.8	254.2 ± 239.9	0.7457	260.8 ± 246.7	260.4 ± 252.4	0.7521

Data are presented as mean ± SD unless stated otherwise. The interquartile range (IQR) is the 25th–75th percentile.
Note: Statistical significant of *P*-values are in bold.

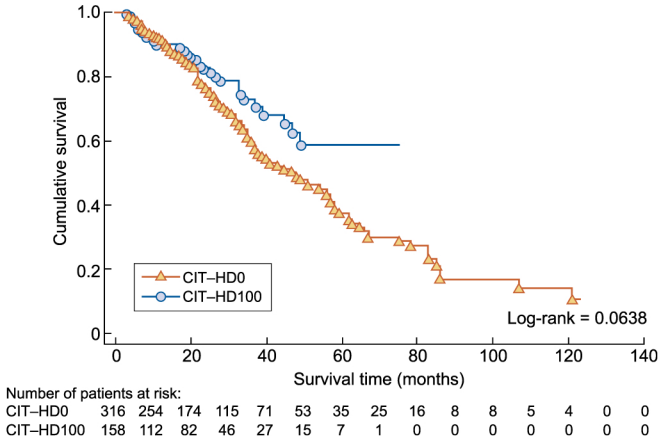

FIGURE 3: Kaplan–Meier analysis comparing all-cause mortality between the CIT-HD0 and CIT-HD100 study groups after PSM.

decade but remains limited, ranging from 13% to 20% of dialysis patients in Europe, indicating a strong bias of indication and reflecting mostly local practices or policies in patients at risk. In western France, CIT was introduced in 2013 and its use increased from 17% in 2014 to 57% in 2018, mainly as a substitute for HCl, which had replaced CH_3COOH (CH_3COOH: 26.5% in 2012, 9.6% in 2014 and 0% in 2018), except for the Saint-Malo sector, where some dialysis machines were damaged by HCL-HD (leakage on hydraulic circuit) and continued to use CH_3COOH acidifier until CIT-HD was available. CH_3COOH is potentially deleterious, notably from a haemodynamic aspect [1], even with low concentrations (e.g. 3–4 mmol/L), particularly in elderly, cardiac or fragile patients, and amplified with high-volume online HDF [19]. These pathophysiologic considerations may explain why CIT-HD was indicated mainly for in-centre patients receiving online HDF and having a higher comorbid profile.

Table 4. Comparison between CIT-HD0 and CIT-HD100

	Univariate		Multivariate	
Characteristics	HR (95% CI)	P-value	HR (95% CI)	P-value
Age (years)	1.04 (1.03–1.06)	**<0.0001**	1.03 (1.03–1.05)	**<0.0001**
BMI (kg/m^2)	0.97 (0.95–1.00)	**0.0312**	0.97 (0.94–0.99)	**0.0261**
CCI	1.17 (1.10–1.26)	**<0.0001**	1.05 (0.94–1.17)	0.4071
CVD (ref. no) yes	1.52 (1.09–2.10)	**0.0125**	1.31 (0.92–1.86)	0.1320
Dialysis modality (ref. HD)		**<0.0001**		**<0.0001**
Online HDF <50%	0.71 (0.45–1.11)		0.66 (0.40–1.09)	
Online HDF ≥50%	0.42 (0.28–0.63)		0.29 (0.13–0.49)	
Facility type (ref. HDC/UDM) UAD/HDD	0.29 (0.14–0.60)	**0.0010**	0.29 (0.14–0.56)	**<0.0001**
WDT (TAV)	0.98 (0.97–0.99)	**0.0066**	1.00 (1.00–1.00)	0.1538
(Ref. CIT-HD0) CIT-HD100	0.69 (0.47–1.03)	0.0698	0.87 (0.57–1.33)	0.5176
All-cause mortality				

Univariate and multivariate Cox regression analysis for all-cause mortality
Note: Statistical significant of *P*-values are in bold.

Table 5. Time-averaged laboratory variables of the matched CIT-HD0 and CIT-HD100 patients after PSM

		Matched cohort		
Characteristics	Measurements (*n*/year)	CIT-HD0	CIT-HD100	P-value
n		316	158	
Laboratory (TAV)				
Alb (g/L)	10.2	36.30 ± 4.77	34.38 ± 3.92	**<0.0001**
CRP (mg/L), median (IQR)	12.5	10.0 (3.0–17.0)	8.0 (1.0–15.0)	0.7940
Hb (g/dL)	18.5	11.46 ± 0.66	11.17 ± 0.59	**<0.0001**
ERI (UI/kg/week/gHb)	16	10.49 ± 9.88	8.35 ± 6.55	**0.0139**
Creatinine index (mg/kg/day)	9.8	17.97 ± 2.28	17.64 ± 1.91	0.1240
nPCR (g/kg/24 h)	10.2	1.14 ± 0.24	1.17 ± 0.24	0.2578
Ferritin (µg/L)	8.8	343.4 ± 181.9	318.2 ± 139.3	0.1271
Ca (mmol/L)	14.7	2.20 ± 0.12	2.17 ± 0.11	**0.0084**
Corrected Ca (mmol/L)	9.8	2.30 ± 0.14	2.30 ± 0.23	0.6463
P (mmol/L)	13.5	1.54 ± 0.36	1.53 ± 0.29	0.5548
iPTH (ng/L)	3.9	299.2 ± 184.9	331.4 ± 231.6	0.0921
eqK_t/V	10.1	1.75 ± 0.36	1.74 ± 0.35	0.7650
HCO_3 pre (mmol/L)	14.8	22.31 ± 1.74	21.95 ± 1.61	**0.0331**
HCO_3 post (mmol/L)	10.3	26.73 ± 1.79	26.02 ± 1.44	**<0.0001**

Data are presented as mean ± SD unless stated otherwise. The interquartile range (IQR) is the 25th–75th percentile.
Note: Statistical significant of *P*-values are in bold.

Interestingly, the introduction of CIT-HD in our region has been associated with an early increase in dCa prescription to prevent hypocalcaemia and parathyroid gland stimulation. This practice change may be illustrated by comparing the average dCa before and after 498 switches—concerning 378 patients—from non-CIT-HD to CIT-HD. The average dCa went from 1.50 ± 0.05 to 1.63 ± 0.08 mmol/L. Furthermore, these values are certainly downplayed to the extent that nearly 25% of the cases had no immediate adjustment of their dCa prescription. This reactivity of clinicians has certainly been beneficial for patients in the long run and may explain the lack of changes in bone mineral metabolism markers (e.g. Cor-Ca and iPTH) between CIT-HD0 and CIT-HD100. Other findings of our study are of clinical relevance. Dialysis efficiency (e.g. eq$K_t/V = 1.75$) and acid–base status remained similar between the two groups. However, it is notable that pre- and post-dialysis plasma HCO_3 concentrations remained significantly lower in the CIT-HD100 group. This finding is likely due to a lower $dHCO_3$ prescription, but also reflects a new acid–base equilibrium resulting from a reduction of HCO_3 load while the production of protein remained constant, as suggested by the stability of the normalized protein catabolic rate over time. Finally, an interesting finding relates ERI to citrate use. As shown, CIT-HD100 is associated with a significantly lower ERI. This is likely associated with the anti-inflammatory effect of citrate [7, 10, 20, 21]. Taken together, these intermediary clinical and biological outcomes, as well as dialysis performance data, confirm the efficacy and safety of CIT-HD while not disclosing any significant differences with other acidifiers provided electrolyte concentration adjustment is performed.

Furthermore, this is the first study reporting on long-term outcomes of CIT acidifier use in dialysis. As shown in the most pertinent PSM analyses, patient outcomes and clinical endpoints did not reveal any significant differences between patients receiving CIT and those receiving other acidifiers. In the first analysis, the survival rate of patients from the CIT-HD >80 group was superimposable to those propensity score matched from the CIT-HD ≤ 80 group. Due to the lag time of citrate marketing, patients from the CIT-HD ≤ 80 group are likely to have a time bias that tends to attribute a significant survival benefit to incident patients dialysed with CH_3COOH-HD or HCl-HD and then transferred to CIT-HD. To avoid this bias, the second PSM explanatory study was necessary. Interestingly, in this analysis the survival rate tends to be better in the CIT-HD100 group as compared with the CIT-HD0 group, but the difference did not reach statistical significance. Several hypotheses could be formulated to support this finding. Ca adaptation in CIT concentrate may have prevented hypocalcaemia and related cardiac events [22]. Regarding the specific role of Mg, our study could not address this concern since plasma Mg levels were not measured on a routine basis. However, it is well documented that low serum Mg concentrations may facilitate severe cardiovascular events in dialysis patients and might have additional side effects, such as triggering inflammation, decreasing immunity, inducing insulin resistance [23–25] and promoting vascular calcifications [26]. Corroborating these facts, it has been shown that high dMg levels are associated with lower cardiovascular mortality risk [27, 28] and Mg supplementation tends to reduce carotid intima–media thickness of dialysis patients [29]. Because dMg was not adjusted for CIT content by manufacturers, our study is reassuring since it reveals a negative impact of CIT on standard dMg. This finding could raise further concerns about optimal dMg with CIT-HD. The beneficial role of CIT on vascular calcification propensity has been recently highlighted in a prospective randomized study showing a favourable impact of CIT on *in vitro* half-life bioassays [30].

The current study has some limitations. We acknowledge that given the retrospective nature of our study, several confounding and remaining factors could not be accounted for. An important bias of selection was already avoided before performing PSM to the extent that the CIT-HD prescription relied on local and institutional policy more than on an individual basis, even for its antithrombotic effect in the case of haemorrhagic-risk patients. To explore further the effects of CIT on dialysis patient outcomes, we designed the PSM analyses in two steps, taking advantage of having access to a large dataset (1132 patients). In addition, to analyse more precisely the role of CIT versus other acidifiers (CH_3COOH or HCl) on patient outcomes, we used the effective time exposure to citrate. In the first part of the analysis, the relative risk of partial time exposure ($\leq$80% of treatment time) to CIT was analysed in 1132 patients with PSM on more pertinent parameters in a 2:1 ratio to minimize bias. The weakness of this exploratory study is the time bias introduced that favours the CIT-HD ≤ 80 group. It thus makes essential the second part of the study where the relative risk of full or no exposure to CIT was analysed in 731 patients. The PSM developed in that case to explore the most critical time exposure risk to citrate is also quite reassuring. As shown, matching provided adequate pairs of data, resulting in almost identical population subsets either on patient characteristics or on treatment modalities. Nevertheless, higher AECi/ARB exposure—even though it was not significant in univariate Cox regression analysis [$\geq$50% versus $<$50% exposure group; HR 0.74 (95% CI 0.53–1.04)]—in the CIT-HD100 group could be interpreted as better cardiovascular protection and considered as a residual bias. The online HDF definition could also have increased the survival benefit of this technique in the interpretation of the Cox analysis. Therefore, and despite its limitations, our study is of high clinical relevance since it confirms the safety and efficacy of CIT-HD in long-term use. To the best of our knowledge, this is the first large cohort study reporting on outcomes of incident dialysis patients receiving CIT-HD over a 6-year period.

In conclusion, our findings support the notion that CIT-HD is not associated with additional risk. Such findings are of great interest for the nephrology and patient communities, as it confirms the long-term safety of CIT-HD. In addition, considering the high proportion of patients receiving online HDF in this cohort, one could assume that citrate is also safe in high-volume online HDF, provided dialysate Ca and Mg concentrations are adequately dosed in the dialysis fluid.

ACKNOWLEDGEMENTS

We thank the nephrologists who participated in the care of patients and the collection of medical data during the study: Julien Bouet, Jérôme Potier and Aure Rauline (Cherbourg),

Marie-Laure Lombart, Simon Duquennoy and Gérard Cam (Saint-Malo), Loay Al Moussa and Solveig Aussant (Lisieux), Laurène Blacher (Alençon) and Thibault Besselièvre (Saint-Lô).

AUTHORS' CONTRIBUTIONS

J.P., G.Q., I.L., E.C., E.Z., T.D.H., D.H. and E.R. were involved in the control of the data. J.P. aggregated, anonymized and analysed the data. J.P., B.C., N.M., L.G., J.P.C. and M.M. were involved in the design of the work and interpretation of the data. N.M. and L.G. ensured the statistics. J.P. and B.C. were involved in drafting the manuscript and all authors were involved in revising the manuscript and approved the final version.

CONFLICT OF INTEREST STATEMENT

B.C. is a part-time consulting employee for Fresenius Medical Care. E.Z. reports non-financial support from Meditor and Sanofy-Genzyme, personal fees and non-financial support from Amicus and personal fees from Shire outside the submitted work. The other authors declare no conflicts of interest.

REFERENCES

1. Noris M, Todeschini M, Casiraghi F *et al.* Effect of acetate, bicarbonate and acetate-free biofiltration on nitric oxyde synthesis: implications for dialysis hypotension. *Am J Kidney Dis* 1998; 32: 115–124
2. Mercadal L, Franck JE, Metzger M *et al.* Improved survival associated with acetate-free haemodialysis in elderly: a registry based study. *Nephrol Dial Transplant* 2015; 30: 1560–1568
3. Bauer E, Derfler K, Joukhadar C *et al.* Citrate kinetics in patients receiving long-term hemodialysis therapy. *Am J Kidney Dis* 2005; 46: 903–907
4. Aniort J, Petitclerc T, Créput C. Safe use of citric acid-based dialysate and heparin removal in postdilution online hemodiafiltration. *Blood Purif* 2012; 34: 336–343
5. Šafránek R, Moučka P, Vávrová J *et al.* Changes of serum calcium, magnesium and parathyroid hormone induced by hemodialysis with citrate-enriched dialysis solution. *Kidney Blood Press Res* 2015; 40: 13–21
6. Kuragano T, Furuta M, Yahiro M *et al.* Acetate free citrate-containing dialysate increase intact-PTH and BAP levels in the patients with low intact-PTH. *BMC Nephrol* 2013; 14: 18
7. Grundström G, Christensson A, Alquist M *et al.* Replacement of acetate with citrate in dialysis fluid: a randomized clinical trial of short term safety and fluid biocompatibility. *BMC Nephrol* 2013; 14: 216
8. Ahmad S, Callan R, Cole JJ *et al.* Dialysate made from dry chemicals using citric acid increases dialysis dose. *Am J Kidney Dis* 2000; 35: 493–499
9. Schmitz M, Loke O, Fach B *et al.* Effects of citrate dialysate in chronic dialysis: a multicentre randomized crossover study. *Nephrol Dial Transplant* 2016; 31: 1327–1334
10. Molina Nuñez M, de Alarcón R, Roca S *et al.* Citrate versus acetate-based dialysate in on-line haemodiafiltration. A prospective cross-over study. *Blood Purif* 2015; 39: 181–187
11. Gabutti L, Lucchini B, Marone C *et al.* Citrate vs. acetate-based dialysate in bicarbonate haemodialysis: consequences on haemodynamics, coagulation, acid-base status, and electrolytes. *BMC Nephrol* 2009; 10: 7
12. Rocha AD, Padua VC, Oliveira E *et al.* Effects of citrate-enriched bicarbonate based dialysate on anticoagulation and dialyzer reuse in maintenance hemodialysis patients. *Hemodial Int* 2014; 18: 467–472
13. Daimon S, Dan K, Kawano M. Comparison of acetate-free citrate hemodialysis and bicarbonate hemodialysis regarding the effect of intra-dialysis hypotension and post-dialysis malaise. *Ther Apher Dial* 2011; 15: 460–465
14. Dolley-Hitze T, Oger E, Hamel D *et al.* Is anticoagulation discontinuation achievable with citrate dialysate during HDF sessions? *Int J Nephrol* 2016; 2016: 1
15. Leung KC, Tai DJ, Ravani P *et al.* Citrate vs. acetate dialysate on intradialytic heparin dose: a double blind randomized crossover study. *Hemodial Int* 2016; 20: 537–547
16. Sands JJ, Kotanko P, Segal JH *et al.* Effects of citrate acid concentrate (citrasate®) on heparin *N* requirements and hemodialysis adequacy: a multicenter, prospective noninferiority trial. *Blood Purif* 2012; 33: 199–204
17. Kossmann RJ, Gonzales A, Callan R *et al.* Increased efficiency of hemodialysis with citrate dialysate: a prospective controlled study. *Clin J Am Soc Nephrol* 2009; 4: 1459–1464
18. Ortiz Pd S, Ramón MA, Pérez-García R *et al.* Acute effect of citrate bath on post dialysis alkalaemia. *Nefrologia* 2015; 35: 164–171
19. Pizzarelli F, Cerrai T, Dattolo P *et al.* On-line haemodiafiltration with and without acetate. *Nephrol Dial Transplant* 2006; 21: 1648–1651
20. Panichi V, Fiaccadori E, Rosati A *et al.* Post-dilution on line haemodiafiltration with citrate dialysate: first clinical experience in chronic dialysis patients. *Sci World J* 2013; 2013: 70361
21. Jung SW, Kim DR, Cho KS *et al.* Effects of dialysate acidification with citrate versus acetate on cell damage, uremic toxin levels, and inflammation in patients receiving maintenance hemodialysis. *Am J Kidney Dis* 2019; 73: 432–434
22. Pun PH, Horton JR, Middleton JP. Dialysate calcium concentration and the risk of sudden cardiac arrest in hemodialysis patients. *Clin J Am Soc Nephrol* 2013; 8: 797–803
23. Ishimura E, Okuno S, Yamakawa T *et al.* Serum magnesium concentration is a significant predictor of mortality in maintenance hemodialysis patients. *Magnes Res* 2007; 20: 237–244
24. Floege J. Magnesium in CKD: more than a calcification inhibitor? *J Nephrol* 2015; 28: 269–277
25. João Matias P, Azevedo A, Laranjinha IT *et al.* lower serum magnesium is associated with cardiovascular risk factors and mortality in haemodialysis patients. *Blood Purif* 2014; 38: 244–252
26. Kircelli F, Peter ME, Sevinc Ok ET *et al.* Magnesium reduces calcification in bovine vascular smooth muscle cells in a dose-dependent manner. *Nephrol Dial Transplant* 2012; 27: 514–521
27. Schmaderer C, Braunisch MC, Suttmann YT *et al.* Reduced mortality in maintenance haemodialysis patients on high versus low dialysate magnesium: a pilot study. *Nutrients* 2017; 9: 926
28. Lacson E Jr, Wang W, Ma L *et al.* Serum magnesium and mortality in hemodialysis patients in the United States: a cohort study. *Am J Kidney Dis* 2015; 66: 1056–1066
29. Turgut F, Kanbay M, Metin MR *et al.* Magnesium supplementation helps to improve carotid intima media thickness in patients on hemodialysis. *Int Urol Nephrol* 2008; 40: 1075–1082
30. Lorrentz G, Mayer CC, Bachman Q *et al.* Acetate-free, citrate-acidified bicarbonate dialysis improves serum calcification propensity—a preliminary study. *Nephrol Dial Transplant* 2018; 33: 2043–2205