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Citric Acid-Containing Dialysate and Survival Rate in the Dialysis Outcomes and Practice Patterns Study

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Key Points

- Citric acid-containing dialysate for hemodialysis was prescribed to 20%–25% of patients in Japanese, Italian, and Belgium centers in the Dialysis Outcomes and Practice Patterns Study.
- The use of citric acid-containing bicarbonate-based dialysate was not associated with mortality in the international Dialysis Outcomes and Practice Patterns Study cohort.

Abstract

Background Metabolic acidosis is a common threat for patients on hemodialysis, managed by alkaline dialysate. The main base is bicarbonate, to which small amounts of acetic, citric, or hydrochloric acid are added. The first two are metabolized to bicarbonate, mostly by the liver. Citric acid-containing dialysate might improve dialysis efficiency, anticoagulation, calcification propensity score, and intradialytic hemodynamic stability. However, a recent report from the French dialysis registry suggested this dialysate increases mortality risk. This prompted us to assess whether citric acid-containing bicarbonate-based dialysate was associated with mortality in the international Dialysis Outcomes and Practice Patterns Study (DOPPS).

Methods Detailed patient-based information on dialysate composition was collected in DOPPS phases 5 and 6 (2012–2017). Cox regression was used to model the association between baseline bicarbonate dialysate containing citric acid versus not containing citric acid and mortality among DOPPS countries and phases where citric acid-containing dialysate was used.

Results Citric acid-containing dialysate was most commonly used in Japan, Italy, and Belgium (25%, 25%, 21% and of patients who were DOPPS phase 6, respectively) and used in <10% of patients in other countries. Among 11,306 patients in DOPPS country and phases with at least 15 patients using citric acid-containing dialysate, patient demographics, comorbidities, and laboratories were similar among patients using (14%) versus not using (86%) citric acid-containing dialysate. After accounting for case mix, we did not observe a directional association between citric acid-containing dialysate use (any versus none) and mortality (HR, 1.14; 95% CI, 0.97 to 1.34), nor did we find evidence of a dose-dependent relationship when parameterizing the citric acid concentration in the dialysate as 1, 2, and 3+ mEq/L.

Conclusions The use of citric acid-containing dialysate was not associated with greater risk of all-cause mortality in patients on hemodialysis participating in DOPPS. Clinical indications for the use of citric acid-containing dialysate deserve further investigation.

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Introduction

Metabolic acidosis is a common complication of CKD (1,2) and needs correction. In hemodialysis, the dialysate fluid is used to remove fixed and volatile acids, but also to provide enough alkaline salts. The use of acetate dialysate was rapidly abandoned because of plasmatic accumulation and the undesirable side effects of acetate, leading to its replacement by bicarbonate (1,3).

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However, the simultaneous presence of bicarbonate and calcium ion in the preparation of such dialysate risked the precipitation of insoluble calcium carbonate. For this reason, bicarbonate-based dialysate was prepared using two concentrates, the first containing the electrolytes and the second the bicarbonate ion. The addition of an acid, either acetic, hydrochloric, or citric, in the first concentrate, called "acid" concentrate, was necessary to acidify the dialysate and avoid calcium-carbonate precipitation.

Acetic acid is still the most commonly used acid concentrate worldwide in standard bicarbonate-based dialysate. However, even at the low concentration of 3–4 mmol/L, it accumulates in many patients, and induces several side effects including headache, nausea, abdominal pain, intradialytic arterial hypotension, postdialysis asthenia, and chronic inflammation, as evidenced by increased TNF alpha (4–7).

Citric acid is safe because the low concentration (0.8–3 mmol/L) used does not significantly affect ionized calcium concentration, and the citrate is rapidly metabolized to bicarbonate by the liver and muscles. Several beneficial effects have been attributed to the use of citric acid-containing dialysate, including fewer episodes of intradialytic arterial hypotension (6), improved dialysis performance (8), better control of metabolic acidosis (9), reduced dose of anticoagulation (10), improved calcification propensity score or T50 (11,12), and improved nutritional status (13). However, some negative effects have also been described, such as muscular cramps (14), negative calcium balance, and the exacerbation of secondary hyperparathyroidism (15), and most importantly an increased risk of mortality (16).

Since its introduction in 2013 in France, the use of citric acid-containing bicarbonate-based dialysate appeared to be safe and no major issues were reported, until a safety signal was reported on the basis of a retrospective national database analysis of the Renal Epidemiology and Information Network registry (Mercadal *et al.* [16], oral presentation, annual meeting of Société Francophone de Néphrologie, Dialyze et Transplantation, October 2018, Lille, France and abstract, MON-110, World Congress of Nephrology, Melbourne, New South Wales, Australia, 2019). This communication led to a controversy in the mainstream press; *Le Monde*, a leading national newspaper, ran an article about "a 40% increased risk of mortality in hemodialysis patients treated by citrate" (Dialyze au citrate: l'ANSM demande des études complémentaires, *Le Monde*, 8 Feburary, 2019). The French National Agency for Medicine and Health Products Safety and other dialysis groups in France and Europe have since initiated analyses of their databases to assess the safety of citrate-containing dialysate. The aim of our study was to assess whether there was an increase or a reduction in the risk of mortality with the use of citric acid-containing dialysate, compared with dialysate not containing citric acid, in a large international cohort of patients on in-center hemodialysis from the Dialysis Outcomes and Practice Patterns Study (DOPPS).

Materials and Methods

Study Design and Population

The DOPPS is an international prospective cohort study of patients on in-center hemodialysis who are ≥18 years of age (17). Patients in the DOPPS are enrolled randomly from a representative sample of dialysis facilities within each nation at the start of each study phase, as described previously (18,19). The concentration of citrate in the dialysate was added to the DOPPS questionnaires starting in 2013. This manuscript is restricted to the following countries from DOPPS phase 5 (2013–2014) and DOPPS phase 6 (2015–2018) where citric acid-containing dialysate was consistently reported: Belgium, Canada, Germany, six Gulf Cooperation Council Countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, and United Arab Emirates), Italy, Japan, Spain, Sweden, and the United Kingdom. The following were patient dialysate-based exclusion criteria (*1*): patients with missing citric acid-containing values (*2*), patients with values of dialysate bicarbonate considered implausible (<20 or >46 mEq/L), (*3*) patients with total dialysate base (bicarbonate, citrate, acetate) concentrations outside of 25–46 mEq/L, and (*4*) dialysate citrate values >8 mEq/L leaving 14,421 patients from 268 facilities (Figure 1; patient characteristics for included versus excluded patients are included in Supplemental Table 1). Models were further restricted to patients in DOPPS countries or phases with at least 15 patients using citrate-containing dialysate and follow-up after the initial dialysate record (n=11,318 patients in 221 facilities). Study approval was obtained by a central institutional review board. Additional study approval and patient consent were obtained as required by national and local ethics committee regulations.

Demographics, comorbid conditions, laboratory values, and dialysis prescription details were abstracted from patients' medical records at study entry. Mortality was reported continuously during study follow-up and primary and secondary causes of death recorded by study coordinators.

Statistical Analyses

The primary outcome of interest was mortality, and the primary exposure of interest was citric acid-containing dialysate exposure. Cox regression was used to analyze the association between citric acid-containing dialysate and mortality, stratified by country and DOPPS phase, accounting for facility clustering using robust sandwich covariance estimators, and adjusted for potential confounders (see Table 2, Supplemental Table 1). Exposure to citric acid-containing dialysate was assessed at a single time point, the latest of (*1*) DOPPS study enrollment or (*2*) the first study follow-up round in which citric acid-containing dialysate became available in DOPPS phase 5 (2013). Time at risk started immediately after exposure assessment and continued until the time of death, 7 days after leaving the facility due to transplant or transfer, 7 days after changing modality, loss to follow-up, or as of the most recent date of data availability (for patients who were currently enrolled). The median follow-up time was 1.7 years. Overall, missingness for model covariates was low (*e.g.*, <4% for the majority of covariates; <20% for all). For missing data, we used the Sequential Regression Multiple Imputation Method implemented by IVEware (20), and analyzed using the MIAnalyze procedure in SAS/STAT 9.4.

All analyses used SAS software, version 9.4 (SAS institute, Cary, NC).

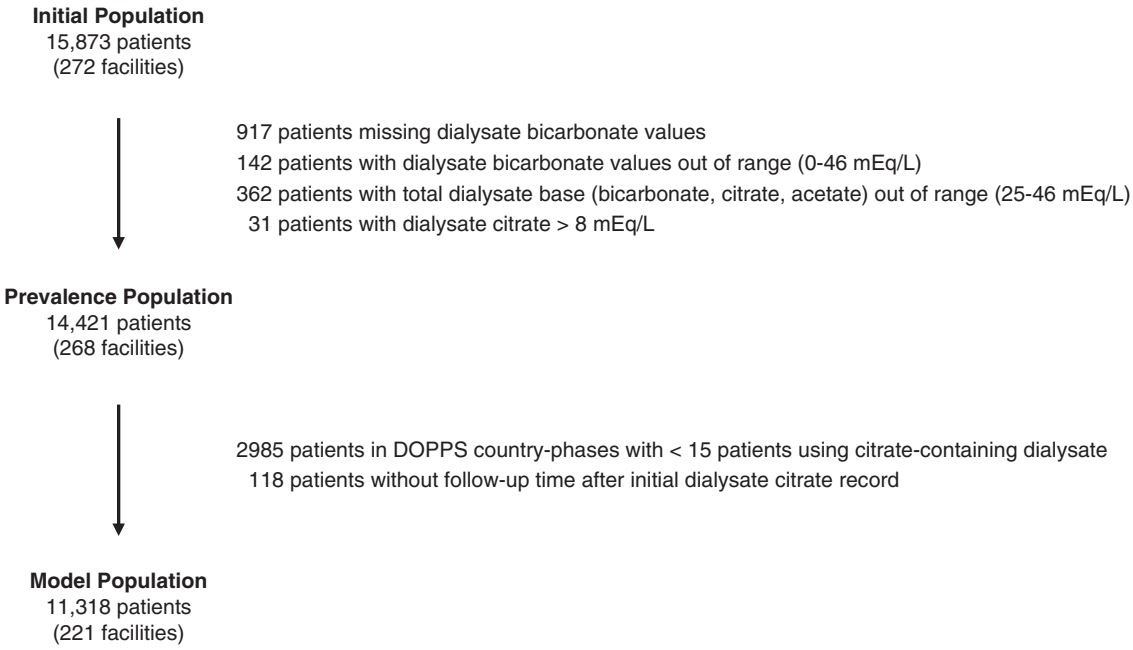

Figure 1. | **Patient selection from the Dialysis Outcomes and Practice Patterns Study (DOPPS) phase 5 and 6 population where dialysate citrate queried.**

Results

Study Population

Citric acid-containing bicarbonate dialysate is still an emerging dialysis therapy as illustrated by its very low usage during DOPPS phase 5, representing <5% in most of the participating countries (Figure 2). Only Belgium, Italy, and Japan had >10% of patients using citric acid-containing dialysate during 2012 and 2015, respectively. Subsequently, there has been a progressive increase in use of this therapy resulting in 21%, 25%, and 25% of patients using citric acid-containing dialysate in Belgium, Italy, and Japan, respectively, in DOPPS phase 6. However, among countries with >20% of patients using citric acid-containing dialysis, use was concentrated among a small proportion of facilities and the majority of facilities reported no use (Figure 3).

A total of 11,318 patients were included in the study; 1630 patients (14%) were using citric acid-containing dialysate and 9688 were not (86%). In total, 83% of these patients came from three countries (Belgium, Italy, or Japan). The mean±SD age for the whole cohort was 66±14 years, and 34% were women. Because of the well-known differences of dialysis vintage and survival rate between Japan and other countries, demographic, comorbidity, and laboratory results are presented and analyzed separately (Table 1). Japanese patients had a longer mean±SD dialysis vintage, 6.2±7.6 versus 3.9±5.7 years; higher predialysis serum magnesium concentration, 2.5±0.5 versus 2.2±0.4 mg/dl; and lower percentage of central catheter use (2% versus 33%) than patients from other countries. However, they did not differ in any of the remaining parameters from the other

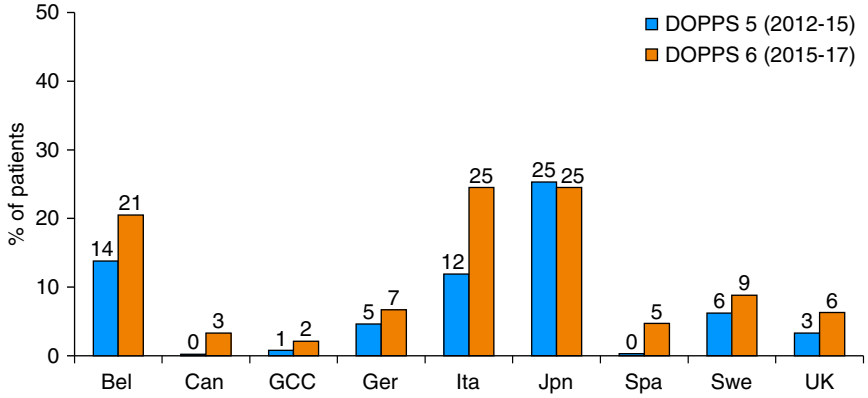

Figure 2. | **Citric acid-containing dialysate use, by country and DOPPS phase.** Bel, Belgium; Can, Canada; GCC, Gulf Cooperation Council Countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates); Ger, Germany; Ita, Italy; Jpn, Japan; Spa, Spain; Swe, Sweden; UK, United Kingdom.

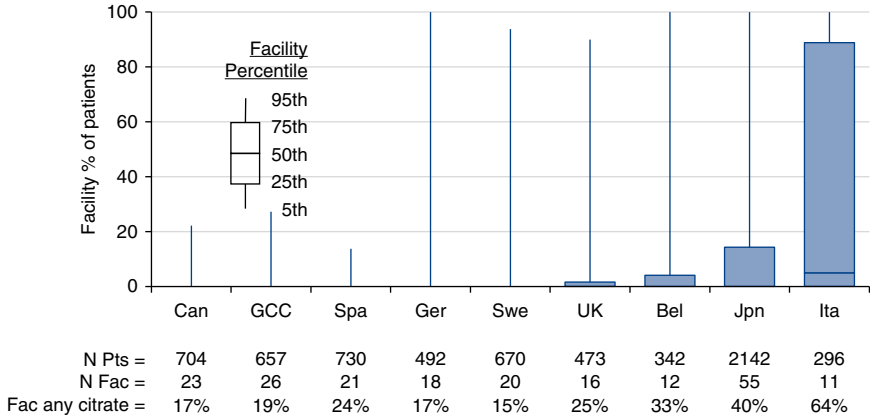

Figure 3. | Facility % of patients with citric acid–containing dialysate use, by country in DOPPS phase 6 (2015–2017). Restricted to facilities with at least five patients with dialysate citrate data. Bel, Belgium; Can, Canada; GCC, Gulf Cooperation Council Countries (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates); Ger, Germany; Ita, Italy; Jpn, Japan; Spa, Spain; Swe, Sweden; UK, United Kingdom; Fac, facility.

participating countries. Patients using citric acid-containing dialysate were notably older than those not using citric acid in countries other than Japan (66.2±14.7 versus 70.3±13.7 years) (Table 1).

During the 2-year follow-up, 1862 of the 11,318 patients died (16%). After accounting for case mix, we did not observe a clear association between citric acid-containing dialysate use (any versus none) and mortality (Table 2; hazard ratio [HR], 1.14; 95% confidence interval [95% CI], 0.97 to 1.45; note that model 5 was considered potentially overadjusted for variables in the causal pathway between citric acid-containing dialysate and mortality). Results were similar across countries (Supplemental Table 2, *P* value for interaction = 0.73). Nor did we find evidence of a dose-dependent association when parameterizing dialysate citric acid-concentrations as 1, 2, and 3+ (*i.e.*, 3–8) mEq/L. Likewise, the risk of cardiovascular mortality was comparable between patients using, versus not using, citrate-containing dialysate (HR, 1.27; 95% CI, 0.98 to 1.65; Supplemental Table 3).

Discussion

Over 2 years of longitudinal follow-up, and after adjustment for numerous potentially confounding variables, we found the use of citric acid-containing bicarbonate-based dialysate was not associated with an increased or decreased risk of all-cause or cardiovascular mortality compared with patients using other types of dialysate.

Dialysate prescription is still very subjective, somewhat arbitrary, and on the basis of inexistent, scarce, or very low-grade scientific evidence. For instance, acetic acid, which is the most widely used acid in bicarbonate-based dialysates for standard hemodialysis, and hemodiafiltration is being replaced by other acids, such as citric (21), lactic (22), and hydrochloric acid, because of the high frequency of undesirable side effects and intolerance to acetate (7).

Citrate ($C_6H_7O_7$) ions play an important role in the regulation of bone metabolism because they bind to calcium and stabilize hydroxyapatite crystals and bone resorption (23,24). Citrate is also a key player in the acid-base balance and is a major player in the oxidative metabolism through the Krebs cycle (25). Intracellular citrate is metabolized first to *cis*-aconitate, and then to d-isocitrate and α-ketoglutarate, in total releasing three carbon dioxide molecules during one full circle of the Krebs cycle; the negatively charged citrate is thus converted 1:1 to bicarbonate (26,27). Since 1990, citrate has been used in intensive care units to avoid clotting of the extracorporeal circuit for patients with acute kidney failure needing kidney replacement therapy (28). Subsequently, during the last decade, citric acid-containing dialysate has been proposed to be one of the best acids for bicarbonate-based dialysate in chronic hemodialysis and hemodiafiltration (7,29,30), without any evidence of the long-term effects on clinical outcomes and safety issues.

An increased risk of mortality was attributed to the use of citric acid-containing dialysate in a French dialysis registry (Renal Epidemiology Information Network) presentation in 2018 (16). It was found that during exposition in a mixed unit using both acetic and citric acids, the all-cause mortality risk was increased by 44%. Similar results were observed after adjusting Cox models for the calcium dialysate concentration, reclassifying calcium concentration on the basis of citric acid-containing dialysate (16). The results of the present DOPPS analysis do not support these conclusions. After adjustment for multiple confounders, we did not observe a difference in the risk of mortality for patients using citric acid-containing bicarbonate-based dialysate compared with those not using it. Likewise, the risk of cardiovascular mortality was comparable between patients using citric acid-containing dialysate and those not using it. Due to the slightly positive HR for patients exposed to citric acid-containing dialysate, we also explored whether higher levels of citric acid concentrations were associated with higher risk. As shown in Table 2, we detected no dose-related relationship, which provides no support to the hypothesis of citric acid-containing dialysate-related association with mortality risk.

Four recent observational studies could not support the increased mortality risk found in this French study. The first

Table 1. Patient characteristics, by the use of citric acid-containing dialysate in Japan and Europe/Canada

Characteristic	Japan		Europe[a]/Canada	
	No Citrate	Any Citrate	No Citrate	Any Citrate
Demographics				
Sample patients, *N*	3133	1031	6555	599
Age, yr, mean (SD)	65.7 (12.3)	65.8 (11.9)	66.2 (14.7)	70.3 (13.7)
Male, %	68	67	65	64
Yr on dialysis, median (interquartile range)	3.2 (0.4–8.7)	3.5 (0.5–9.2)	1.7 (0.3–5.0)	2.0 (0.3–4.9)
Dialysis prescription				
Total dialysate base[b], mEq/L, mean (SD)	33.0 (4.8)	36.4 (2.1)	35.7 (3.0)	37.5 (3.8)
Dialysate bicarbonate, mEq/L, mean (SD)	27.4 (3.0)	33.7 (2.7)	33.9 (2.5)	34.0 (2.6)
Dialysate acetate, mEq/L, mean (SD)	7.0 (2.9)	0.1 (1.0)	3.3 (1.1)	2.1 (1.4)
Dialysate calcium, mEq/L (%)				
<2.5 mEq/L	0	1	2	1
2.5 mEq/L	26	8	47	20
2.75 mEq/L	26	0	1	0
3.0 mEq/L	48	91	46	65
Dialysis session length, min, mean (SD)	236 (30)	234 (26)	239 (37)	237 (28)
Single pool Kt/V, mean (SD)	1.4 (0.3)	1.4 (0.3)	1.5 (0.3)	1.5 (0.3)
Catheter use (%)	2	1	34	28
Hemodiafiltration (%)	10	1	29	49
Comorbidities (%)				
Coronary artery disease	25	26	35	35
Cerebrovascular disease	16	11	15	15
Congestive heart failure	18	15	19	16
Peripheral vascular disease	14	12	25	29
Other cardiovascular disease	23	19	30	37
Hypertension	82	87	87	87
Cancer	12	14	18	22
Diabetes	44	43	40	39
Gastrointestinal bleed in last yr	3	3	4	4
Lung disease	4	2	13	16
Neurologic disorder	7	5	11	12
Psychologic disorder	4	4	15	14
Recurrent cellulitis	3	3	9	9
Cirrhosis	1	3	2	2
Laboratory parameters, mean (SD)				
Total calcium (mg/dl)	8.7 (0.8)	8.7 (0.7)	8.9 (0.7)	8.9 (0.8)
Phosphate (mg/dl)	5.3 (1.4)	5.3 (1.4)	5.0 (1.6)	4.8 (1.4)
Albumin (g/dl)	3.6 (0.5)	3.6 (0.4)	3.6 (0.5)	3.6 (0.5)
PTH (pg/ml)	134 (74,222)	129 (73,226)	247 (134,428)	231 (136,383)
Alanine transaminase (ALT), U/L	12.0 (11.9)	11.1 (7.8)	17.4 (22.4)	17.3 (10.4)
Aspartate transaminase (AST), U/L	14.6 (9.1)	14.4 (14.1)	18.4 (20.7)	17.5 (7.5)
S. magnesium, mg/dl	2.5 (0.4)	2.5 (0.5)	2.2 (0.4)	2.1 (0.5)

PTH, serum parathyroid hormone concentration.
[a]European countries participating in Dialysis Outcomes and Practice Patterns Study include Belgium, Germany, Italy, Spain, Sweden, and the United Kingdom.
[b]Sum of dialysate bicarbonate + acetate or citrate.

enrolled 10,121 patients on incident hemodialysis and followed them for 3.8 years. Of them, 371 were exposed at least 70% of the time spent on dialysis to citric acid-containing dialysate (CiD70%). After propensity-score matching, annual mortality was 11.43 (95% CI, 8.86 to 14.75) and 12.04 (95% CI, 9.44 to 15.35) deaths/100 person-years in the CiD0% and CiD70% groups, respectively (P=0.80) (31). The second study, also in patients on incident hemodialysis and after a median follow-up of 23 months, did not show any increased risk of mortality with the use of citric acid-containing dialysate, despite higher comorbidities in the citric acid-exposed group (32). The third study was a long-term, retrospective, observational study, including 1132 patients starting incident dialysis over a span of 10 years, from 2008 to 2018, in five sanitary territories in the western region of France with a high prevalence of citric acid-containing dialysate citrate (57% in 2018). Again, comparing patients who spent >80% of their dialysis time on citric acid-based dialysate to those who have never been exposed, the exposure to citric acid-containing dialysate up to a 6-year period showed no significant difference in all-cause mortality (33). Finally, the fourth study reported the results of a questionnaire survey sent to 1300 French dialysis units (34). They observed that the crude mortality rate per 1000 patient-months with citric acid-containing dialysate was 11.5 (95% CI, 11.1 to 12.0), which was significantly lower than with either acetic acid (12.9; 95% CI, 12.8 to 13.1) or hydrochloric acid-containing dialysates (34).

The potential beneficial effects of citrate on patients on dialysis deserve to be stressed here. The full anticoagulation

Table 2. Citric acid-containing dialysate and mortality risk, effect of progressive adjustment

Exposure	% of Patients	Hazard Ratio (95% Confidence Interval)				
		Model 1	Model 2	Model 3	Model 4	Model 5
No citrate	86	1.00	1.00	1.00	1.00	1.00
Citrate=1 mEq/L	2	1.13 (0.82 to 1.56)	1.10 (0.81 to 1.51)	1.09 (0.80 to 1.50)	1.15 (0.84 to 1.56)	1.25 (0.90 to 1.74)
Citrate=2 mEq/L	9	1.30 (1.00 to 1.70)	1.25 (0.96 to 1.63)	1.24 (0.95 to 1.62)	1.24 (0.95 to 1.62)	1.24 (0.93 to 1.64)
Citrate=3+mEq/L	3	1.13 (0.85 to 1.50)	0.99 (0.76 to 1.28)	1.00 (0.77 to 1.31)	1.02 (0.79 to 1.31)	0.88 (0.66 to 1.16)
Any citrate (versus none)	14 (86)	1.20 (1.02 to 1.42)	1.12 (0.96 to 1.32)	1.12 (0.95 to 1.32)	1.14 (0.97 to 1.34)	1.10 (0.92 to 1.32)

Restricted to countries/phases (Belgium/5 and 6, Canada/6, Germany/5 and 6, Italy/5 and 6, Japan/5 and 6, Spain/6, Sweden/5 and 6, United Kingdom/5 and 6) with at least 15 patients prescribed citric acid-containing dialysate n=11,318 patients and 1862 deaths; dialysate composition assessed at a single time point: earliest of Dialysis Outcomes and Practice Patterns Study (DOPPS) study enrollment or the first study follow-up round in which citric acid-containing dialysate became available in DOPPS phase 5 (2013).
Model 1: stratified by country and phase; accounting for facility clustering.
Model 2: additionally adjusted for age and sex.
Model 3: additionally adjusted for diabetes and body mass index <18 kg/m^2.
Model 4: additionally adjusted for hemodiafiltration use, catheter use, single pool Kt/V, and dialysis session length.
Model 5: additionally adjusted for total dialysate base concentration (sum of bicarbonate + acetate or citrate), dialysate calcium ≤2.5 versus >2.5 mEq/L, albumin, phosphate, calcium, and parathyroid hormone concentration (PTH); model 5 considered as potentially overadjusted for variables in the causal pathway.

properties of citrate are obtained only with concentrations between 4 and 6 mmol/L, which can decrease ionized calcium on average by 0.35 mmol/L, thus preventing activation of both coagulation cascades and platelets (35). During standard hemodialysis using citric acid-containing dialysate, the citrate concentrations achieved are lower (0.8–3.0 mmol/L), but sufficient to allow the reduction of heparin dose by 20%–55% as shown in several studies (8,36,37). This large variability in the final circulating citrate concentration might explain the small, and still controversial, higher dialysis efficiency seen inconsistently across studies. For example, Kt/V increased from 1.51 to 1.57 in one study (8), but no meaningful difference in Kt/V has been seen in other studies (37,38).

Unlike what happens with acetate, the metabolism of citrate is incomplete during dialysis, because liver and muscle metabolism occurs partly after the end of the dialysis. In addition, citrate metabolism may differ between patients who can be considered as either fast or slow citrate metabolizers, depending on their liver function and muscle mass, more specifically the mitochondrial function of these two organs. However, patients on hemodialysis show similar citrate levels to those with normal eGFR (1 mmol/L) after infusion of citrate for regional anticoagulation. In the case of liver failure, citrate clearance can be reduced as much as 50%, contraindicating the use of citric acid-containing dialysate in some patients with liver disease (39). This does not appear to be the case with acetate because it is metabolized regardless of liver function, and may be the most efficient bicarbonate precursor (40).

Citric acid-containing dialysate can also have several detrimental effects. It can induce hypocalcemia and negative calcium balance because citrate chelates calcium, and some of this calcium citrate complex is lost during the passage through the dialysis filter. The negative calcium balance may exacerbate secondary hyperparathyroidism (15). Lower intradialytic systolic BP, muscle cramps, and fatigue have also been described during the first 2 weeks of citric acid-containing dialysate utilization and associated with low dialysate calcium concentration (1.50 mM) (38,41). In our study, we did not find differences in serum calcium, phosphate, or PTH between patients receiving citric acid-containing dialysate or not. Muscular cramps occur in more than 30% of patients, do not respond to palliative measures, and might regress after switching those patients to dialysate not containing citrate (42). These muscle cramps do not appear to be associated with low serum calcium or magnesium levels, and could be due to a disorder of muscle energy metabolism or even an altered gut microbiota (42,43).

This study has several strengths. The DOPPS cohort provides a unique high-quality international dataset, reflecting the most contemporary information regarding the use of different types of dialysate and their associations with survival rate. Because there are no evidence-based guidelines concerning the selection of different types of dialysate, prescription of citric acid-containing dialysate may be essentially random with respect to patient characteristics (*i.e.*, not by clinical indication), thus reducing the likelihood of patient-level confounding. The standardized data-collection protocol, on the basis of medical records, ensures a high degree of data uniformity and accuracy across countries and regions.

The study also has limitations, including its observational design, which cannot provide the same level of confidence as randomized clinical trials considering the risk of mortality. Second, the proportion of patients using citric acid-containing dialysate is still low compared with acetic acid dialysate. The study may thus be underpowered to detect differences between different dialysates, and restriction of the analysis predominantly to Belgium, Italy, and Japan limits generalizability of these results internationally. Length of exposure to citric acid-containing dialysate could not be ascertained, limiting our ability to assess the cumulative effect of exposure.

In conclusion, the use of this emerging practice of citric acid-containing dialysate was not associated with an elevated risk of mortality in patients on hemodialysis participating in the DOPPS. Clinical indications for the use of citric

acid-containing dialysate deserve further investigation in future studies.

Disclosures

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Author Contributions

B. Bieber, F. Port, B. M. Robinson, and P. Ureña-Torres conceptualized the study; B. Bieber, C. Combe, F. Guebre Egziabher, M. Inaba, C. Jacquelinet, M. Jadoul, R. Ossman, B. M. Robinson, and P. Ureña-Torres were responsible for the formal analysis; R. Ossman, F. Port, B. M. Robinson, and P. Ureña-Torres were responsible for investigation; B. Bieber, B. M. Robinson, and P. Ureña-Torres provided supervision; B. Bieber, B. M. Robinson, and P. Ureña-Torres wrote the original draft; and all authors reviewed and edited the manuscript.

Supplemental Material

This article contains the following supplemental material online at http://kidney360.asnjournals.org/lookup/suppl/doi:10.34067/KID.0006182020/-/DCSupplemental.

Supplemental Table 1. Patient characteristics, by inclusion in Table 1 in Japan and Europe/Canada.

Supplemental Table 2. Citric acid-containing bicarbonate-based dialysate and mortality risk, by country.

Supplemental Table 3. Citric acid-containing dialysate and cardiovascular mortality risk, effect of progressive adjustment.

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