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 DOPPS
- The use of citric acid-containing bicarbonate-based dialysate was not associated with mortality in the international DOPPS cohort

ABSTRACT

Background: Metabolic acidosis is a common threat for hemodialysis patients, managed by alkaline dialysate. The main base is bicarbonate, to which small amounts of acetic, citric, or hydrochloric acid are added. The first two ones 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 that 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 to 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 country/phases where citric acid-containing dialysate was used.

Results: Citrate-containing dialysate was most commonly used in Japan, Italy, and Belgium (25%, 25%, 21% of DOPPS phase 6 patients) and used in < 10% of patients in other countries. Among 11,306 patients in DOPPS country-phases with at least 15 patients using citrate-containing dialysate, patient demographics, comorbidities, and labs were similar among
patients using (14%) vs. not using (86%) citrate-containing dialysate. After accounting for case mix, we did not observe a directional association between citric acid-containing dialysate use (any vs. none) and mortality [HR (95% CI) = 1.14 (0.97-1.34)], nor did we find evidence of a dose-dependent relationship when parameterizing the citrate 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 hemodialysis patients participating in DOPPS. Clinical indications for the use of citric acid-containing dialysate deserve further investigation.
INTRODUCTION

Metabolic acidosis is a common complication of chronic kidney disease (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 undesirable side effects of acetate, leading to its replacement by bicarbonate (1, 3).

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 acid 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, post-dialysis asthenia, and chronic inflammation as evidenced by increased tumour necrosis factor alpha (4-7).

Citric acid is safe because the low concentration (0.8 to 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 based on a retrospective national database analysis of the Renal Epidemiology and Information Network registry (REIN) (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) (16). 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" (Dialyse au citrate : l’ANSM demande des études complémentaires. Le Monde 08 Feb 2019). The French National Agency for Medicine and Health Products Safety (ANSM) 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 in-center hemodialysis patients from the Dialysis Outcomes and Practice Patterns Study (DOPPS).

METHODS
Study design and population

The DOPPS is an international prospective cohort study of patients on in-center hemodialysis who are $\geq$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. The current 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, 6 Gulf Cooperation Council Countries (GCC; Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates), Italy, Japan, Spain, Sweden, and the United Kingdom. The following were dialysate-based patient 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 vs. excluded patients are included in Supplemental Table 1). Models were further restricted to patients in DOPPS country-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 patient 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 analysis**

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 (a) DOPPS study enrollment or (b) 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 currently enrolled patients). 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).

**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 less than 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%, 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; 1,630 patients (14%) were using citric acid-containing dialysate and 9,688 were not (86%). Eighty-three percent 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, comorbidities, and laboratory results are presented and analyzed separately (Table 1). Japanese patients had a longer mean (±SD) dialysis vintage, 6.2 ± 7.6 years versus 3.9 ± 5.7 years; higher pre-dialysis 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 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 two-year follow-up, 1,862 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 vs. none) and mortality (Table 2; HR 95%, CI = 1.14, 0.97-1.45; note that model 5 was considered as potentially over-adjusted 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 95%, CI = 1.27, 0.98-1.65; Supplemental Table 3).

**DISCUSSION**

Over two years of longitudinal follow-up, and after adjustment for numerous potentially confounding variables, we found that 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 based on 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 actually 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 (C₆H₇O₇) ions play an important role in the regulation of bone metabolism since 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 (REIN, 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 based on 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 to 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 hazard ratio 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 one enrolled 10,121 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% confidence interval (CI) 8.86–14.75] and 12.04 (95% CI 9.44–15.35) deaths/100 person-years in the CiD0% and CiD70% groups, respectively (P=0.80) (31). The second study, also in incident hemodialysis patients 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 1,132 incident patients starting dialysis over a time 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% 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) 11.1–12.0], which was significantly lower than with either acetic acid [12.9 (95% CI 12.8–13.1)] or hydrochloric acid-containing dialysates (34).
The potential beneficial effects of citrate on dialysis patients deserve to be stressed here. The full anticoagulation properties of citrate are obtained only with concentrations between 4-6 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, since 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, hemodialysis patients show similar citrate levels to those with normal eGFR (1 mmol/L) following infusion of citrate for regional anticoagulation. In case of liver failure, the 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 since 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 blood pressure, muscle cramps, and fatigue have also been described during the first two 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 data set reflecting the most contemporary information regarding the use of different types of dialysate and their associations with survival rate. Since 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, based on 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 to 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 hemodialysis patients 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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Patient consent: All patients provided informed consent to participate DOPPS 5 and 6.

**Author Contributions**

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F Guebre Egziabher: Formal analysis; Writing - review and editing

R Ossman: Formal analysis; Investigation; Writing - review and editing

M Jadoul: Formal analysis; Writing - review and editing

M Inaba: Formal analysis; Writing - review and editing

B Robinson: Conceptualization; Formal analysis; Investigation; Supervision; Writing - original draft; Writing - review and editing

F Port: Conceptualization; Investigation; Writing - review and editing

C Jacquelinet: Formal analysis; Writing - review and editing

C Combe: Formal analysis; Writing - review and editing
**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
REFERENCES


## TABLES

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Japan No citrate</th>
<th>Japan Any citrate</th>
<th>Europe/Canada No citrate</th>
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<tr>
<td><strong>Demographics</strong></td>
<td></td>
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<td></td>
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<td>3133</td>
<td>1031</td>
<td>6555</td>
<td>599</td>
</tr>
<tr>
<td>Age, years</td>
<td>65.7(12.3)</td>
<td>65.8(11.9)</td>
<td>66.2(14.7)</td>
<td>70.3(13.7)</td>
</tr>
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<td>Male, %</td>
<td>68%</td>
<td>67%</td>
<td>65%</td>
<td>64%</td>
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<tr>
<td>Years on dialysis</td>
<td>3.2[0.4,8.7]</td>
<td>3.5[0.5,9.2]</td>
<td>1.7[0.3,5.0]</td>
<td>2.0[0.3,4.9]</td>
</tr>
<tr>
<td><strong>Dialysis Prescription</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Total dialysate base(^b), mEq/L</td>
<td>33.0(4.8)</td>
<td>36.4(2.1)</td>
<td>35.7(3.0)</td>
<td>37.5(3.8)</td>
</tr>
<tr>
<td>Dialysate bicarbonate, mEq/L</td>
<td>27.4(3.0)</td>
<td>33.7(2.7)</td>
<td>33.9(2.5)</td>
<td>34.0(2.6)</td>
</tr>
<tr>
<td>Dialysate acetate, mEq/L</td>
<td>7.0(2.9)</td>
<td>0.1(1.0)</td>
<td>3.3(1.1)</td>
<td>2.1(1.4)</td>
</tr>
<tr>
<td>&lt; 2.5 mEq/L</td>
<td>0%</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>2.5 mEq/L</td>
<td>26%</td>
<td>8%</td>
<td>47%</td>
<td>20%</td>
</tr>
<tr>
<td>2.75 mEq/L</td>
<td>26%</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
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<tr>
<td>3.0 mEq/L</td>
<td>48%</td>
<td>91%</td>
<td>46%</td>
<td>65%</td>
</tr>
<tr>
<td>Dialysis session length, min</td>
<td>236(30)</td>
<td>234(26)</td>
<td>239(37)</td>
<td>237(28)</td>
</tr>
<tr>
<td>Single pool Kt/V</td>
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<td>1.4(0.3)</td>
<td>1.5(0.3)</td>
<td>1.5(0.3)</td>
</tr>
<tr>
<td>Catheter use</td>
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<td>1%</td>
<td>34%</td>
<td>28%</td>
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<tr>
<td>Hemodialfiltration</td>
<td>10%</td>
<td>15%</td>
<td>29%</td>
<td>49%</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Coronary artery disease</td>
<td>25%</td>
<td>26%</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
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<td>11%</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
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<td>15%</td>
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<tr>
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<td>12%</td>
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</tr>
<tr>
<td>Other cardiovascular disease</td>
<td>23%</td>
<td>19%</td>
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<td>37%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82%</td>
<td>87%</td>
<td>87%</td>
<td>87%</td>
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<tr>
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<td>12%</td>
<td>14%</td>
<td>18%</td>
<td>22%</td>
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<tr>
<td>Diabetes</td>
<td>44%</td>
<td>43%</td>
<td>40%</td>
<td>39%</td>
</tr>
<tr>
<td>Gastrointestinal bleed in last year</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
<td>4%</td>
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<tr>
<td>Lung Disease</td>
<td>4%</td>
<td>2%</td>
<td>13%</td>
<td>16%</td>
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<tr>
<td>Neurologic disorder</td>
<td>7%</td>
<td>5%</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Psychologic disorder</td>
<td>4%</td>
<td>4%</td>
<td>15%</td>
<td>14%</td>
</tr>
<tr>
<td>Recurrent cellulitis</td>
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<td>3%</td>
<td>9%</td>
<td>9%</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>1%</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Laboratory parameters</td>
<td>Value 1</td>
<td>Value 2</td>
<td>Value 3</td>
<td>Value 4</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Total calcium (mg/dL)</td>
<td>8.7 (0.8)</td>
<td>8.7 (0.7)</td>
<td>8.9 (0.7)</td>
<td>8.9 (0.8)</td>
</tr>
<tr>
<td>Phosphorus (mg/dL)</td>
<td>5.3 (1.4)</td>
<td>5.3 (1.4)</td>
<td>5.0 (1.6)</td>
<td>4.8 (1.4)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.6 (0.5)</td>
<td>3.6 (0.4)</td>
<td>3.6 (0.5)</td>
<td>3.6 (0.5)</td>
</tr>
<tr>
<td>Alanine transaminase (ALT), U/L</td>
<td>12.0 (11.9)</td>
<td>11.1 (7.8)</td>
<td>17.4 (22.4)</td>
<td>17.3 (10.4)</td>
</tr>
<tr>
<td>Aspartate transaminase (AST), U/L</td>
<td>14.6 (9.1)</td>
<td>14.4 (14.1)</td>
<td>18.4 (20.7)</td>
<td>17.5 (7.5)</td>
</tr>
<tr>
<td>S. magnesium, mg/dL</td>
<td>2.5 (0.4)</td>
<td>2.5 (0.5)</td>
<td>2.2 (0.4)</td>
<td>2.1 (0.5)</td>
</tr>
</tbody>
</table>

Values are shown as prevalence, mean (standard deviation), or median [interquartile range].

Abbreviations: PTH = serum parathyroid hormone concentration;

a. European countries participating in DOPPS include Belgium, Germany, Italy, Spain, Sweden, the United Kingdom
b. Sum of dialysate bicarbonate + acetate or citrate
<table>
<thead>
<tr>
<th>Exposure</th>
<th>% of patients</th>
<th>Model 1</th>
<th>Model 2</th>
<th>Model 3</th>
<th>Model 4</th>
<th>Model 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>No citrate</td>
<td>86</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Citrate=1 mEq/L</td>
<td>2</td>
<td>1.13(0.82-1.56)</td>
<td>1.10(0.81-1.51)</td>
<td>1.09(0.80-1.50)</td>
<td>1.15(0.84-1.56)</td>
<td>1.25(0.90-1.74)</td>
</tr>
<tr>
<td>Citrate=2 mEq/L</td>
<td>9</td>
<td>1.30(1.00-1.70)</td>
<td>1.25(0.96-1.63)</td>
<td>1.24(0.95-1.62)</td>
<td>1.24(0.95-1.62)</td>
<td>1.24(0.93-1.64)</td>
</tr>
<tr>
<td>Citrate=3+mEq/L</td>
<td>3</td>
<td>1.13(0.85-1.50)</td>
<td>0.99(0.76-1.28)</td>
<td>1.00(0.77-1.31)</td>
<td>1.02(0.79-1.31)</td>
<td>0.88(0.66-1.16)</td>
</tr>
<tr>
<td>Any Citrate (vs. none)</td>
<td>14 (86)</td>
<td>1.20(1.02-1.42)</td>
<td>1.12(0.96-1.32)</td>
<td>1.12(0.95-1.32)</td>
<td>1.14(0.97-1.34)</td>
<td>1.10(0.92-1.32)</td>
</tr>
</tbody>
</table>

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, UK/5 and 6) with at least 15 patients prescribed citric acid-containing dialysate n=11,318 patients and 1,862 deaths; dialysate composition assessed at a single time point - earliest of 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/m²
Model 4: additionally adjusted for HDF 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 vs. > 2.5 mEq/L, albumin, phosphorus, calcium, and PTH; model 5 considered as potentially over-adjusted for variables in the causal pathway
FIGURE LEGENDS

**Figure 1:** Patient selection from the DOPPS phase 5 and 6 population where dialysate citrate queried.

**Figure 2:** Citric acid-containing dialysate use, by country and DOPPS phase. Abbreviations: 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 5 patients with dialysate citrate data. Abbreviations: 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.
Initial Population
15,873 patients
(272 facilities)
- 917 patients missing dialysate bicarbonate values
- 142 patients with dialysate bicarbonate values out of range (0-46 mEq/L)
- 362 patients with total dialysate base (bicarbonate, citrate, acetate) out of range (25-46 mEq/L)
- 31 patients with dialysate citrate > 8 mEq/L

Prevalence Population
14,421 patients
(268 facilities)
- 2985 patients in DOPPS country-phases with < 15 patients using citrate-containing dialysate
- 118 patients without follow-up time after initial dialysate citrate record

Model Population
11,318 patients
(221 facilities)
Figure 2

% of patients

<table>
<thead>
<tr>
<th></th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Bel</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>Can</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>GCC</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Ger</td>
<td>5</td>
<td>7</td>
</tr>
<tr>
<td>Ita</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>Jpn</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Spa</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Swe</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>UK</td>
<td>3</td>
<td>6</td>
</tr>
</tbody>
</table>
Facility % of patients

N Pts = 704  657  730  492  670  473  342  2142  296
N Fac = 23   26   21   18   20   16   12   55    11
Fac any citrate = 17%  19%  24%  17%  15%  25%  33%  40%  64%